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Microwave Parallel Library Generation: Comparison of a Conventional- and Microwave-Generated Substituted 4(5)-Sulfanyl-1*H*-imidazole Library

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A methodology for the microwave parallel synthesis of libraries is described. The procedure involves the use of an array of expandable reaction vessels, which can accommodate pressure buildup within the vessel due to heating without loss of volatile solvents or reagents. A demonstration 24-membered library of substituted 4(5)-sulfanyl-1*H*-imidazoles was generated by both conventional and microwave procedures, achieving a reduction from 12 h to 16 min in library generation time for the microwave approach.

Introduction

In the past 15 years the drug-discovery process has undergone extraordinary changes. High-throughput biological screening of potential drug candidates has led to an ever-increasing demand for collections of novel druglike compounds. Combinatorial approaches to compound synthesis have superseded the sequential generation of individual molecules in providing the numbers of compounds required for a drug-discovery program. As combinatorial chemistry was establishing itself as the premiere mode of generating large numbers of druglike molecules, almost concurrently the significant benefits of microwave-assisted organic synthesis were being demonstrated, albeit on an individual reaction basis. Substantial reductions in reaction times and improved yields have been reported for a wide selection of organic reactions, which have been extensively reviewed.[1] Although initially both thermal and nonthermal microwave heating effects were claimed, it is now generally accepted that the different temperature profile caused by microwave heating is the main contributing factor to the reaction accelerations observed.[2] Clearly, the ability of microwave technology to rapidly synthesize organic compounds would be of significant benefit for library generation and its potential as a future tool for drug-discovery programs has recently been recognized.[3]

To date, few have attempted to exploit this benefit for combinatorial library synthesis, although initial investigative studies have been reported. Parallel libraries of various heterocyclic rings have been generated in open reaction vessels using microwave heating where the reagents are impregnated onto a solid support such as alumina, silica, or clay in a solvent-free system.[4] Solid-phase synthesis with functionalized Wang and TentaGel resins,[5] polypropylene membranes,[6] and polymer-supported reagents[7] have been utilized in conjunction with microwave heating. There exists a need for new practical methods to be developed that would allow the possibilities of microwave synthesis to be examined by the combinatorial chemist. Only then will it become apparent if the potential of microwave combinatorial chemistry will be fulfilled.

Results and Discussion

The choice facing a researcher who wishes to carry out microwave-assisted solution- and solid-phase parallel library generation is whether to use multiple open or sealed vessels. Library generation in multiple open vessels is impractical because of the loss of solvent and/or volatile reagents during the heating process, resulting in possible cross contamination of vessels, uneven reaction distributions, and lack of reproducibility. A sealed vessel will contain the solvent/reagents but could have practical implications due to the buildup of pressure within multiple reaction vessels. This necessitates a pressure control system for a multivessel apparatus with varying pressures in individual vessels, or the possibility of overpressurizing vessels becomes a safety issue with the risk of a possible explosion. Recently a microwave apparatus, which utilizes a sealed vessel, has become commercially available for use in individual reaction synthesis.[8] While sealed vessels are used in a single vessel format, it remains to be shown viable for parallel synthesis.

Apparatus Description. Our goal is to successfully combine the advantages of microwave heating with combinatorial chemistry to facilitate the rapid parallel synthesis of solution- and solid-phase libraries. The principal advantage of microwave synthesis are gained from the ability to very rapidly reach and maintain solvent reflux (or superheated) temperature; the drawback is how to do this with multiple vessels in a practical manner. While certain applications of microwave heating exploit the high pressures generated in a

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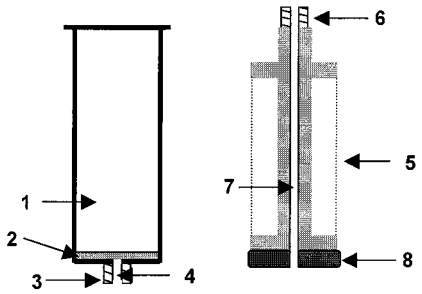


Figure 1. Microwave vessel components: (1) reaction chamber; (2) frit; (3) Luer lock; (4) product outlet; (5) piston; (6) Luer lock; (7) hollow bore; (8) seal.

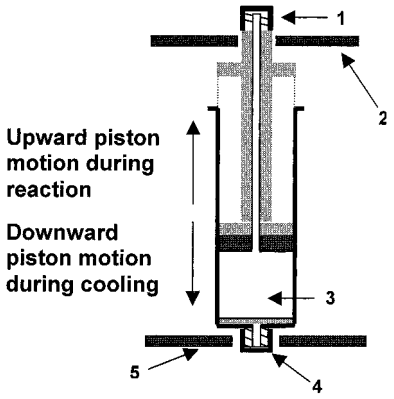


Figure 2. Single microwave vessel during reaction: (1) central bore closed; (2) cover plate; (3) reaction components; (4) product outlet closed; (5) supporting plate.

sealed vessel, synthetic organic reactions typically do not require such high pressures to gain significant reduction in reaction times. As a result, we view the pressure buildup in a sealed vessel to be a consequence of the heating process and not necessarily a beneficial one. Here, we describe an expandable reaction vessel that accommodates the pressure buildup during microwave irradiation without loss of solvents or reagents. The vessel is easily constructed from readily available materials, and its compact design allows for the combination of multiples of such reaction vessels into a parallel array.

An individual reaction vessel is composed of a 10 mL cylindrical reaction chamber with a porous frit mounted above a product outlet carrying a conventional Luer lock (Figure 1). Each reaction vessel has a piston with a straight hollow bore running the length of the piston. A gastight seal is mounted at the base of the piston, and a Luer locking mechanism controls the opening at the top of the piston bore (Figure 1). Reagents and solvent are loaded into the reaction chamber with the product outlet closed, and a piston is inserted into the reaction chamber (piston bore open) to the top of the solvent level, thereby expelling air from the reaction chamber. The Luer lock at the top of the piston bore is then closed. As microwave radiation is applied to the system, the pressure within the individual vessels increases and the rising of the piston alleviates this pressure. Once the irradiation ceases and the reaction components cool, the piston contracts back into the reaction vessel (Figure 2). The expansion/contraction motion of the piston allows for a specific mode of use of the vessel with a programmable laboratory microwave.[9] A programmed microwave reaction

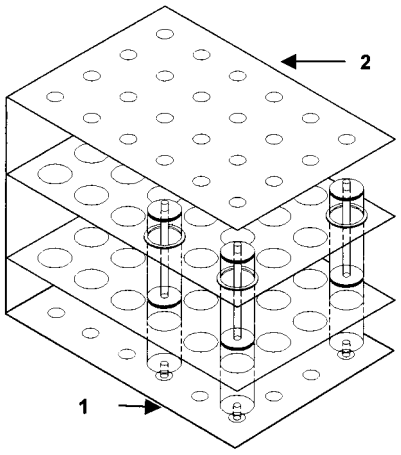


Figure 3. Microwave parallel reactor block: (1) supporting plate; (2) cover plate.

event is cycled through an irradiation on/off sequence, and during the off periods, the vessels are fan-cooled by a venting of air through the microwave cavity. This on/off sequence allows for a controlled heating environment, which can be easily determined and set up by the operator (Chart 1).

Chart 1. Microwave Library Generation Sequence

1. Close Luer lock on reaction chambers
2. Load reagents into reaction chambers
3. Insert pistons with bore open to level of solvent
4. Close Luer locks at top of piston bore
5. Place individual vessels into reactor block
6. Place block in microwave cavity
7. Run programmed reaction sequence
8. Open Luer locks on product elution channel
9. Depress piston fully to dispense products

We allow for an expansion of 20 times the volume of the solvent/reagents within each vessel, but because microwave reactions typically require only small quantities of solvent, we do not view this as a drawback. As a result of the smaller quantity of solvent required for the microwave procedure, this leads to a further acceleration in the reaction without any charring of reagents or products. Although most of the reagents in each reaction vessel are not dissolved prior to the microwave irradiation, we find that specific agitation is not required because of the vigorous rapid heating. The piston action overcomes the problem of uneven reaction distribution at various positions in the microwave field, which is a recurring problem in open vessels. Each reaction vessel can be placed in an individual position within a reactor block (Figure 3). The reactor block consists of a base into which individual reaction vessels fit and a cover plate. The cover plate is positioned at a height lower than the full extension of the piston, thereby ensuring that the piston cannot separate from the reaction vessel. Upon completion of the reactions the products are dispensed out of the reaction vessels by opening the bottom Luer lock and fully depressing the pistons, allowing the reaction products to be directly

dispensed into a workup apparatus, (Chart 1). The reaction chamber, the piston, and the reactor block are constructed of heat-resistant, microwave-transparent materials. For cost and ease of construction our vessels are constructed of polypropylene, but other microwave-transparent materials could be utilized. We have identified an inexpensive commercial source for the reaction chamber, which allows us to use each reaction chamber only once, whereas the piston is reused indefinitely.[10]

When using our apparatus, microwave conditions are principally determined by the type and quantity of solvent used and the quantity of reagents. The rate of heating of a solvent in a microwave field is dependent on its dielectric loss tangent.[11] A reaction event is carried out at a specific microwave power setting and irradiation time to allow for full expansion of the piston. The irradiation is then switched off for a period of time to allow piston contraction, which is assisted by fan cooling, and the cycle is repeated. For a researcher unfamiliar with microwave-heating procedures we would anticipate that only an initial familiarization period would be required to be competent in the use of this technique. This should be carried out using a single vessel, paying due attention to safety. Prior to making a library, we always optimize a number of single reactions to determine a suitable irradiation power and time and the cooling times required between irradiations. We find that because the reaction times are fast, optimization of conditions is not a long or difficult process. The apparatus we have described is an inexpensive method to overcome the practical problems associated with microwave parallel synthesis and would facilitate the generation of small to medium size libraries.

Demonstration Library. In our efforts to develop new multicomponent routes to diversely substituted druglike scaffolds, we have targeted the imidazole ring system. The imidazole pharmacophore is present in a wide number of therapeutic agents, and as such, the development of new combinatorial routes to highly diverse imidazole libraries is of considerable value. We are currently interested in generating libraries of substituted sulfanylimidazoles. Specifically, sulfanylimidazoles have been shown to be potential acyl-CoA/cholesterol acyltransferase inhibitors,[12] analgesic agents,[13] and angiotensin II receptor antagonists.[14] We have developed a three-component route to substituted sulfanylimidazoles that builds on previously reported syntheses of substituted 4(5)-mercaptoimidazoles **1** from an aldehyde, a 2-oxothioacetamide, and ammonium acetate (Scheme 1, route A).[15] We have found it is possible to make substituted 4(5)-sulfanyl-1*H*-imidazoles **2** directly by including an alkyl bromide and base in a reaction with the 2-oxothioacetamide, aldehyde, and ammonium acetate (Scheme 1, route B). The wide range of commercially available aldehydes and alkyl bromides allows for the generation of structurally diverse libraries. The 2-oxothioacetamides are readily synthesized in one step from commercially available aroyl cyanides[16] or in two steps from aroyl chlorides.[17]

As a demonstration of our microwave technique, we have generated a 24-membered library using both a conventional heating method and our microwave approach. Prior to library generation we undertook a study to optimize the chemical

Scheme 1. Three-Component Synthesis of Substituted 4(5)-Sulfanyl-1*H*-imidazoles

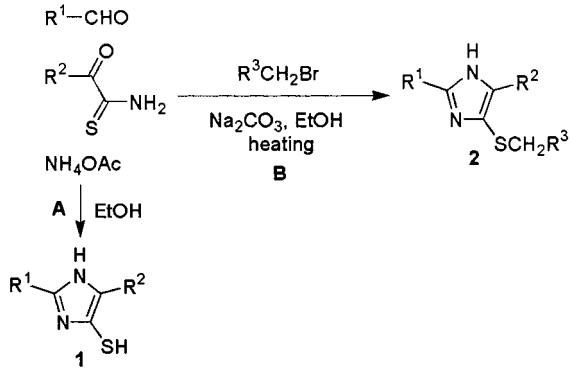


Table 1. Optimization of Conventional Heating Conditions

entry	R^1	R^2	R^3	time, h	yield,[a] %
2i	4-FC_6H_4	C_6H_5	CO_2H	5	77
2ii	4-FC_6H_4	C_6H_5	$CONH_2$	6	86
2iii	4-FC_6H_4	C_6H_5	CH_2OH	5	80
2iv	4-FC_6H_4	C_6H_5	CH_3	7	73
2v	C_4H_9	C_6H_5	$CONH_2$	7	74
2vi	3-$NO_2C_6H_4$	C_6H_5	CH_3	5	81
2vii	4-$CH_3OC_6H_4$	C_6H_5	CH_3	10	72

[a] Isolated purified yield.

events associated with conventional and microwave library generation. Typical sequential reactions took between 4 and 10 h in ethanol under conventional reflux depending on the substituents, with the products isolated in purified yields of 72−86% (Table 1). To allow the slower reactions to reach completion, a reaction time of 12 h was chosen for the conventional library synthesis. We found the optimal microwave conditions to be a cycle of 2 min of irradiation at 180 W followed by 2 min off, repeated four times, giving a total reaction event time of 16 min, which had allowed all model reactions to reach completion.[18] While the conditions used in the microwave library may appear very specific, there is considerable flexibility between irradiation time and power without loss of reaction integrity. The time required to optimize reaction conditions for the microwave library was less than that of the conventional library. We found that for reactions that contained less reactive alkylating agents the principal impurity was the imidazolethiols **1** (and the corresponding disulfides). This was easily overcome by the use of a 5 M excess of these alkylating agents. Products from both procedures were isolated by precipitation from the reaction mixture with aqueous HCl, which facilitated the removal of the remaining starting materials.

We have generated a 24-membered 4(5)-sulfanyl-1*H*-imidazole library from 21 different aldehydes, 12 alkyl bromides, and 2 2-oxothioacetamides (Figure 4). The 2-oxothioacetamides and ammonium acetate were loaded into the vessels as ethanol solutions, while the sodium carbonate, aldehyde, and alkyl bromides were added as neat solids or liquids. In the microwave method many of the reagents were not in solution prior to the reaction, but we found that this did not hinder the reactions because they rapidly dissolved once microwave heating commenced. All our additions were

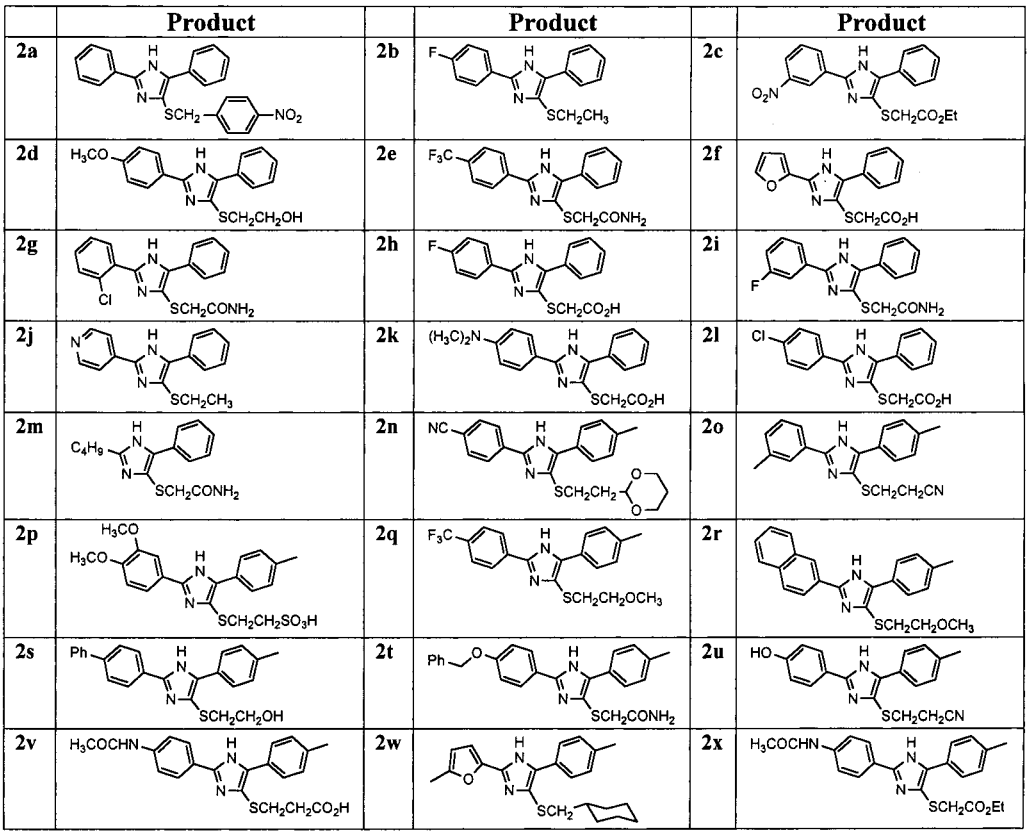


Figure 4. Substituted 4(5)-sulfanyl-1*H*-imidazole library.

carried out manually, but we see no reason that the vessel loading could not be carried out in an automated manner.

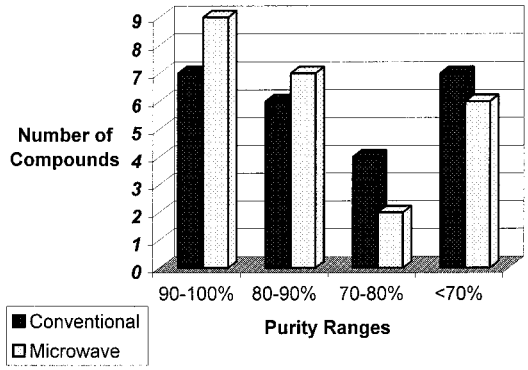
Upon reaction completion, the products were precipitated from the reaction mixture, and without any further purification, they were analyzed by HPLC, MS, and ^{1}H NMR (Table 2). The structure of **2h** has been confirmed by single-crystal X-ray structure analysis (see Supporting Information). The multicomponent reaction was successful in tolerating a wide diversity of functional groups with the desired product formed in every reaction. Comparison of the microwave library with the conventional-generated library is favorable, with the reaction time reduced from 12 h to 16 min. If the overall average purity and yield of each library are considered, the purity of the microwave library and that of the conventional library are comparable at 76% and 78%, respectively. The microwave library has a marginally higher average isolated yield than the conventional library (68% and 63%). If individual reactions within the library are examined, it can be seen that not all reactions are improved in terms of purity in the microwave procedure. This may seem unexpected, but we feel it is unlikely that in a diverse library, which has good results using conventional methods, a further significant improvement in purity for all the reactions will be obtained with a parallel microwave method. If the compounds from each library are classified into 10% purity ranges, the microwave library has more derivatives above 80% purity than the conventional, but the overall differences are minimal (Chart 2). We conclude that for this library the principal advantage gained by the microwave procedure is a significant reduction in library generation time. We are currently using our microwave methodology to develop larger libraries for biological screening. An interesting advantage that has emerged from this library is that it has allowed us to rapidly define our library into sets of reagent types that are likely to yield products of above 90% purity or not. This will allow us to focus on developing two

Table 2. Comparison of Conventional and Microwave 4(5)-Sulfanyl-1*H*-imidazole Library

entry	conventional purity,[a] %	conventional yield,[b] %	microwave purity,[a] %	microwave yield,[b] %
2a	94	71	90	96
2b	55	76	94	94
2c	86	55	87	40
2d	81	52	95	82
2e	95	80	91	76
2f	95	58	89	40
2g	97	69	95	59
2h	95	55	93	56
2i	94	71	92	57
2j	61	79	28	82
2k	69	66	94	51
2l	88	73	89	68
2m	56	71	67	75
2n	70	53	71	74
2o	87	73	81	56
2p	43	52	20	69
2q	63	80	43	81
2r	60	31	46	85
2s	89	95	90	94
2t	90	96	82	87
2u	82	26	81	21
2v	75	34	87	81
2w	73	40	53	70
2x	75	61	78	47

[a] Purity determined by HPLC peak area at 254 nm. [b] Yield refers to isolated unpurified yield.

Chart 2. Comparison of Conventional and Microwave Libraries



types of larger libraries, one that will require minimal workup (precipitation) and another that will require a more complex workup to improve product purity prior to screening.

Any comparison of a conventional and microwave method will obviously be strongly dependent on the chemistry being utilized for the library. The most significant reported improvements in purity and yields for microwave reactions are for reactions that work poorly under conventional heating conditions, but these types of reaction are not commonly utilized in a combinatorial framework. Thus, two types of applications for microwave parallel libraries could be predicted: a more general one that reduces the library generation time for a library that yields good results in a conventional procedure and a library that does not yield good results by a conventional manner that may provide improvements in both the overall library purity and reduced library generation time.

Conclusion

The scope of microwave parallel library generation is wide and as yet remains largely unexplored. The ability of microwave heating to funnel a spectrum of chemical reactivity found in a combinatorial library into a very short time span has the potential to become a new practical tool for the combinatorial chemist. We have described a new methodology that can overcome some of the technical problems associated with microwave parallel synthesis. We have developed a diversity-tolerant multicomponent route to sulfanylimidazoles and have shown that a comparable microwave-generated library can be achieved with a dramatic reduction in library generation time. Further investigations of the use of microwave technologies for solid-phase synthesis are currently in progress. In the future, as methodologies 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 by Aldrich Chemical Co. unless otherwise stated. Absolute ethanol from Merck was used as reaction solvent without any prior purification. Dry flash chromatography was performed on Merck silica gel 60 PF_{254}. Diethyl ether was distilled from sodium benzophenone ketyl. Ammonium acetate was recrystallized from ethanol and stored under vacuum prior to use. The alkyl bromides used in 5 M excess (32 mmol) were for derivatives $BrCH_2CH_2OH$, $BrCH_2CH_2CN$, $BrCH_2CH_2OCH_3$, $BrCH_2C_6H_{11}$, and $BrCH_2CH_2C_4H_7O_2$.

Analysis. HPLC−MS was recorded on a Finnigan MAT LC-Q instrument (220 and 254 nm). Purities were determined by HPLC analysis using a Shimadzu SPD-10A UV−vis detector (254 nm), LC-10AT liquid chromatograph, and DGU-14A degasser coupled to a C-R6A chromatopac integrator. A Hichrom 5 C18, (25 cm, 4.6 mm) column was used for all HPLC and HPLC−MS experiments using a solvent system of water/methanol (80:20); the flow rate was 1.0 mL/min. Mass spectral analyses were performed on a Finnigan MAT Incos 50 B mass spectrometer (EI), and high-resolution mass spectra were collected from a VG analytical 70-E mass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 MHz FT spectrometer. The ^{13}C spectra of the imidazoles are not reported because, as a result of annular tautomerism, several signals are not detectable. Melting points were determined on a Reichert Thermovar melting point platform and are uncorrected. Infrared spectra were recorded on a Mattson Instruments Galaxy series FTIR 3000 spectrometer.

Equipment. Thermal libraries were performed using a Firstmate synthesizer from Argonaut technologies using 13 mm diameter test tubes. Microwave libraries were performed in a CEM Corp. MDS-2000 laboratory microwave. The polypropylene reaction chamber without frit was from Sigma-Aldrich. Reaction chamber frits are from Bio-Rad. All library product precipitation and filtration procedures were carried out using Poly-Prep columns (0.8 cm × 4 cm) from BIO-RAD.

2-Oxo-2-phenylthioacetamide. Hydrogen sulfide was bubbled through a solution of benzoyl cyanide (25 g, 0.19 mol) and triethylamine (1.5 mL, 0.01 mol) in dry diethyl ether (400 mL) at 0−5 °C for 2 h. The solution was stirred for an additional 1.5 h at room temperature, and the solvent was evaporated to give an orange solid, which was added to ice and stirred for 1 h. The product was filtered, washed with water (2 × 50 mL), and dried under vacuum over phosphorus pentoxide to give a yellow solid (27.7 g, 88%), mp 96−97 °C, from ethanol/water (1:1). (If the orange solid does not crystallize in ice, it can be purified by dry flash chromatography eluting with a diethyl ether/hexane gradient (1:9 to 1:1) to give a yellow solid.) IR (KBr disk): 3309, 3133, 1671 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.52 (bs, 1H), 10.28 (bs, 1H), 7.93 (m, 2H), 7.68 (m, 1H), 7.56 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 200.9, 189.3, 134.8, 133.3, 130.2, 129.5. HRMS calcd for C_8H_7NOS, 165.0248; found, 165.0248.

2-Oxo-2-*p*-tolylthioacetamide. Hydrogen sulfide was bubbled through a solution of oxo-*p*-tolylacetonitrile (3.4 g, 23.4 mmol) and triethylamine (0.2 mL, 1.43 mmol) in dry diethyl ether (250 mL) at 0−5 °C for 2 h. The solution was stirred for an additional 1.5 h at room temperature, and the solvent was evaporated to a red oil that was added to ice and stirred for 1 h. The product was filtered washed with water (2 × 20 mL) and dried under vacuum over phosphorus pentoxide to give a yellow solid (3.1 g, 76%), mp 109−110

°C, from ethanol/water (1:1). (If the yellow solid does not crystallize in ice, it can be purified by dry flash chromatography eluting with a diethyl ether/hexane gradient (1:9 to 1:1) to give a yellow solid.) IR (KBr disk): 3259, 3134, 1655, cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 10.47 (bs, 1H), 10.25 (bs, 1H), 7.8 (d, $J = 8.2$ Hz, 2H), 7.37 (d, 2H) 3.4 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 201.0, 189.2, 145.5, 130.8, 130.3, 130.1, 22.0. MS (EI) *m*/*z*: 179.

General Procedure for the Sequential Synthesis of 4-(5)-Sulfanyl-1*H*-Imidazoles. 2-Oxo-2-arylthioacetamide (6.4 mmol), sodium carbonate (6.4 mmol), alkyl bromide (6.4 or 32 mmol), ammonium acetate (6.4 mmol), and aldehyde (6.4 mmol) in absolute ethanol (75 mL) were heated under reflux for 5−12 h. The solution was concentrated to 20 mL, cooled to room temperature, and added to a stirred 50 mL solution of 1 M HCl. The precipitate was collected by filtration and dried under vacuum. The product was purified by either (a) recrystallization from methanol or methanol/ethyl acetate (1:1) or (b) stirred in 0.5 M NaOH and purified by flash column chromatography (silica gel) using a gradient system of diethyl ether/hexane/methanol.

Analysis for Derivatives in Table 1: 2-(4-Fluorophenyl)-5-phenyl-1*H*-imidazol-4-ylsulfanyl]acetic acid (2i). The crude precipitate was recrystallized from methanol to give a white solid (77%), mp 157−158 °C. IR (KBr disk): 3229, 1708, cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 12.8 (1H, bs), 8.37 (2H, m), 7.94 (2H, m), 7.49−7.58 (5H, m), 3.9 (2H, s), 3.2 (bs, 1H). HRMS calcd for $C_{17}H_{13}FN_2O_2S$, 328.0681; found, 328.0697. (X-ray crystal structure in Supporting Information.)

2-[2-(4-Fluorophenyl)-5-phenyl-1*H*-imidazol-4-ylsulfanyl]acetamide (2ii). The crude precipitate was recrystallized from methanol to give a white solid (86%), mp 211−212 °C. IR (KBr disk): 3422, 3233, 1673 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.34 (m, 2H), 7.94 (m, 2H), 7.66 (bs, 1H), 7.57−7.45 (m, 5H), 7.17 (bs, 1H), 3.72 (s, 2H). HRMS calcd for $C_{17}H_{14}FN_3OS$, 327.0841; found, 327.0849.

2-[2-(4-Fluorophenyl)-5-phenyl-1*H*-imidazol-4-ylsulfanyl]ethanol (2iii). The crude precipitate was subjected to silica gel flash chromatography using a solvent gradient of methanol/diethyl ether/hexane 0.5:1.5:8 to 0.5:6:3.5 to give a white solid (80%), mp 202−203 °C. IR (KBr disk): 3094 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.44−8.39 (m, 2H), 7.99−7.95 (m, 2H), 7.59−7.48 (m, 5H), 3.57 (t, $J =$ 6.2 Hz, 2H), 3.30 (bs, 1H), 1.06 (t, 2H). HRMS calcd for $C_{17}H_{15}FN_2OS$, 314.0889; found, 314.0877.

4-Ethylsulfanyl-2-(4-fluorophenyl)-5-phenyl-1*H*-imidazole (2iv). The precipitate was recrystallized from methanol/ethyl acetate (1:1) to give white needles (73%), mp 116−117 °C. IR (KBr disk): 3343 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.33 (m, 2H), 7.92 (m, 2H), 7.58−7.46 (m, 5H), 3.5 (bs, 1H), 2.99 (q, $J = 7.3$ Hz, 2H), 1.15 (t, 3H). HRMS calcd for $C_{17}H_{15}FN_2S$, 298.0940; found, 298.0951.

2-(2-Butyl-5-phenyl-1*H*-imidazol-4-ylsulfanyl)acetamide (2v). The aqueous layer was extracted with ethyl acetate (2 × 50 mL), and the aqueous layer was concentrated and neutralized using 0.5 M NaOH to give a white solid (74%), mp 101−102 °C. IR (KBr disk): 3336, 3206, 1672, cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 7.92 (m, 2H), 7.63 (bs, 1H), 7.56−7.45 (m, 3H), 7.16 (bs, 1H), 3.65 (s, 2H), 3.5 (bs, 1H), 2.98 (t, $J = 7.5$ Hz, 2H), 1.78 (dt, 2H), 1.35 (m, 2H), 0.91 (t, $J = 7.3$ Hz, 3H). HRMS calcd for $C_{15}H_{19}N_3OS$, 289.1249; found, 289.1258.

4-Ethylsulfanyl-2-(3-nitrophenyl)-5-phenyl-1*H*-imidazole (2vi). The precipitate was recrystallized from methanol to give yellow needles (81%), mp 131−133 °C. IR (KBr disk): 3397 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.96 (d, $J = 1.9$ Hz, 1H), 8.52 (dd, $J = 1.2$, 8.2 Hz, 1H), 8.28 (dd, 1H), 7.98 (m, 2H), 7.82 (m, 1H), 7.50 (m, 2H), 7.35 (m, 1H), 4.2 (bs, 1H), 2.95 (q, $J = 7.3$ Hz, 2H), 1.20 (t, 3H). HRMS calcd for $C_{17}H_{15}N_3O_2S$, 325.0884; found, 325.0875.

4-Ethylsulfanyl-2-(4-methoxyphenyl)-5-phenyl-1*H*-imidazole (2vii). The precipitate was recrystallized from methanol/ethyl acetate (1:1) to give a white solid (72%), mp 157−160 °C. IR (KBr disk): 3277 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.10 (dd, $J = 1.7$, 8.8 Hz, 2H), 7.95 (m, 2H), 7.52−7.49 (m, 2H), 7.47−7.36 (m, 1H), 7.13−7.10 (dd, 2H), 3.84 (s, 3H), 3.5 (bs, 1H), 2.92 (q, $J = 7.3$ Hz, 2H), 1.16 (t, 3H). HRMS calcd for $C_{18}H_{18}N_2SO$, 310.1140; found, 310.1138.

Conventional-Generated Library. The conventional library was generated using an Argonaut first mate synthesizer. Reaction components aldehyde (0.15 mmol), ammonium acetate (0.15 mmol), 2-oxothioacetamide (0.15 mmol), and alkyl bromide (0.15 or 0.75 mmol) were loaded into each reaction vessel with EtOH (2 mL). The library was heated under reflux for 12 h and cooled to room temperature, and the products were precipitated with 1 M HCl (5 mL), filtered, and dried under vacuum. Each reaction product was analyzed by HPLC (254 nm), HPLC−MS, and ^1H NMR without any further purification. Overall library purity was 78%, and the average library yield was 63%.

Microwave-Generated Library. The library was generated using a reactor block of 10 mL microwave vessels. Reaction components aldehyde (0.15 mmol), ammonium acetate (0.15 mmol), 2-oxothioacetamide (0.15 mmol), alkyl bromide (0.15 or 0.75 mmol), and EtOH (0.5 mL) were loaded into each reaction chamber (product outlet closed with Luer lock). A piston (bore open) was inserted into each reaction vessel and was depressed to the top of the solvent level. The opening at the top of the piston was closed using a Luer lock cap. The reaction vessels were assembled into the reactor block and placed in the microwave. A programmed microwave[9] irradiation cycle of 2 min on (180 W) and 2 min off (fan-cooled) was executed four times (total irradiation time of 8 min, reaction event time of 16 min). The reactor block is rotated on a turntable during this process. The product outlet was opened, and the products were added (depress piston) to EtOH (1.5 mL) and precipitated with 1 M HCl (5 mL), filtered, and dried under vacuum. Each reaction product was analyzed by HPLC (254 nm), MS, and ^1H NMR without any further purification. Overall library purity was 76%, and the average library yield was 68%.

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Supporting Information Available. ^{1}H NMR and HPLC−MS data for the library **2**{**a**−**x**} and single-crystal X-ray crystallographic data for compound **2h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Both the conventional and microwave reaction times are determined for the library as a whole. In both procedures many of the reactions will be complete before these times. As a result, direct comparison of individual reaction times should not be made.

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