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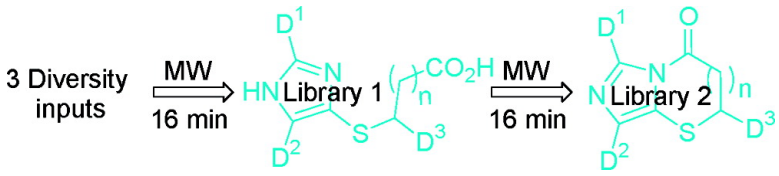

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Parallel Microwave-Assisted Library of Imidazothiazol-3-ones and Imidazothiazin-4-ones

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A methodology for the generation of a microwave-assisted parallel library and its conversion into a second library is described. A 24-membered library of substituted 4(5)-sulfanyl-1*H*-imidazoles was generated and subsequently converted into a second library of bicyclic imidazo[5,1-*b*]thiazol-3-ones and imidazo[5,1-*b*]-thiazin-4-ones. The first library was generated using a three-component reaction and transformed into a daughter library with a polymer-supported coupling agent. The procedure involved the use of an array of expandable reaction vessels, which can accommodate pressure buildup due to microwave heating without loss of volatile solvents or reagents. Library generation time for each library was 16 min.

Introduction

Since 1999, the number of reported uses of microwave technologies for combinatorial library synthesis has risen dramatically.[1] This increase in reports can be linked directly to the commercial availability of microwave laboratory devices specifically tailored to combinatorial applications. Prior to this time, commercial equipment was not available, and earlier reports concentrated on using modified nonlaboratory microwave devices.[2] Over the past 6 years, two approaches have emerged to microwave library generation: one applying the microwave field in a mono-mode[3] manner to one reaction vessel at a time, the other exploiting multimode[4] irradiation in which all reaction vessels are irradiated simultaneously. The monomode sequential approach offers temperature and pressure control of each reaction vessel, though each reaction must be executed individually. In contrast, multimode irradiation facilitates a more conventional combinatorial parallel approach in which all reactions are carried out simultaneously, with internal temperature and pressure controls from only one of the vessels. To date, the most widely reported technique involves the use of monomode devices, which would appear to have an inherent throughput limitation because they are designed to carry out reactions in a sequential manner. This provides the advantages of microwave heating but in a low-throughput consecutive fashion. As such, the exploitation of parallel microwave-driven reactions could be viewed as a complementary approach, which would assist in overcoming the sequential reaction bottleneck.[5] Comparative reports of sequential and parallel microwave heating methodologies have shown similar reproducibility for both approaches.[6]

We have previously described a parallel microwave-assisted library method and illustrated a side-by-side comparison with a conventional heating technique.[7] We have found that for chemistry that works well under conventional heating methods, the most significant advantage to be gained from a diversely substituted library was a reduction in library generation time. Because there still exists a need for the investigation of parallel microwave methods, herein we describe a solution-phase microwave-assisted generation of a parallel library from a library using a three-component reaction to generate the first library and a polymer-supported reagent (PSR) for the library-to-library transformation.

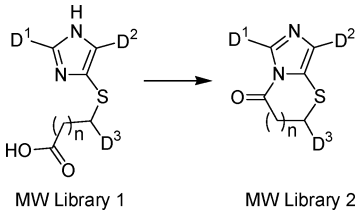

Figure 1. Diversity positions of substituted sulfanyl-1*H*-imidazole library and imidazo[5,1-*b*]thiazol-3-one ($n = 0$)/imidazo[5,1-*b*]-thiazin-4-one ($n = 1$) libraries.

In our work to develop new routes to diversely substituted druglike heterocycles, we previously communicated a two-step synthesis of the imidazo[5,1-*b*]thiazol-3-one and imidazo[5,1-*b*]thiazin-4-one ring systems utilizing conventional heating methods in good yields and high purities.[8] The synthetic route involved a three-component reaction to form a substituted sulfanyl-imidazole ring and an intramolecular coupling of a carboxylic acid and imidazole nitrogen to generate the bicyclic products (Figure 1). Our objective was to apply this chemistry to generate parallel libraries using microwave heating. In particular, we chose to explore the potential of a libraries to a library conversion for parallel microwave-assisted synthesis as a means of producing new scaffolds.[9] A sequential microwave-generated library from a library of allylic amides and cyclopropylamides has been recently reported.[10]

Results and Discussion

The principal advantages of microwave synthesis are gained from the ability to very rapidly reach and maintain

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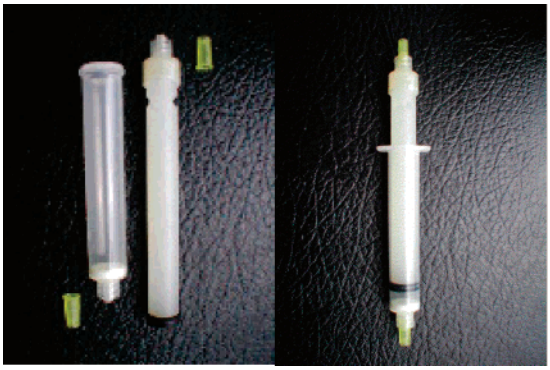


Figure 2. Individual vessel components, disassembled and assembled.

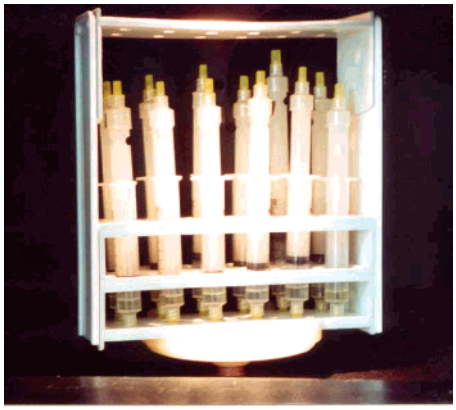
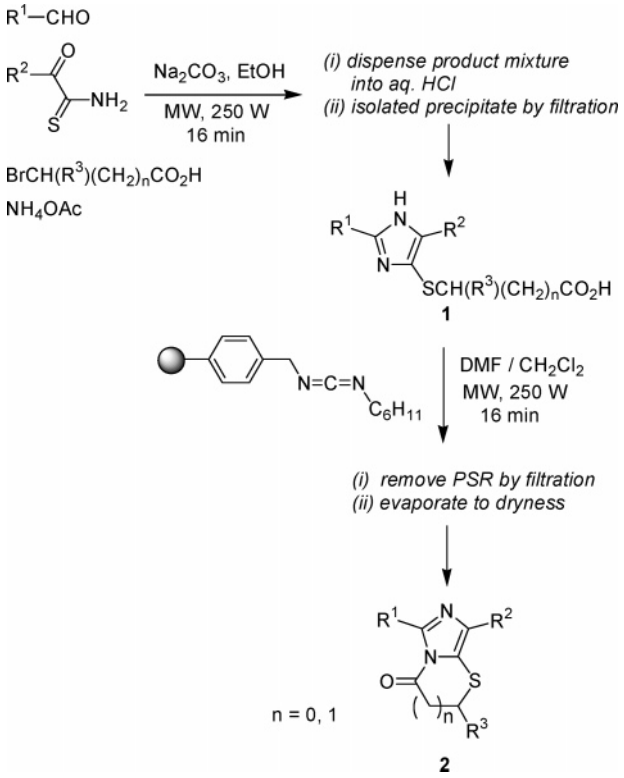


Figure 3. Prototype microwave parallel reactor block.

solvent boiling point temperature (or above). In the case of parallel synthesis, the technical challenge is how to do this with multiple vessels in a practical, controllable manner. We have used a commercial laboratory multimode microwave[4a] with custom-built reaction vessels, which offer an advantage in reaction workup and product isolation. We have previously described a parallel array of expandable reaction vessels that can accommodate the pressure buildup during microwave irradiation without loss of solvents or reagents.[7] Each vessel comprises a cylindrical reaction chamber with a porous frit mounted above a product outlet port. The pressure regulator consists of a hollow-bored piston with a gastight seal at the base and an outlet port at the top of the piston (Figure 2).

After loading reagents and solvent into the vessel, the piston is inserted into the reaction chamber to the top level of the solvent (air expelled from reaction chamber), and the outlet port is closed. Each reaction vessel is placed in an individual position within a reactor block (Figure 3). A laboratory multimode microwave source is used to irradiate the reactor block, during which time the pressure within the individual vessels increases, causing the piston to rise and alleviate the pressure. Once the irradiation ceases and the reaction components cool, the piston contracts back into the reaction vessel. A programmed microwave reaction event is cycled through an irradiation on/off sequence. During the off-periods, the vessels are fan-cooled by venting air through the microwave cavity, and the pistons contract back into the reaction vessel. Temperature was monitored within the microwave manufacturers' reference vessel through a software interface.[11]

Scheme 1. Microwave-Assisted Library Strategy



Although different parallel vessel designs are commercially available, we find that the inclusion of a product outlet port and a porous frit at the base of the vessel has several advantages in the reaction workup and product isolation operations. This outlet provides the user with the ability to dispense the reaction product mixture directly out of the base of the reaction vessel into a workup apparatus, and the frit allows for an in situ filtration.

The strategy for generation of the first library was to exploit a three-component reaction of an aldehyde, a 2-oxothioacetamide and bromoalkylcarboxylic acid with ammonium acetate to provide the sulfanyl imidazoles **1** (Scheme 1). The diverse set of commercially available aldehydes and bromoalkylcarboxylic acids would allow for the generation of structurally diverse libraries. The 2-oxoarylthioacetamides could be synthesized in one step from commercially available aroyl cyanides[12] or in two steps from aroyl chlorides.[13] Our aim was to isolate library **1** by precipitation of the products from aqueous acid, and if the products were of sufficiently high purity, they could be converted directly into the daughter library.

The generation of the second library would be accomplished by an intramolecular coupling of the carboxylic acid and imidazole nitrogen of **1** using the polystyrene-supported *N*-benzyl-*N*′-cyclohexylcarbodiimide[14] to effect the transformation. Our aim was to achieve product isolation by filtration of the polymer-bound byproduct and evaporation of solvent.

To establish the scope of this procedure, a diversely substituted 24-membered library of **1** was generated and converted into the corresponding library of **2**. Both libraries were directly analyzed by LC/MS, with library **2** also analyzed by ^{1}H NMR.

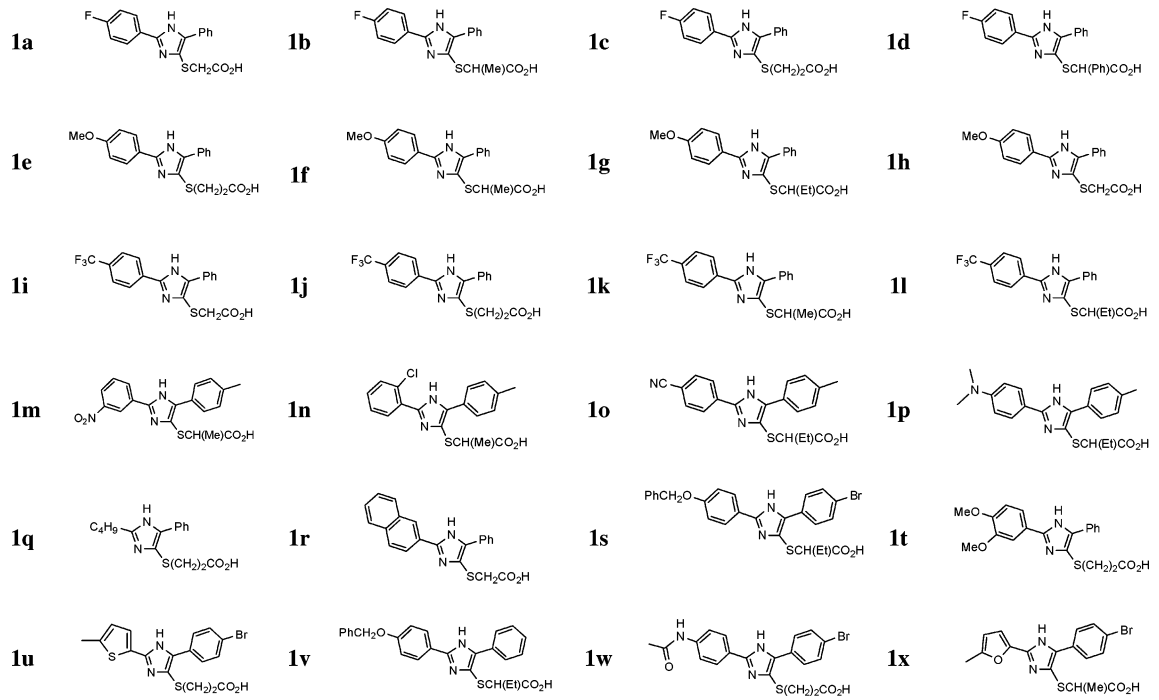


Figure 4. Library **1** of substituted 4(5)-sulfanyl-1*H*-imidazoles.

Table 1. Analysis of Library **1a**−**x**

entry	product	yield[a] %	purity[b] %	entry	product	yield[a] %	purity[b] %
1	**1a**	52	98	13	**1m**	40	80
2	**1b**	41	98	14	**1n**	57	97
3	**1c**	37	96	15	**1o**	67	82
4	**1d**	50	93	16	**1p**	47	90
5	**1e**	41	98	17	**1q**	33	95
6	**1f**	49	94	18	**1r**	94	87
7	**1g**	47	95	19	**1s**	59	88
8	**1h**	45	96	20	**1t**	61	88
9	**1i**	41	98	21	**1u**	35	87
10	**1j**	54	97	22	**1v**	77	98
11	**1k**	57	98	23	**1w**	49	97
12	**1l**	54	94	24	**1x**	46	97

[a] Isolated unpurified crude yield. [b] Purity determined by HPLC peak area at 254 nm.

For the first library, we generated a 24-membered 4(5)-sulfanyl-1*H*-imidazole library from 14 different aryl, heteroaryl, and alkyl aldehydes, five bromoalkylcarboxylic acids, and three different 2-oxoarylthioacetamides. The 2-oxo-2-aryl-thioacetamides and ammonium acetate were loaded into the vessels as ethanol solutions; the sodium carbonate, aldehydes, and bromoalkyl acids were added as neat solids or liquids. A programmable microwave irradiation cycle of 2 min at 250 W and 2 min off (fan-cooled) was executed four times, giving a total irradiation time of 8 min and a reaction event time of 16 min. Upon reaction completion, the products were precipitated from the reaction mixture by addition to aqueous HCl; isolated by filtration; and without any further purification, analyzed by LC/MS (Figure 4).

The multicomponent reaction was successful in tolerating the varied set of functional groups used with the desired product formed in every reaction, with an average library purity of 93% and an isolated yield of 51% (Table 1). Analyses of the filtrates revealed remaining product in solution, which accounted for the lower than expected isolated yield due to incomplete precipitation in some cases. But the direct isolation of **1a**−**x** in very high average purity was key, because it indicated that it should be possible to take these compounds directly onto the next step in a library format without any further purification.

The choice of a polystyrene-supported coupling agent to carry out the second library transformation offered the potential for a straightforward removal of the reaction byproduct by filtration and isolation of products by parallel evaporation of solvent. The successful use of polymer-supported reagents in conjunction with microwave heating has been previously demonstrated but in a surprisingly limited number of examples.[15] Because the polymer backbone of the polystyrene resin would be microwave-transparent, their use in a microwave field is viable, although at high temperatures, some bead fragmentation may be anticipated. The products isolated from the first library synthesis were loaded into individual reaction vessels with 3 equiv of the polymer-supported coupling agent. The solvent system chosen for the reaction was a 1:1 mixture of DMF and dichloromethane. This combination both facilitated the swelling of the PSR and allowed for efficient coupling with the microwave field. An identical microwave irradiation cycle and power (four cycles of 2 min at 250 W and 2 min 0 W) was used to complete the reactions. Products were isolated by filtration to remove the polymer-bound byproduct and excess PSR, followed by parallel evaporation of solvent (Figure 5). To gain insight into the efficiency of the reaction, the products were analyzed for purity by LC/MS and ^{1}H NMR prior to any further purification. Analysis revealed that with the exception of one case (**2d**), the desired product was formed, with the daughter library being generated with a good average library purity of 75% and a yield of 72% (Table

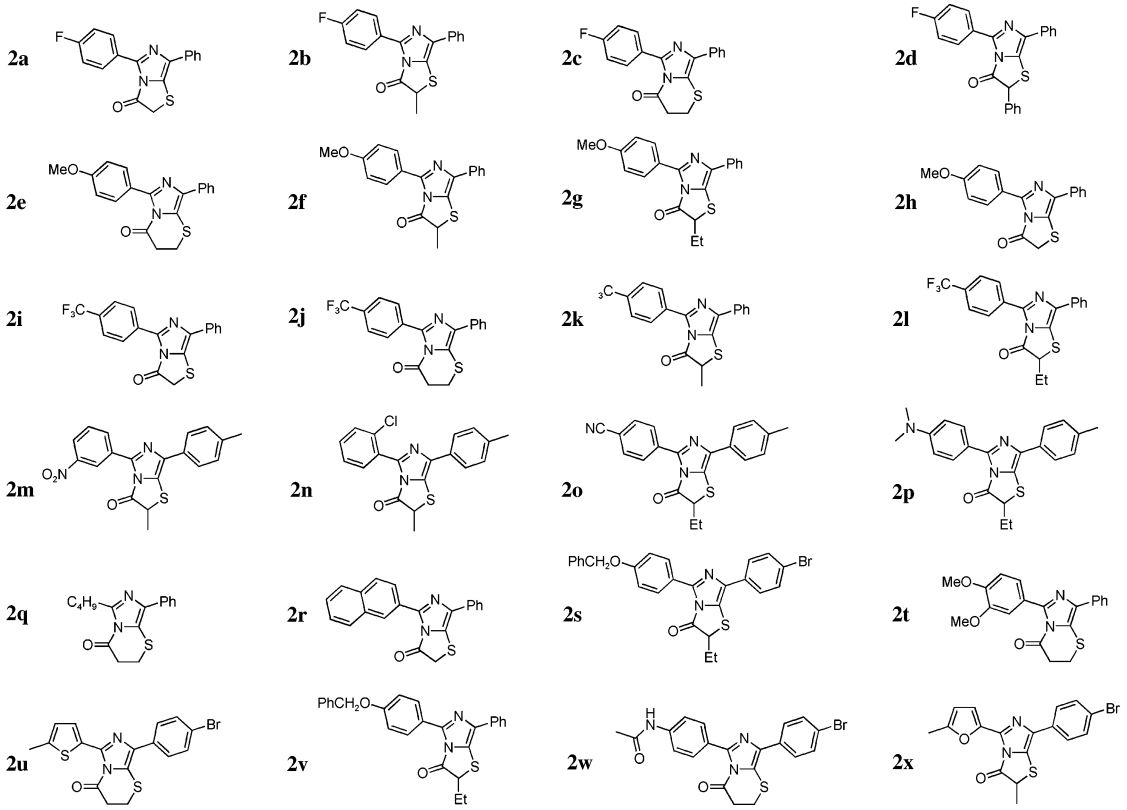


Figure 5. Library **2** of imidazo[5,1-*b*]thiazol-3-ones and imidazo[5,1-*b*]thiazin-4-ones.

Table 2. Analysis of Library **2a**−**x**

entry	product	yield[a] %	purity[b] %	entry	product	yield[a] %	purity[b] %
1	**2a**	95	96	13	**2m**	96	70
2	**2b**	85	96	14	**2n**	88	89
3	**2c**	66	96	15	**2o**	91	71
4	**2d**	-	-	16	**2p**	63	95
5	**2e**	95	98	17	**2q**	64	19
6	**2f**	96	92	18	**2r**	65	96
7	**2g**	96	94	19	**2s**	72	75
8	**2h**	90	54	20	**2t**	47	58
9	**2i**	34	51	21	**2u**	62	74
10	**2j**	40	79	22	**2v**	57	76
11	**2k**	93	78	23	**2w**	59	85
12	**2l**	90	85	24	**2x**	96	65

[a] Isolated unpurified crude yield. [b] Purity determined by HPLC peak area at 254 nm.

2). This purity level could be considered an excellent outcome considering the only purification operations utilized were precipitation and filtration.

Analysis of the HPLC/MS data for the derivatives which gave lower purity values, such as **2q** and **2t**, showed that the main impurity was starting material, indicating that conversion could be improved for theses derivatives by inclusion of a suitable additive to improve coupling reactivity. In a diversely substituted library, it is not altogether surprising that some reactions will perform poorly under a common set of parallel reaction conditions. But an advantage of a microwave parallel approach is that it allows for the rapid identification of substituent subsets that may require modified reaction conditions or a more elaborate work up purification procedure.

Conclusion

We have described an efficient microwave parallel methodology suitable for the generation of substituted sulfanyl imidazole, imidazo[5,1-*b*]thiazol-3-one, and imidazo[5,1-*b*]-thiazin-4-one libraries. The use of a polymer-supported reagent with parallel microwave heating was successful for the second library transformation. The scope of the microwave parallel library generation would appear to be far-reaching because the ability of microwave heating to funnel a spectrum of chemical reactivity found in a parallel library into a very short time span is a powerful tool for the combinatorial chemist. In the future, as methodologies and equipment continue to develop, microwave parallel synthesis should play a contributing role in the continuing advancement of combinatorial chemistry.

Experimental Section

Materials. All commercially available solvents and reagents were used as supplied unless otherwise stated. Absolute ethanol was used as reaction solvent without prior purification. Ammonium acetate was recrystallized from ethanol and stored under vacuum prior to use. *N*,*N*-Benzylcyclohexylcarbodiimide polymer-bound was provided at 1.3 mmol/g loading level. 2-Oxo-2-phenylthioacetamide, 2-oxo-2-*p*-tolylthioacetamide, and 2-oxo-2-(*p*-bromo)-phenylthioacetamide were synthesized following literature procedures.[7,12]

Analysis. HPLC/MS was recorded on an LCT instrument with purities determined by a UV−vis detector. ^{1}H NMR spectra were recorded on an automated 300-MHz FT spectrometer in $CDCl_3$. Full characterization analysis of compounds **1a**, **b**, **c**, **e**, **f**, **g** and **2a**, **b**, **c**, **e**, **f**, **g** can be found

in ref 8. HPLC analyses were performed with a reversed-phase Atlantis C18 (4.6 × 250 mm, 5 μm) column using water/acetonitrile/formic acid (20/80/0.002) as solvent system. The flow rate was 1 mL/min. The UV detection was performed at 254 and 220 nm.

Equipment. Microwave libraries were performed in a Milestone MicroSYNTH laboratory microwave using the easyWave version 3.5 control software with a reference vessel containing an internal fiber-optic temperature sensor and the QPS automatic gas detector safety system. Polypropylene reaction chambers without frit were from Sigma-Aldrich, and reaction chamber frits were from Bio-Rad. All library product precipitation and filtration procedures were carried out using Poly-Prep columns (0.8 × 4 cm) from Bio-Rad.

Substituted 4(5)-Sulfanyl-1*H*-imidazoles Library 1. Reaction components aldehyde (0.15 mmol), ammonium acetate (0.15 mmol), 2-oxothioacetamide (0.15 mmol), alkyl bromide (0.19 mmol), sodium carbonate (0.3 mmol), and ethanol (0.5 mL) were loaded into the reaction chamber (product outlet closed). A piston (bore opened) was inserted into the reaction vessel and depressed to the top of the solution, and the vessel was closed. The reaction vessels were placed in a reactor block in the microwave. A programmable microwave irradiation cycle of 2 min on (250 W) and 2 min off (fan-cooled) was executed four times (total irradiation time, 8 min; reaction event time, 16 min). The reactor block was rotated on a turntable during this process. The product outlet was opened, and the solution was added (depress piston) to ethanol (1.5 mL). Aqueous hydrochloric acid (1 M, 1 mL) and water (1 mL) were added. The pH was adjusted to 5−6 with aqueous $NaHCO_3$ (10%), and the mixture was allowed stand for 16 h. The precipitate was filtered and dried under vaccum and phosphorus pentoxide. They were analyzed by LC/MS and used for generation of library 2 without further purification.

Substituted Imidazo[5,1-*b*]thiazol-3-ones/Imidazo[5,1-*b*]thiazin-4-ones Library 2. Reaction products from library **1** (1 equiv), *N*-benzyl-*N*′-cyclohexylcarbodiimide polymer-bound (3 equiv), DMF (0.3 mL), and dichloromethane (0.3 mL) were loaded into the reaction chamber (product outlet closed). A piston (bore opened) was inserted into the reaction vessel and depressed to the top of the solution, and the vessel was closed. The reaction vessels were placed in a reactor block in the microwave. A programmable microwave irradiation cycle of 2 min on (250 W) and 2 min off (fan-cooled) was executed four times (total irradiation time, 8 min; reaction event time, 16 min). The reactor block was rotated on a turntable during this process. The product outlet was opened, and the solution was filtered (depress piston). The resin was washed with dichloromethane (2 × 1.5 mL). The combined solutions were filtered through a Gelman Acrodisc filter (CR PTFE 0.2 μm). The solutions were evaporated under vacuum using an ActeVap rack heated to 70 °C. Products were analyzed without any further purification by LC/MS and ^{1}H NMR.

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Supporting Information Available. LC/MS characterization data for libraries **1a**−**x** and **2a**−**x**. ^{1}H NMR characterization data for crude compounds **2a**−**l**. This material is free of charge via the Internet at http://pubs.acs.org.

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