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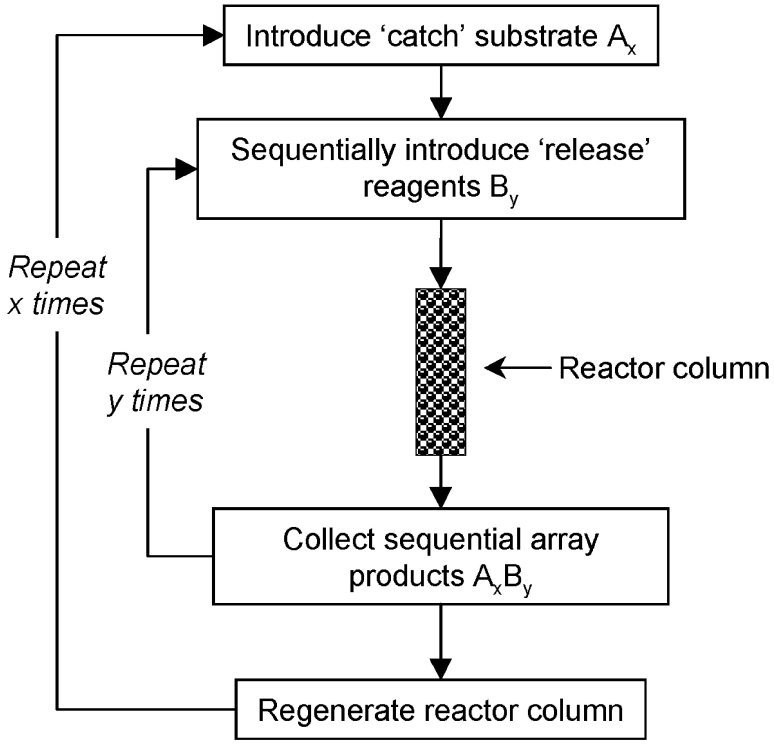

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Automated Flow-Through Synthesis of Heterocyclic Thioethers

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The fully automated, sequential flow-through synthesis of a 44-member array of thioethers **10**{*1*−*4*,*1*−*11*} employing a resin "capture and release" reactor column is described. The array incorporates four different heterocyclic scaffolds, and the synthesis was performed using a custom-built robotic synthesizer that is able to (i) load and regenerate the reactor column and (ii) array each product into a single vial using UV threshold detection. All the compounds were obtained in high yield (>75%) and excellent purity (>95%) without the need for further purification.

Introduction

The high-throughput synthesis and screening of targeted and exploratory compound libraries has emerged as a key objective within the pharmaceutical industry as a means of identifying lead molecules with desirable biological activities.[1] Large numbers of compounds can be efficiently synthesized by combining solid-phase organic synthesis with combinatorial methods.[2] However, in recent years, in an attempt to circumvent some of the limitations associated with solid-phase organic synthesis, there has been a resurgence of interest in identifying complementary high-throughput solution-phase synthesis strategies.

One such approach is polymer-assisted solution-phase (PASP) synthesis, in which, contrary to conventional solid-phase approaches, the reagents are attached to an insoluble polymeric support, and the substrates remain in solution.[3] The advantages associated with PASP synthesis have been well-documented and include simplified workup (filtration) and the ability, through the judicious use of scavenger resins and resin "capture and release" techniques, to effect in-line purification and thereby produce high-purity products directly. Moreover, the general applicability of multistep, polymer-assisted solution-phase techniques has been broadly exemplified by the synthesis of a diverse selection of compounds ranging from complex natural products[4] to arrays of small drug-like molecules.[5]

As an alternative to conventional batch synthesis procedures, polymer-supported reagents also present opportunities for the implementation of flow-through processes using cartridge (or column)-based reactors.[6] This has the potential to deliver compounds in high intrinsic purities by automated, workup-free, solution-phase methods without the need for subsequent chromatographic purification. Moreover, the automation of such processes is likely to aid replication and lead to high reproducibility.

Indeed, flow-through processes utilizing catalytic reactors are widely exploited in industry, where the ability to continuously produce material facilitates scale-up.[7] However, noncatalytic (i.e., stoichiometric) cartridge-based reactors are also useful, particularly where limitations arising from the finite capacities of the incorporated immobilized reagents can be overcome by in-line reactor regeneration protocols. As a consequence, flow-through reactors are increasingly being viewed as attractive for implementing smaller laboratory-scale processes.[8]

We are particularly interested in the use of reusable stoichiometric reactor cartridges as a component of automated flow-through systems for the preparation of compound arrays. Herein, we describe the development and implementation of an automated flow-through process leading to the synthesis of an array of thioethers incorporating a number of different heterocyclic scaffolds. The synthesis was performed by a custom-built, software-controlled synthesizer which was able to perform automated column regeneration and reloading and utilized UV threshold to direct each array product into a single sample vial prior to isolation by parallel evaporation.

Although many combinatorial processes depend on the decoration of a predetermined structural scaffold with a set of diversity elements or building blocks, the ability to incorporate multiple scaffolds represents an appealing alternative strategy that is likely to lead to enhanced structural diversity;[9] however, in general, this is difficult to achieve in a high-throughput manner. We were attracted to the possibility of using a resin "capture and release" strategy to address this problem in a flow-through reactor.[10] We envisaged a repetitive, single-pass procedure whereby, following the initial "capture" of substrate by a suitable reactor cartridge, sequential elution of the column with substoichiometric quantities of a set of "release" monomers would result in the elution of an array of the corresponding adducts as discrete compounds. Where the loading capacity of the column is not exceeded, and the rate of the release reaction is sufficiently rapid, we anticipated that the array members would be obtained in high purities without the need for inconvenient recycling of the reaction solutions through the

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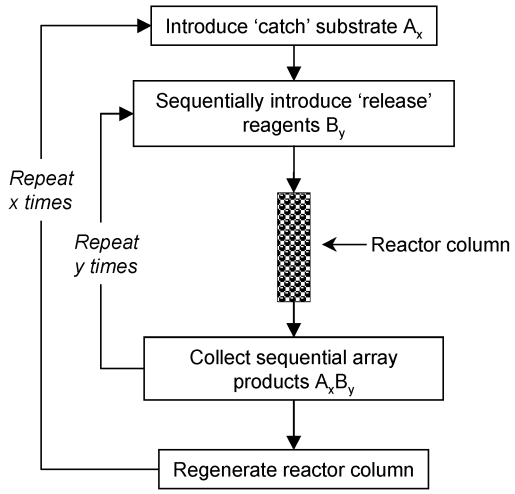
Scheme 1. Sequential Flow-Through Synthesis of Compound Arrays Using A "Catch and Release" Reactor Column



reactor, prohibitively long column residence times, or the need for postreactor scavenger purification (Scheme 1).

Results and Discussion

Acidic heterocycles containing thiourea moieties are readily deprotonated and, thus, can be scavenged by strong immobilized bases, such as the polymer-supported phosphazene base PS-BEMP[11] or the immobilized guanidino base PS-TBD[12] to form stable ionic complexes.[13] To determine whether this process could be exploited in a flow-through manner, we first examined the kinetics associated with the "capture" of the thiobenzimidazole **1** by PS-BEMP, and subsequent alkylative release upon the introduction of benzyl bromide (Figure 1). Although this batch process does not replicate the conditions encountered in a flow reactor, in which the eluting material is continually exposed to fresh reactive sites as it flows throught the column, the comparitively rapid "capture and release" reaction rates observed (<1 h) suggested that the corresponding flow-through process ought to be viable in a single pass with an acceptably short column residence time.

Therefore, we prepared a glass reactor column packed with PS-BEMP resin, preswollen in chloroform ($CHCl_3$), which had been previously loaded with 1.0−1.1 mmol thiobenzimidazole **1** in a separate batch process. The column was then eluted with each of a series of alkylating agents (0.2 mmol), in turn at a flow rate of 0.1 mL min^{-1} for 25 min each (corresponding to a residence time on column of ∼15 min), followed by flushing the reactor at 1.0 mL min^{-1} for 5 min to wash any remaining soluble material from the column. The thioethers obtained were analyzed by NMR to establish purity and, in particular, whether unreacted alkylating agent or leached thiobenzimidazole **1** contaminants were present (Table 1).

Importantly, in the absence of alkylating agent, the ionic PS-BEMP/thiobenzimidazole complex was found to be stable under the flow-through conditions employed, and no leaching of thiobenzimidazole starting material **1** was observed on continued elution of the loaded column with chloroform (for several hours), or in any of the collected product fractions.

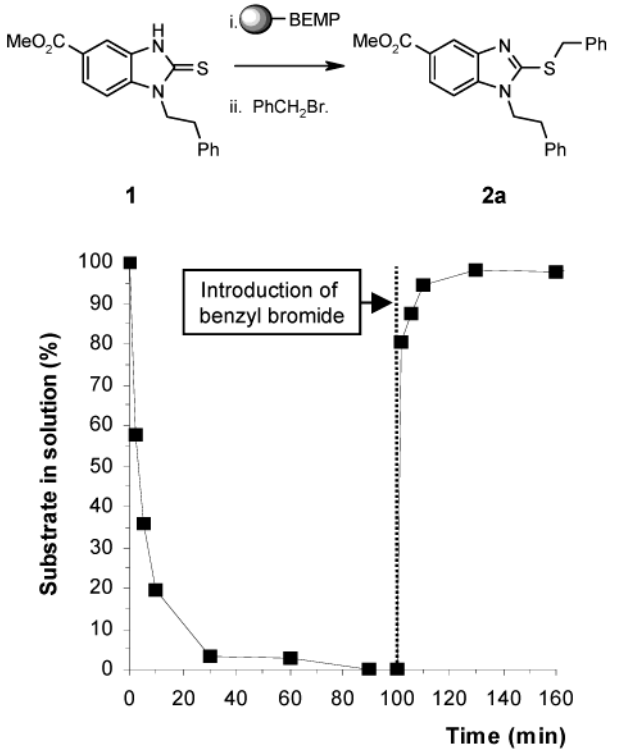
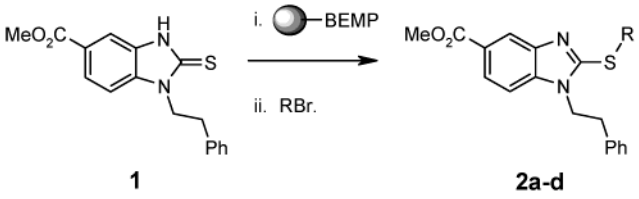


Figure 1. Kinetic study of the "capture" of **1** by PS-BEMP and subsequent alkylative release of **2a** upon introduction of benzyl bromide. Reagents and conditions: (i) PS-BEMP (5 equiv), **1**, rt; (ii) benzyl bromide (2 equiv), rt.

Table 1. Purity Profile of Flow-Through Thioether Products **2a**−**d**



injection.	alkylating agent RBr	product	yield (%)[a]	residual RBr (%)[a]
1	$PhCH_2-$	**2a**	90	0
2	$MeO_2C(CH_2)_3-$	**2b**	100	0
3	$HC{:}CHCH_2-$	**2c**	100	0
4	$^tBuO_2CCH_2-$	**2d**	100	0
5	$PhCH_2-$	**2a**	97	3
6	$PhCH_2-$	**2a**	80	20
7	$PhCH_2-$	**2a**	0	100

[a] Product compositions determined by integration of relevant signals in the ^1H NMR spectrum.

Moreover, a sharp breakthrough point for unreacted benzyl bromide was observed in the sixth injection, where a total of 1.0−1.2 mmol of alkylating agent had been eluted, which corresponded closely with the predetermined loading of the column used.

While functionalized gel-phase polystyrene beads are unlikely to represent the optimal support for flow-through applications and, in particular, do not benefit from the more consistent fluid dynamics and geometries associated with monolithic materials,[14] they are nevertheless readily available with a wide range of functionalities and currently represent a more accessible and affordable alternative. By utilizing

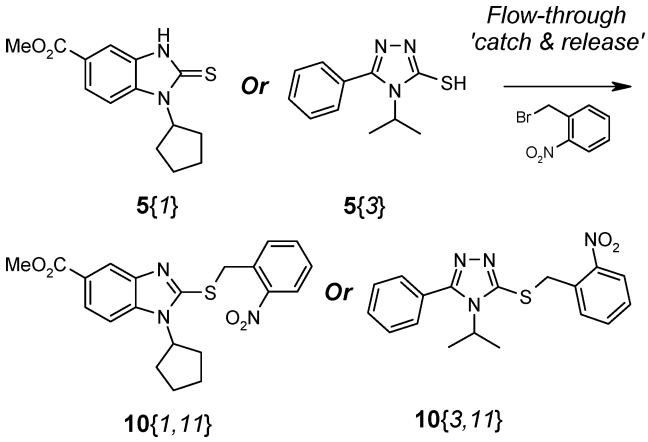
preswollen polymer beads which were packed under a slight positive pressure (to avoid column voiding), we did not observe any noticeable volume changes as the column was eluted, nor did we observe any significant pressure increases under the flow conditions employed ($\leq$1.0 mL min^{-1}). In fact, for more consistent results, it proved beneficial to artificially introduce a slight positive backpressure by incorporating a backpressure regulator into the outflow stream.

Having established that thiobenzimidazoles, such as **1**, can participate in an alkylative release under flow-through conditions, we next turned our attention to the possibility of column regeneration and reloading. The ability to regenerate and reuse a stoichiometric column reactor is a desirable and cost-effective objective that also leads to increased process efficiency. In this way, we envisaged preparing multidimensional compound arrays based upon a variety of heterocyclic scaffolds. Each scaffold would be captured in turn by the same reactor cartridge and used to generate a compound array by alkylative release with a common set of electrophiles. It was anticipated that regeneration of the reactor could be accomplished by first eluting with an excess of a reactive electrophile (e.g., allyl bromide) to fully discharge the column of any residual bound heterocycle and then treating with a solution of a suitable base to deprotonate and regenerate the basic support. Initial experiments with large excesses of bases much weaker than BEMP (in an attempt to displace the acid−base equilibrium) met with limited success; however, elution of the column with a solution of a stronger base, such as a P_4-phosphazene,[15] was found to be particularly effective,[6] and led to a rapid regeneration of the reactor.

At this stage, the column was washed free of the soluble phosphazene and could then be reloaded by recirculating a solution of excess thiobenzimidazole **1** in tetrahydrofuran (THF). Analysis of the circulating solution indicated a rapid "capture" of substrate (<0.5 h) consistent with the functional capacity of the reactor observed previously, thereby indicating that no significant loss of activity had occurred upon column regeneration.

However, we had previously noted that when the PS-BEMP column was loaded with thiobenzimidazole substrate, some degradation of the chloroform solution of **1** occurred over time. The resulting unidentified impurities were apparently partially "captured" by the PS-BEMP and subsequently eluted when the column was treated with an electrophile, thereby contaminating slightly the first eluted product (cf. Table 1, injection 1). In an attempt to circumvent this problem and to avoid the inconvenient need to use an air- and moisture-sensitive P_4-phosphazene for column regeneration, we elected to evaluate the weaker, polystyrene-supported guanidine base PS-TBD as an alternative support. When protonated, this support can be more conveniently regenerated by elution with a solution of the P_1-phosphazene BEMP under aerobic conditions. In addition, to study the viability of regenerating and reloading the column reactor with different heterocyclic substrates, we prepared the alternative substrates **5**{*1*−*4*} (Scheme 2) and selected compounds **5**{*1*} and **5**{*3*} as representatives of this set for a preliminary study.

Table 2. Analysis of Thioether Product Profiles **10**{*x,11*} before and after Regeneration of Reactor Column



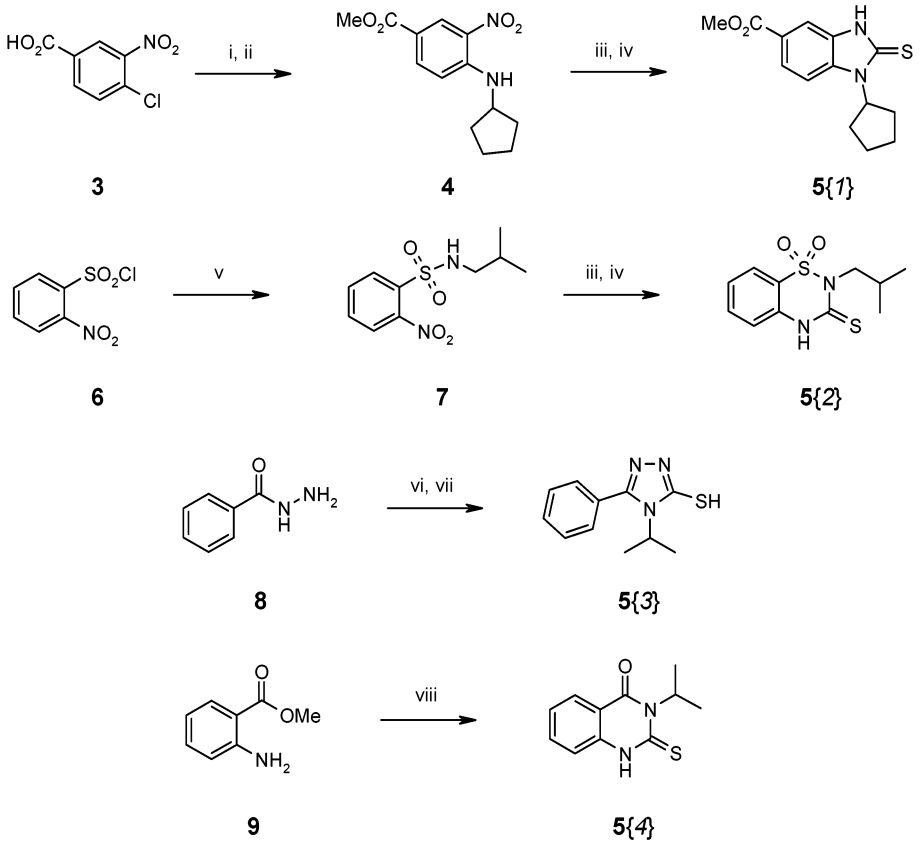
		10{*x,11*}	
substrate	injection.	% yield[a]	% purity[b]
5{*1*}	1	97	>99
5{*1*}	2	100	>99
5{*1*}	3	95	>99
5{*1*}	4	100	>99
5{*1*}	5	100	>99
5{*1*}	6	98	>99
5{*1*}	7	93	>99
5{*1*}	8	90	95
5{*1*}	9	55	84
5{*1*}	10	15	29
5{*1*}	11	0	
5{*3*}	1	100	>99
5{*3*}	2	100	>99
5{*3*}	3	100	>99
5{*3*}	4	93	>99
5{*3*}	5	93	>99
5{*3*}	6	0	

[a] Isolated yield by weight. [b] HPLC purity at 254 nm.

Thus, a reactor column containing PS-TBD (1.32 mmol theoretical loading), packed as previously described was loaded by elution with a chloroform solution containing a substoichiometric amount of the thiobenzimidazole **5**{*1*} (0.5 mmol). The loading was performed at a flow rate of 0.1 mL min^{-1}, which corresponded to an on-column residence time of ~10 min. HPLC analysis of the eluate did not show any remaining **5**{*1*}, indicating complete "capture" of the substrate in a single pass through the reactor. The reactor column was then sequentially eluted with 11 solutions of *o*-nitrobenzyl bromide in chloroform (54 μmol, 0.1 mL min^{-1}, 10 min column residence times). The resulting thioethers **10**{*1,11*} were collected and analyzed by HPLC−UV. Products from injections 1−8 were obtained in excellent yield and purity. Unreacted alkylating agent only began to appear as a contaminant in the product from injection 9 (Table 2).

This corresponded to displacement of ~90% of the starting material present on the reactor column (0.5 mmol) before breakthrough was observed. One further injection was required to completely discharge the column of any remaining residual thiobenzimidazole. In contrast to the use of PS-BEMP, no degradation of the chloroform solutions of the thiobenzimidazoles was observed with PS-TBD. Encouraged by these results and, in particular, the comparatively sharp

Scheme 2[a]



[a] Reagents and conditions: (i) concentrated H_2SO_4, MeOH, reflux, 17 h; (ii) cyclopentylamine, $^{i}Pr_2NEt$, DMF, EtOH, reflux, 16 h; (iii) $Pd(OH)_2$, EtOH, H_2(g), rt, 3.5 h; (iv) 1,1′-thiocarbonyldiimidazole, $CHCl_3$, rt, 48 h; (v) $^{i}BuNH_2$, Et_3N, CH_2Cl_2, rt, 64 h; (vi) ^{i}PrNCS, EtOH, 90 °C, 3 h; (vii) 2 M NaOH (aq), 95 °C, 17 h; (viii) ^{i}PrNCS, EtOH, 90 °C, 72 h.

breakthrough point for unreacted alkylating agent observed, we next attempted flow-through regeneration of the reactor.

The discharged PS-TBD column was eluted with a solution of BEMP in tetrahydrofuran at a flow-rate of 0.1 mL min^{-1}, followed by a wash step. The regenerated reactor was then reloaded in a flow-through manner, as before, with a solution of the thiotriazole **5**{*3*} (0.5 mmol) as an example of a different heterocyclic scaffold. Sequential elution with chloroform solutions of *o*-nitrobenzyl bromide (6 × 100 μmol; 0.1 mL/min, 10 min column residence times) lead to isolation of the corresponding thioethers **10**{*3,11*}. In this case, no breakthrough of unreacted alkylating agent was observed, and the reactor column was cleanly exhausted by the fifth injection of electrophile. Only a trace amount of thiotriazole-derived material was isolated following injection 6. Further, none of the thioethers **10**{*3,11*} were cross-contaminated with material derived from the previous thiobenzimidazole starting material **5**{*1*}.

These experiments clearly demonstrated the potential to prepare arrays of thioethers based upon different heterocyclic scaffolds in both high yield and excellent purities without cross-contamination in a sequential flow-through process using a reactor column containing PS-TBD, which may be regenerated and reused. In fact, we subsequently determined that this regeneration protocol is highly reproducible and now routinely use the same PS-TBD column in excess of 30 times before replacement.

With procedures for (i) column loading, (ii) alkylative release, (iii) column discharging, and (iv) column regeneration established, we next considered automation of these iterative flow-through processes. In contrast to the automation of batch processes, which require complex robotic synthesizers, the automation of flow-through processes is a more straightforward process, and we were quickly able to assemble a suitable flow-through synthesizer, which was constructed using commercial HPLC components as shown in Figure 2.[16]

Moreover, the equipment could be controlled by adapting preexisting autopreparative HPLC software. In contrast to flow-through synthesis using a recirculating protocol, our strategy of multiple-single-pass processing required precise flow control and a knowledge of any associated system dead volumes in order to ensure we could accurately position substrates on the reactor column (and not elsewhere in the system) and thereby benefit from the minimum necessary residence time to ensure complete conversion to the desired reaction products. Clearly, for linear, as opposed to parallel, processing, prolonged individual run times have a significant detrimental effect on overall throughput. The necessary precision was achieved by replacing the HPLC pumps used in our earlier work with syringe pumps. In addition, since it is desirable to minimize solvent volumes collected and to array each product into a single container, we incorporated UV threshold detection at the point of sample collection in order to minimize the amount of solvent collected.[17] Substrates, monomers, and array products were arranged in allocated positions on the bed of the liquid handler, which was used to both auto-inject substrates and monomers into

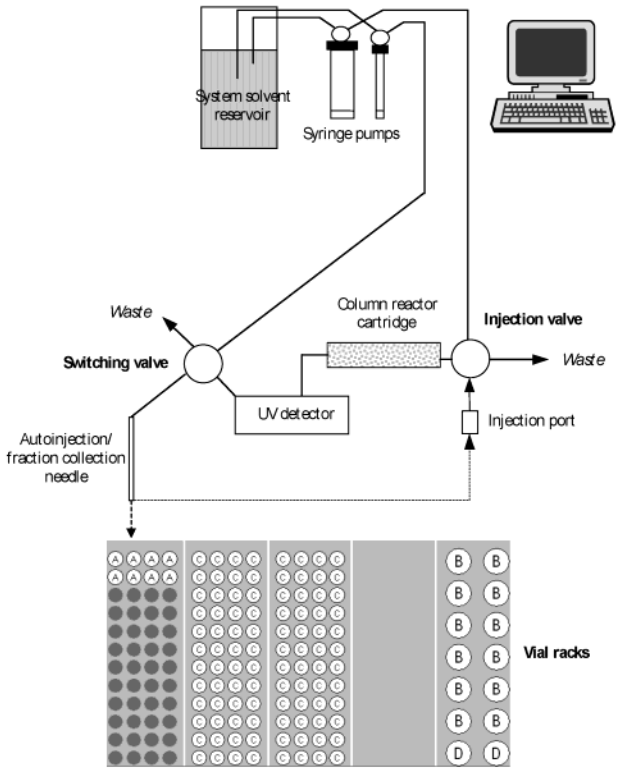
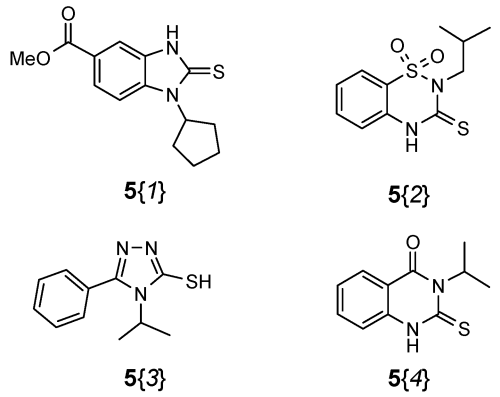


Figure 2. Schematic drawing of automated flow-through synthesizer with example of tray layout showing locations of substrates (A), monomers (B), products (C), and regeneration solutions (D).

Chart 1. Monomer Set A



the system and then collect eluted products, as directed by the system control software.

A simple program was compiled to enable automated array synthesis consisting of a module to control column regeneration, loading of the required heterocycle from monomer set A (Chart 1), and setting of any associated system parameters (UV detection wavelength, etc.) and a second module to control the introduction of the appropriate alkylating agent from monomer set B (Chart 2) and elution/collection of the product. These protocols were combined in repetitive embedded loops to afford an array of the desired dimensions (Figure 3). To exhaust the column between loadings with the different heterocycles, we simply incorporated a more concentrated solution of allyl bromide as the final monomer in the set of alkylating agents B.

Initially, reproducibility of both the automated flow-through synthesizer and the proposed chemistry was tested

Chart 2. Alkylating Agent Monomer Set B

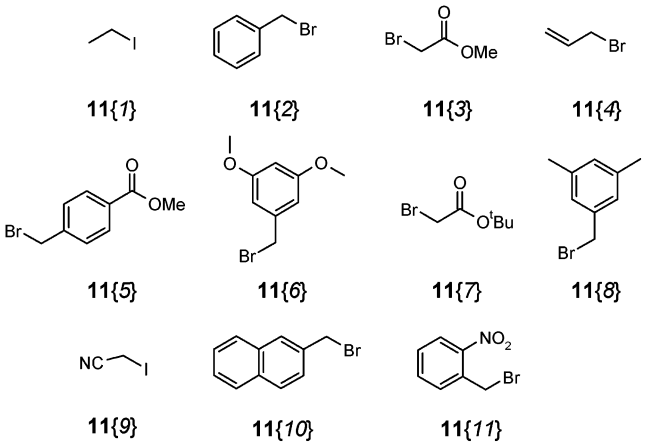
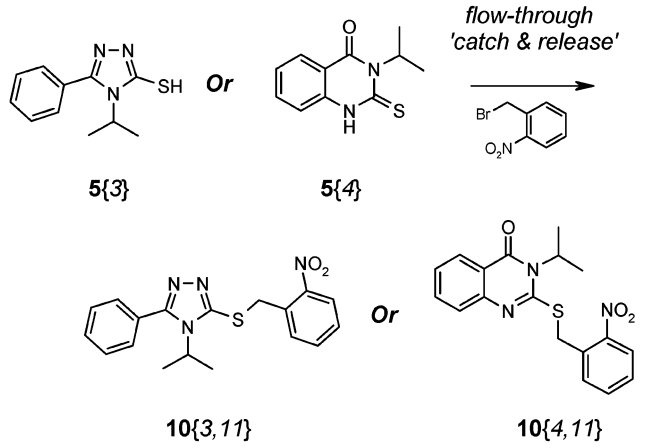


Table 3. Results of Sequential Alkylative Release Following Automated Reactor Column Regeneration



		% yield[a] **10**{3,11} or **10**{4,11}					
	monomer A	1st	2nd	3rd	4th	5th	av % yield
run 1	**5**{*3*}	97	95	96	93	94	95 ± 2
run 2	**5**{*4*}	90	90	90	90	90	90 ± 0
run 3	**5**{*3*}	92	92	91	90	88	91 ± 3
run 4	**5**{*4*}	92	90	87	88	88	89 ± 3

[a] Sequential % yields of **10**{*3,11*} and **10**{*4,11*} obtained following sequential elution with 0.1-mmol aliquots of *o*-nitrobenzyl bromide determined by weight. Column was regenerated and reloaded with either heterocycle **5**{*3*} or **5**{*4*} as appropriate between runs.

by performing six sequential alkylations (5 × *o*-nitrobenzyl bromide, then 1 × allyl bromide) in a repetitive manner alternating between scaffolds **5**{*3*} and **5**{*4*}. Each heterocyclic scaffold was loaded onto the column reactor twice with an intermediate column regeneration step between loadings. The whole process was performed in a fully automated manner without any manual intervention to test all aspects of the proposed array synthesis. All the resulting products were isolated in high yields and in excellent purities (>90% according to LC/MS) without the need for any further purification. Importantly, the isolated yields of compounds both before and after column regeneration displayed good reproducibility (±5%), attesting to the overall robustness of the automated flow-through process (Table 3).

With the operation of the flow-through synthesizer and control software validated, a full 2-D array synthesis using

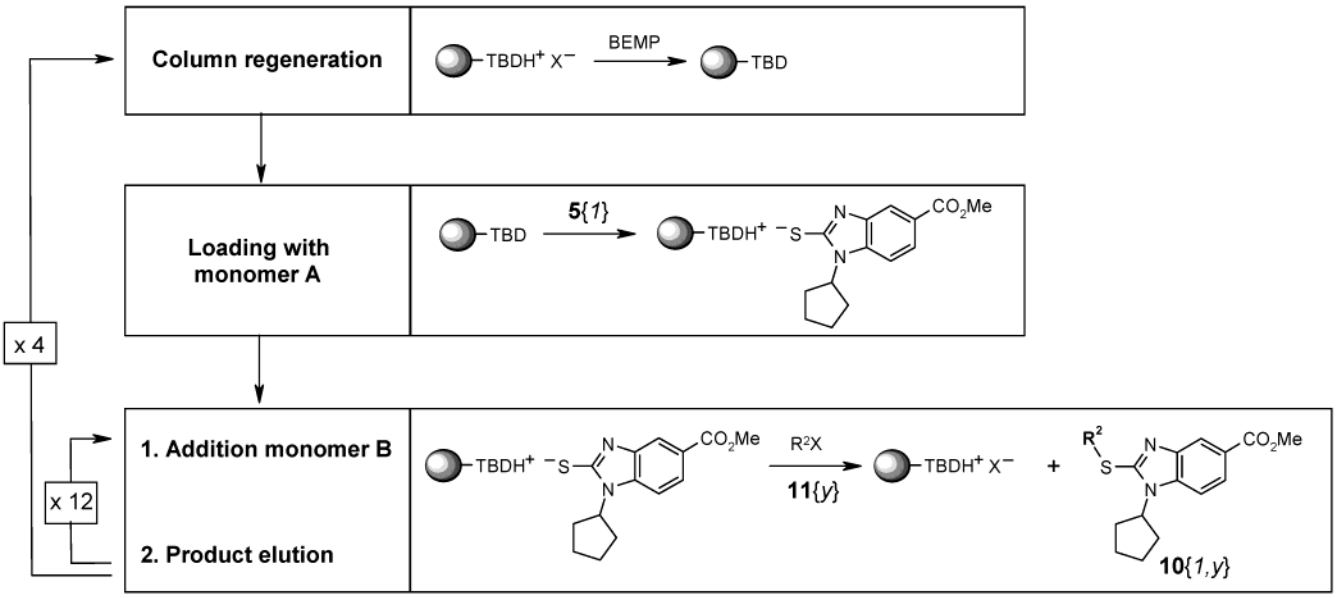


Figure 3. Automated flow-through synthesis of compound array **10**{*x,y*} exemplified for **10**{*1,y*}.

Table 4. Isolated Yields and Purities for S-Alkylated Heterocylic Ethers **10**{*1-4,1-11*}

alkylating agent **11**{*x*}	% yield (purity)[a]			
	10{*1,x*}	**10**{*2,x*}	**10**{*3,x*}	**10**{*4,x*}
11{*1*}	89 (97)[b]	75 (>99)	88 (98)	81 (>99)
11{*2*}	98 (95)[b]	93 (>99)	98 (>99)	92 (>99)
11{*3*}	91 (>99)[b]	89 (>99)[b]	90 (>99)	88 (>99)
11{*4*}	89 (>99)[b]	89 (>99)[b]	90 (>99)	84 (>99)
11{*5*}	100 (99)[b]	100 (>99)[b]	95 (>99)[b]	100 (>99)
11{*6*}	94 (98)	90 (>99)[b]	93 (>99)[b]	94 (>99)
11{*7*}	93 (>99)	93 (>99)[b]	89 (>99)[b]	88 (>99)[b]
11{*8*}	93 (>99)	93 (>99)	90 (>99)[b]	87 (>99)[b]
11{*9*}	78 (>99)	90 (>99)	86 (>99)[b]	81 (>99)[b]
11{*10*}	75 (>99)	90 (>99)	75 (98)	83 (>99)[b]
11{*11*}	85 (>99)	91 (>99)	88 (>99)	90 (>99)[b]

[a] Isolated yields were determined gravimetrically and purities were measured by HPLC at 254 nm. [b] Isolated yields were determined gravimetrically and purities were measured by ^{1}H NMR.

monomer sets A and B was initiated. The program was run overnight without any manual intervention except to perform the final parallel evaporation of solvent from the array products. Quantitative analysis of the 44 thioethers **10**{*1−4,1−11*} obtained revealed that all flow-through products were obtained in high yield (>75%)[18] and excellent purities (>95% according to LC/MS or ^{1}H NMR) with no requirement for further purification (Table 4). No cross-contamination or contamination with unreacted monomers from either monomer set was observed in any case.

Conclusions

We have demonstrated the viability of a fully automated flow-through process to conveniently prepare a 44-member array of diverse heterocyclic thioethers **10**{*1−4,1−11*} by sequential, single pass elutions through a PS-TBD reactor column prepared from a commercial beaded polystyrene-supported reagent. The column can be reproducibly regenerated in an automated process using a tetrahydrofuran solution of the phosphazene Schwesinger base BEMP, and we have reused such columns in excess of 30 regenerative cycles. The 2-D array prepared, in contrast to many combinatorial arrays, incorporates multiple heterocyclic core motifs which augment the structural diversity present. Our approach, which is based upon a resin "capture and release" protocol and thereby provides for an intrinsic in-line product purification, leads to adducts in high yields and excellent purities without any requirement for further purification. Studies are ongoing in our laboratory to implement other array syntheses using an automated flow-through approach.

Experimental Section

General. All starting materials, solvents, and reagents were commercially available and used without further purification. Melting points were performed on a Mettler FP5 automtatic melting point apparatus in open tubes heated from 50 °C at 2 °C min^{-1} and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM-400 spectrometer at 400 MHz. ^{13}C NMR (proton-decoupled) spectra were recorded on a Bruker DRX-500 CRYO at 125 MHz or on a Bruker AM-400 spectrometer at 100 MHz. The chemical shifts are in δ units relative to TMS ($\delta = 0$) using the indicated solvent as an internal standard. Multiplicities are indicated as s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublet; td, triplet of doublet; br, broad. RP-HPLC was run on a Hewlett-Packard 1050 instrument. Column: Supelcosil ABZ$^+$-PLUS column, 3.3 cm, 4.6 mm ϕ, 3 μm. Eluents: A: water, 0.1% TFA; B: acetonitrile 95%, water 5%, TFA 0.05%. Gradient: 10−95% B in A (1 mL min^{-1}) over 8 min. Detection: UV (diode array detector). LC/MS analyses were performed on a Waters Alliance 2795XE HT attached to a Micromass ZQ 2000 mass spectrometer using electrospray ionization in positive and negative modes. Column: Supelcosil ABZ$^+$PLUS, 3.3 cm, 4.6 mm ϕ, 3 μm. Eluents: A: 10 mM solution of ammonium acetate in water, 0.1% formic acid; B: acetonitrile 95%, water 5%, formic acid 0.05%. Gradient: 0−100% B in A (3 mL min^{-1}) over 3.5 min. High-resolution mass spectra were obtained using a Micromass Q-TOF 2 under positive ionization conditions.

Methyl 4-Chloro-3-nitrobenzoate.[19a] 4-Chloro-3-nitro benzoic acid **3** (40.0 g, 20.0 mmol) was suspended in methanol (200 mL) and cooled to 0 °C. Concentrated sulfuric acid (22 mL) was slowly added with stirring, and then the mixture was heated at reflux for 17 h. Upon cooling to room temperature, a precipitate formed, which was collected by filtration and washed with cold methanol (2 × 30 mL) and hexane (2 × 30 mL) to afford the methyl ester as a white solid (35.5 g, 83%). mp: 78−79 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.96 (3H, s), 7.64 (H, d, J = 2 Hz), 8.15 (H, d, J = 2 Hz), 8.51 (H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 53.3, 127.0, 130.5, 132.1, 132.6, 134.0, 148.3, 164.6. HPLC (254 nm): t_R = 5.23 min (100%).

Methyl 4-(cyclopentylamino)-3-nitrobenzoate (4). Methyl 4-chloro-3-nitrobenzoate, (3.84 g, 17.8 mmol) was dissolved in a mixture of methanol (25 mL) and *N*,*N*-dimethylformamide (3 mL) and treated with cyclopentylamine (2.12 mL, 21.4 mmol) and *N*,*N*-diisopropylethylamine (3.72 mL, 21.4 mmol). This mixture was heated at reflux for 16 h. Upon cooling to ambient temperature, a precipitate formed, which was collected by filtration and washed with cold methanol (2 × 10 mL) and hexane (2 × 10 mL) to afford the ester **4** as a yellow powder (4.60 g, 98%). mp: 103−104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.6−1.75 (4H, m), 1.8 (2H m), 2.11 (2H m), 3.88 (3H, s), 4.01 (H, m), 6.89 (H, d, J = 2 Hz), 8.02 (H, dd, J = 0.5, 2 Hz), 8.39 (H, d, J = 1 Hz), 8.86 (H, d, J = 1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 23.35, (2C), 32.80 (2C), 51.40, 53.62, 113.67, 116.12, 128.92, 130.44, 135.42, 146.63, 165.01. HPLC (254 nm): t_R = 6.04 min (100%).

Methyl 1-Cyclopentyl-2-thioxo-2,3-dihydro-1*H*-benzimidazole-5-carboxylate (5{*1*}).[19b] Methyl 4-(cyclopentylamino)-3-nitrobenzoate **4** (1.5 g, 5.7 mmol) was dissolved in a mixture of *N*,*N*-dimethylformamide (5 mL) and ethanol (50 mL). Pearlman's catalyst (0.3 g) was introduced under nitrogen, and the mixture was hydrogenated at atmospheric pressure with vigorous stirring for 14 h. The catalyst was removed by filtration, and the solvent was evaporated in vacuo to afford the intermediate aniline as an oil. This was immediately dissolved in chloroform (50 mL), and 1,1′-thiocarbonyldiimidazole (1.51 g, 8.5 mmol) was added to the solution. The resulting mixture was stirred at ambient temperature for 6 h and then concentrated in vacuo. The residue was taken up in ethyl acetate (50 mL), and the organic phase was washed successively with 1 M aqueous hydrochloric acid (3 × 30 mL), 5% aqueous sodium bicarbonate solution (2 × 30 mL), and brine (2 × 30 mL). The organic solution was dried ($MgSO_4$), and the solvent was evaporated in vacuo to give the ester **5**{*1*} as a pale green solid (1.38 g, 88%). mp: 183−184 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.83 (2H m), 1.97−2.22 (6H, br m), 3.93 (3H, s), 5.68 (H, quin, J = 2 Hz), 7.28 (H, d, J = 2 Hz), 7.91 (H, dd, J = 0.5, 2 Hz), 7.95 (H, d, J = 0.5 Hz), 11.62 (H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 24.60 (2C), 28.05 (2C), 51.66, 56.17, 109.28, 111.03, 123.75, 124.39, 130.11, 133.35, 165.99, 169.48. HPLC (254 nm): t_R = 5.23 min (100%); LC/MS (ESI): t_R = 2.99 min (m/z 277.1, MH^+).

***N*-(2-Methylpropyl)-2-nitrobenzenesulfonamide (7).** 2-Nitrobenzensulfonyl chloride **6** (3.32 g, 15 mmol) was dissolved in dichloromethane (50 mL). To this solution was slowly added isobutylamine (1.64 mL, 16.5 mmol) and triethylamine (2.30 mL, 16.5 mmol). The reaction was stirred at ambient temperature for 64 h, after which time the solution was washed with 1 M aqueous hydrochloric acid (3 × 50 mL) and brine (3 × 50 mL). The organic solution was dried ($MgSO_4$), and the solvent was evaporated in vacuo to give the sulfonamide **7** as an off-white powder (3.6 g, 93%). mp: 79−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.90 (6H, d, J = 1.5 Hz), 1.78 (H, m), 2.89 (2H t, J = 1.5 Hz), 5.27 (H, br), 7.73 (2H m), 7.85 (H, m), 8.12 (H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 19.14 (2C), 27.18, 50.49, 124.67, 130.37, 132.13, 132.89, 133.06, 147.40; HPLC (254 nm): t_R = 4.50 min (100%).

2-(2-Methylpropyl)-2*H*-1,2,4-benzothiadiazine-3(4*H*)-thione 1,1-Dioxide (5{*2*}). *N*-(2-methylpropyl)-2-nitrobenzenesulfonamide **7** (1.50 g, 5.80 mmol) was dissolved in ethanol (50 mL), and Pearlman's catalyst (0.3 g) was added. The resulting suspension was hydrogenated at atmospheric pressure for 3.5 h with vigorous stirring. Filtration followed by evaporation of the solvent in vacuo afforded an oil (1.3 g, 98%). [HPLC (254 nm): t_R = 4.4 min (100%).] The oil was immediately redissolved in chloroform (50 mL), and 1,1′-thiocarbonyldiimidazole (1.55 g, 8.7 mmol) was added to the solution. The mixture was stirred at ambient temperature for 48 h, and then the solvent was evaporated in vacuo. The crude residue was taken up in ethyl acetate (50 mL) and water (25 mL). The organic phase was separated and washed with 0.5 M aqueous hydrochloric acid (2 × 25 mL) and brine (2 × 25 mL), then dried ($MgSO_4$) and evaporated in vacuo to afford **5**{*2*} as an off-white powder (1.45 g, 92%). mp: 143−144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.93 (6H, d, J = 1.5 Hz), 2.32 (H, m), 4.17 (2H d, J = 2 Hz), 7.20 (H, d, J = 2 Hz), 7.35 (H, td, J = 0.5, 2 Hz), 7.65 (H, td, J = 0.5, 2 Hz), 7.84 (H, dd, J = 0.5, 2 Hz), 10.10 (H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 19.14 (2C), 26.74, 52.76, 115.90, 122.05, 123.03, 124.39, 133.91, 134.04, 177.23; HPLC (254 nm): t_R = 5.59 min (100%); LC/MS (ESI): t_R = 3.16 min (m/z 271, MH^+).

4-(1-Methylethyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (5{*3*}). Benzoic hydrazide **8** (1.36 g, 10.0 mmol) was dissolved in ethanol (50 mL). To this solution was added isopropyl isothiocyanate (1.07 mL, 10.0 mmol), and the mixture was heated to 90 °C for 3 h. The solution was then allowed to cool, and the ethanol was evaporated in vacuo, affording the intermediate hydrazine carbothioamide as a white powder [HPLC (254 nm): t_R = 3.2 min (100%)]. This material was dissolved in 2 M aqueous sodium hydroxide (50 mL), and the resulting solution was heated to 95 °C for 17 h. The solution was then adjusted to pH 8−9 with 6 M aqueous hydrochloric acid and extracted with ethyl acetate (1 × 100 mL, 3 × 50 mL). The combined organic extracts were washed with brine (3 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo to afford **5**{*3*} as an off-white powder (1.60 g, 73%). mp: 193−194 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.49 (6H, d, J = 1.5 Hz), 4.81 (H, m), 7.44−7.57 (5H, brs m), 12.25 (H, brs); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 19.69 (2C), 49.52, 125.96 (2C), 128.18 (2C), 128.96 (2C), 130.25, 151.69, 165.91. HPLC (254 nm): t_R = 4.06 min (100%). LC/MS (ESI): t_R = 2.50 min (m/z 220.1, MH^+).

3-(1-Methylethyl)-2-thioxo-2,3-dihydro-4(1*H*)-quinazolinone (5{*4*}). Methyl anthranilate **9** (2.58 mL, 20 mmol) was diluted with ethanol (50 mL). To this solution was added isopropyl isothiocyanate (1.07 mL, 10 mmol), and the mixture was heated to 90 °C for 72 h. The solution was allowed to cool, and the solvent was evaporated in vacuo. The residual oil was purified by column chromatography (0−40% ethyl acetate/hexane) to afford **5**{*4*} as an off-white powder (1.30 g, 63%). mp: 176−177 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.61 (6H, d, J = 1.5 Hz), 6.06 (H, m), 7.22 (H, d, J = 2 Hz), 7.28 (H, t, J = 2 Hz), 7.61 (H, td, J = 0.5, 2 Hz) 8.08 (H, dd, J = 0.5, 2 Hz), 11.10 (H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 18.19 (2C), 53.93, 113.80, 116.85, 124.38, 127.41, 134.50, 137.59, 159.11, 175.92. HPLC (254 nm): t_R = 4.86 min (100%). LC/MS (ESI): t_R = 2.85 min (*m*/*z* 221.1, MH^+).

Automated Flow-Through Array Preparation. 1. Column Preparation. Polystyrene-bound (2% cross-linked with DVB) 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PS-TBD: 930 mg × ∼2.6 mmol g^{-1}, ∼2.4 mmol) was preswelled in chloroform ($CHCl_3$), and the resulting slurry was transferred to a 150-mm Omnifit glass column (i.d. 6.6 mm). The column was then eluted with chloroform to obtain good swelling of the resin before a variable-length end piece was fitted and adjusted in order to remove solvent gaps and retain the resin beads under a slightly positive pressure. The void volume of this column was determined to be ∼1 mL.

2. Column Regeneration. 2-*tert*-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,2,3-diazaphosphorine (BEMP: 2.84 g, 10.4 mmol) was diluted with anhydrous tetrahydrofuran (THF: 6 mL) to a concentration of 1.16 M. Of this solution, 2 mL was injected (4 × 500 μL) at 0.2 mL min^{-1} in each regeneration step to deprotonate the PS-TBDH$^+$X$^-$ and regenerate the column reactor. The column was subsequently washed with $CHCl_3$.

3. Column Reloading. Solutions of each heterocycle from monomer set A (0.625 mmol) were dissolved in a mixture of DMF (500 μL) and $CHCl_3$ (2 mL) to a concentration of 0.25 M. In each reloading step, a single substrate solution was injected onto the reactor column (4 × 500 μL) to charge the column with 0.50 mmol of substrate.

4. Fraction Collector Wavelength. To compensate for significant variations in the molar absorptivities (ϵ) associated with products based upon different heterocyclic core motifs and ensure that the UV detection threshold was set appropriately, the detector wavelength (λ) was varied for each core structure to a predetermined value at which the molar absorptivities were approximately the same (λ: **5**{*1*} 302, **5**{*2*} 314, **5**{*3*} 270, **5**{*4*} 308 nm).

5. Alkylative Release. Stock solutions of alkylating agents **5**{*1*−*11*} from monomer set B were prepared in $CHCl_3$ (10 mL, 0.072M) and introduced onto the reactor column as a single injection (500 μL, 36 μmol) for each alkylative release step. The monomer solution used for the 12th injection to fully discharge the column prior to reloading with the next monomer A was a 0.2 M solution of allyl bromide **11**{*4*} in $CHCl_3$.

6. Synthesizer Configuration. The system used was configured from a Gilson liquid handler (233XL), which was used as both an autoinjector and fraction collector, a dual syringe pump (402) fitted with a 1 mL and a 10 mL syringe, and a variable-wavelength UV detector (UV119). One syringe pump (1 mL) was connected to the needle via the collection valve, and the other (10 mL) syringe was connected to the column via the injection valve. This setup made it possible to use the needle for an initial injection/elution followed by elution and washing of the column using the 10 mL syringe pump, meanwhile collecting a threshold-triggered fraction with the needle. The system solvent used was $CHCl_3$, and the whole setup was controlled using Gilson Unipoint v3.3.

7. Synthesis Control Program. The synthesizer was controlled by an operations file consisting of two subroutines to control iteration and looping of common operations. The *S_alkylation control file* controlled column regeneration, reloading from monomer set A, and set the specified wavelength for the UV detector. The *Addmonomer control file* controlled the introduction of alkylating agents from monomer set B. A typical array synthesis run, with variables in brackets, is given in Chart 3.

Chart 3

S Alkylation, control file:

1. Regeneration
   - 1.1. Wash needle and injection port
   - 1.2. Inject 4 × 500 µL of a solution of BEMP in THF onto the column @ 0.2 mL/min
   - 1.3. Elute column with 1 mL @ 0.2 mL/min (using 10 mL syringe pump)
   - 1.4. Wash column with 5 mL @1.0 mL/min (using 10 mL syringe pump)
2. Substrate loading
   - 2.1. Wash needle and injection port
   - 2.2. Inject 4 × 500 µL of [substrate] onto the column @ 0.1 mL/min
   - 2.3. Elute the column with 1 mL @ 0.1 mL/min (using 10 mL syringe pump)
   - 2.4. Washes the column with 5 mL @ 1.0 mL/min (using 10 mL syringe pump)
3. Wavelength
   - 3.1. Set [wavelength]
   - 3.2. Wash column with 5 mL @ 1.0 mL/min (using 10 mL syringe pump)
   - 3.3. Autozero UV channel

Addmonomer, control file (Repeated 12x)

1. Monomer addition
   - 1.1. Wash needle and injection port
   - 1.2. Inject 500 µL of [monomer] onto the column @ 0.1 mL/min
   - 1.3. Home needle
   - 1.4. Wash needle
2. Product elution
   - 2.1. t = 0; Start eluting the column with 1 mL @ 0.1 mL/min (using 10 mL syringe)
   - 2.2. t = 0.3; Open the chromatographic channel
   - 2.3. t = 0.31; Set [sensitivity]
   - 2.4. t = 0.32; Set [peak level]
   - 2.5. t = 3.0; Start collection by threshold
   - 2.6. t = 10; Elute the column with 7 mL @ 1.0 mL/min
   - 2.7. t = 15; Stop collection

8. Charactarization Data for Array Products. 10{*1,1*}. 9.7 mg, 89%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.48 (3H, t, J = 2 Hz), 1.78 (2H, m), 2.3 (2H m), 2.15

(4H, m), 3.48 (2H q, 2 Hz), 3.91 (3H, s), 4.81 (H, quintet, $J = 2$ Hz), 7.33 (H, d, $J = 2$ Hz), 7.88 (H, dd, $J = 1$, 2 Hz), 8.38 (H, d, $J = 1$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 14.64, 25.13, 25.26, 27.14, 29.97 (2C), 52.02, 57.33, 109.80, 120.32, 123.07, 123.67, 137.48, 143.50, 154.37, 167.60. HPLC (254 nm): $t_R = 4.34$ min (97%). LC/MS (ESI): $t_R = 3.46$ min (*m*/*z* 306, MH^+). HRMS: $C_{16}H_{20}N_2O_2S$, MH^+ requires 305.1323, found 305.1326.

10{***1,2***}**.** 12.9 mg, 98%; red oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.77 (2H m), 2.07 (6H, m), 3.93 (3H, s), 4.63 (2H s), 4.70 (H, quin, $J = 2$ Hz), 7.3 (4H, m), 7.43 (2H m), 7.91 (H, d, $J = 2$ Hz), 8.42 (H, s); ^{13}C NMR (125 MHz, $CDCl_3$): 25.09, 25.13, 30.01 (2C), 37.49, 52.06, 57.50, 109.90, 120.45, 123.31, 123.89, 127.78, 128.70 (2C), 129.18 (2C), 136.28, 137.43, 143.10, 153.82, 167.54. HPLC (254 nm): $t_R = 5.84$ min (95%). LC/MS (ESI): $t_R = 3.75$ min (*m*/*z* 368, MH^+). HRMS: $C_{21}H_{22}N_2O_2S$, MH^+ requires 367.1480, found 367.1482.

10{***1,3***}**.** 11.4 mg, 91%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.8 (2H m), 2.03 (2H m), 2.18 (4H, m), 3.75 (3H, s), 3.92 (3H, s), 4.26 (2H s), 4.79 (H, quin, $J = 2$ Hz), 7.34 (H, d, $J = 2$ Hz), 7.89 (H, dd, $J = 1$, 2 Hz), 8.35 (H, d, $J = 1$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 25.10 (2C), 30.16 (2C), 34.68, 52.05, 52.98, 57.69, 109.99, 120.64, 123.35, 123.92, 137.72, 143.21, 152.47, 167.48, 169.04. HPLC (254 nm): $t_R = 4.94$ min (100%). LC/MS (ESI): $t_R = 3.24$ min (*m*/*z* 350, MH^+). HRMS: $C_{17}H_{20}N_2O_4S$, MH^+ requires 349.1222, found 349.1223.

10{***1,4***}**.** (10.1 mg, 89%); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.78 (2H m), 2.02 (2H m), 2.15 (4H, m), 3.92 (3H, s), 4.07 (2H d, $J = 2$ Hz), 4.82 (H, quin, $J = 2$ Hz), 5.17 (H, dd, $J = 0.5$, 2.5 Hz), 5.36 (H, dd, $J = 0.5$, 4 Hz), 6.04 (H, m), 7.33 (H, d, $J = 2$ Hz), 7.89 (H, dd, $J = 1$, 2 Hz), 8.38 (H, s); ^{13}C NMR (125 MHz, $CDCl_3$): 25.13 (2C), 30.06 (2C), 35.65, 52.03, 57.42, 109.90, 119.05, 120.49, 123.17, 123.76, 132.53, 137.56, 143.55, 153.64, 167.57. HPLC (254 nm): $t_R = 5.06$ min (100%). LC/MS (ESI): $t_R = 3.54$ min (*m*/*z* 318, MH^+). HRMS: $C_{17}H_{20}N_2O_2S$, MH^+ requires 317.1323, found 317.1325.

10{***1,5***}**.** 15.9 mg, 100%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.75 (2H m), 2.08 (6H, m), 3.88 (3H, s), 3.93 (3H, s), 4.69 (2H s), 4.80 (H, quin, $J = 2$ Hz), 7.33 (H, d, $J = 2$ Hz), 7.51 (2H d, $J = 2$ Hz), 7.90 (H, dd, $J = 1$, 2 Hz), 7.96 (2H d, $J = 2$ Hz), 8.41 (H, d, $J = 1$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 25.09, 25.13, 30.07 (2C), 36.88, 52.08, 52.13, 57.54, 110.04, 120.48, 123.41, 124.00, 129.18, 129.51, 129.93, 137.48, 141.86, 143.10, 153.86, 166.68, 167.48. HPLC (254 nm): $t_R = 5.93$ min (98%). LC/MS (ESI): $t_R = 3.70$ min (*m*/*z* 426, MH^+). HRMS: $C_{23}H_{24}N_2O_4S$, MH^+ requires 425.1535, found 425.1537.

10{***1,6***}**.** 14.5 mg, 94%; colorless oil; HPLC (254 nm): $t_R = 5.78$ min (98%); LC/MS (ESI): $t_R = 3.72$ min (*m*/*z* 428, MH^+).

10{***1,7***}**.** 13.1 mg, 93%; colorless oil; HPLC (254 nm): $t_R = 5.84$ min (100%); LC/MS (ESI): $t_R = 3.62$ min (*m*/*z* 392, MH^+).

10{***1,8***}**.** 13.2 mg, 93%; colorless oil; HPLC (254 nm): $t_R = 6.44$ min (100%); LC/MS (ESI): $t_R = 4.02$ min (*m*/*z* 396, MH^+).

10{***1,9***}**.** 8.8 mg, 78%; colorless oil; HPLC (254 nm): $t_R = 5.01$ min (100%); LC/MS (ESI): $t_R = 3.19$ min (*m*/*z* 317, MH^+).

10{***1,10***}**.** 11.2 mg, 75%; colorless oil; HPLC (254 nm): $t_R = 6.54$ min (100%); LC/MS (ESI): $t_R = 4.05$ min (*m*/*z* 418, MH^+).

10{***1,11***}**.** 12.6 mg, 85%; yellow oil; HPLC (254 nm): $t_R = 6.22$ min (100%); LC/MS (ESI): $t_R = 3.72$ min (*m*/*z* 413, MH^+).

10{***2,1***}**.** 8.1 mg, 75%; colorless oil; HPLC (254 nm): $t_R = 6.32$ min (100%); LC/MS (ESI): $t_R = 3.62$ min (*m*/*z* 298.4, M^+).

10{***2,2***}**.** 12.1 mg, 93%; colorless oil; HPLC (254 nm): $t_R = 6.68$ min (100%); LC/MS (ESI): $t_R = 3.84$ min (*m*/*z* 360.4, M^+).

10{***2,3***}**.** 11 mg, 89%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.92 (6H, d, $J = 1.5$ Hz), 2.19 (H, m), 3.76 (3H, s), 3.78 (2H d, $J = 2$ Hz), 3.99 (2H s), 7.36 (H, dd, $J = 0.5$, 1.5 Hz), 7.38 (H, m) 7.61(H, td, $J = 0.5$, 2.5 Hz), 7.80(H, dd, $J = 1$, 2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 19.71 (2C), 28.93, 34.16, 52.24, 52.86, 121.21, 126.18 (2C), 126.63, 133.53, 141.92, 155.87, 168.76. HPLC (254 nm): $t_R = 5.51$ min (100%); LC/MS (ESI): $t_R = 3.14$ min (*m*/*z* 342.4, M^+). HRMS: $C_{14}H_{18}N_2O_4S_2$, MH^+ requires 343.0786, found 343.0783.

10{***2,4***}**.** 9.9 mg, 89%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.89 (6H, d, $J = 1.5$ Hz), 2.13 (H, m), 3.76 (2H d, $J = 2$ Hz), 3.90 (2H, td, $J = 0.5$, 1.8 Hz), 5.18 (H, dd, $J = 0.5$, 2.5 Hz), 5.35 (H, dd, $J = 0.5$, 4 Hz), 5.96 (H, m), 7.36 (H, td, 0.5, 2 Hz), 7.44 (H, dd, $J = 0.5$, 2 Hz), 7.62 (H, td, $J = 0.5$, 2.5 Hz), 7.81 (H, dd, $J = 0.5$, 2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 19.69 (2C), 28.92, 35.01, 51.81, 119.03, 121.18, 125.86, 126.36, 126.64, 132.36, 133.44, 142.20, 156.76. HPLC (254 nm): $t_R = 6.33$ min (100%). LC/MS (ESI): $t_R = 3.67$ min (*m*/*z* 310.4, M^+). HRMS: $C_{14}H_{18}N_2O_2S_2$, MH^+ requires 311.0888, found 311.0884.

10{***2,5***}**.** 15 mg, 100%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.85 (6H, d, $J = 1.5$ Hz), 2.05 (H, m), 3.73 (2H d, $J = 2$ Hz), 3.89 (3H, s), 4.51 (2H s), 7.38 (H, td, $J = 0.5$, 2 Hz), 7.46 (2H d, $J = 2$ Hz), 7.49 (2H d, $J = 2$ Hz), 7.64 (H, td, $J = 0.5$, 2 Hz), 7.81 (H, dd, $J = 0.5$, 2 Hz), 7.98 (H, d, $J = 2$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 19.47 (2C), 28.95, 36.06, 51.93, 52.14, 121.25, 126.07, 126.37, 126.54, 129.21 (2C), 129.42, 129.88 (2C), 133.55, 141.71, 142.06, 156.44, 166.69. HPLC (254 nm): $t_R = 6.50$ min (100%). LC/MS (ESI): $t_R = 3.76$ min (*m*/*z* 418.4, M^+). HRMS: $C_{20}H_{22}N_2O_4S_2$, MH^+ requires 419.1099, found 419.1100.

10{***2,6***}**.** 13.6 mg, 90%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.87 (6H, d, $J = 1.5$ Hz), 2.08 (H, m), 3.74 (2H d, $J = 2$ Hz), 3.76 (6H, s), 4.43 (2H s), 6.37 (H, t, $J = 1.3$ Hz), 6.56 (2H d, 0.5 Hz), 7.37 (H, td, $J = 0.5$, 2 Hz), 7.49 (H, d, $J = 2$ Hz), 7.64 (H, td, $J = 0.5$, 2 Hz), 7.81 (H, dd, $J = 0.5$, 2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 19.67 (2C), 28.89, 36.91, 51.86, 55.33 (2C), 99.70, 107.20 (2C), 121.23, 125.92, 126.39, 126.59, 133.49, 138.14, 142.20, 157.07, 160.89 (2C). HPLC (254 nm): $t_R = 6.58$ min (100%). LC/MS (ESI): $t_R = 3.78$ min (*m*/*z* 420.4, M^+). HRMS: $C_{20}H_{24}N_2O_4S_2$, MH^+ requires 421.1256, found 421.1257.

10{***2,7***}**.** 12.8 mg, 93%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.92 (6H, d, J = 1.5 Hz), 1.44 (9H, s), 2.20 (H, m), 3.78 (2H d, J = 2 Hz), 3.89 (2H s), 7.36 (H, td, J = 0.5, 1.5 Hz), 7.40 (H, d, J = 2 Hz), 7.61 (H, td, J = 0.5, 1.5 Hz), 7.80 (H, dd, J = 0.5, 2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 19.71 (2C), 27.93 (3C), 28.89, 35.34, 52.09, 82.35, 121.20, 126.03, 126.22, 126.65, 133.45, 141.96, 156.17, 167.03. HPLC (254 nm): t_R = 6.37 min (100%). LC/MS (ESI): t_R = 3.59 min (*m*/*z* 384.4, M^+). HRMS: $C_{17}H_{24}N_2O_4S_2$, MH^+ requires 385.1256, found 385.1266.

10{***2,8***}**.** 13 mg, 93%; colorless oil; HPLC (254 nm): t_R = 7.28 min (100%); LC/MS (ESI): t_R = 4.13 min (*m*/*z* 388.4, M^+).

10{***2,9***}**.** 10 mg, 90%; colorless oil; HPLC (254 nm): t_R = 5.35 min (100%); LC/MS (ESI): t_R = 3.08 min (*m*/*z* 309.4, M^+).

10{***2,10***}**.** 13.3 mg, 90%; colorless oil; HPLC (254 nm): t_R = 7.20 min (100%); LC/MS (ESI): t_R = 4.13 min (*m*/*z* 410.4, M^+).

10{***2,11***}**.** 13.3 mg, 91%; yellow oil; HPLC (254 nm): t_R = 6.49 min (100%); LC/MS (ESI): t_R = 3.72 min (*m*/*z* 405.4, M^+).

10{***3,1***}**.** 7.8 mg, 88%; white solid; HPLC (254 nm): t_R = 3.71 min (98%); LC/MS (ESI): t_R = 2.83 min (*m*/*z* 247.3, M^+).

10{***3,2***}**.** 10.9 mg, 98%; white solid; HPLC (254 nm): t_R = 4.73 min (100%); LC/MS (ESI): t_R = 3.19 min (*m*/*z* 309.3, M^+).

10{***3,3***}**.** 9.4 mg, 90%; white solid; HPLC (254 nm): t_R = 3.54 min (100%); LC/MS (ESI): t_R = 2.65 min (*m*/*z* 291.3, M^+).

10{***3,4***}**.** 8.4 mg, 90%; white solid; HPLC (254 nm): t_R = 4.02 min (100%); LC/MS (ESI): t_R = 2.87 min (*m*/*z* 259.3, M^+).

10{***3,5***}**.** 12.5 mg, 95%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.37 (6H, d, J = 1.5 Hz), 3.89 (3H, s), 4.42 (H, m), 4.61 (2H s), 7.47 (7H, m), 7.97 (2H d, J = 2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 21.32 (2C), 37.64, 48.92, 52.13, 127.53, 128.79 (2C), 129.24 (2C), 129.43 (2C), 129.46, 129.91 (2C), 130.17, 141.98, 149.35, 155.90, 166.72. HPLC (254 nm): t_R = 4.68 min (100%). LC/MS (ESI): t_R = 3.14 min (*m*/*z* 367.3, M^+). HRMS: $C_{20}H_{21}N_3O_2S$, MH^+ requires 368.1433, found 368.1432.

10{***3,6***}**.** 12.3 mg, 93%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.38 (6H, d, J = 1.5 Hz), 3.76 (6H, s), 4.43 (H, m), 4.51 (2H s), 6.37 (H, t, J = 0.5 Hz), 6.53 (2H d, J = 0.5 Hz), 7.48 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$): 21.34 (2C), 38.70, 48.97, 55.39 (2C), 100.01, 107.03 (2C), 127.32, 128.77 (2C), 129.48 (2C), 130.11, 138.61, 149.87, 155.76, 160.90 (2C). HPLC (254 nm): t_R = 4.75 min (100%). LC/MS (ESI): t_R = 3.16 min (*m*/*z* 369.3, M^+). HRMS: $C_{20}H_{23}N_3O_2S$, MH^+ requires 370.1589, found 370.1588.

10{***3,7***}**.** 10.7 mg, 89%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.47 (9H, s), 1.51 (6H, d, J = 1.5 Hz), 4.15 (2H s), 4.51 (H, s), 7.48 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$): 21.34 (2C), 27.96 (3C), 36.46, 48.92, 82.68, 127.56, 128.78 (2C), 129.44 (2C), 130.13, 149.12, 155.89, 167.43. HPLC (254 nm): t_R = 4.48 min (100%). LC/MS (ESI): t_R = 3.09 min (*m*/*z* 333.3, M^+). HRMS: $C_{17}H_{23}N_3O_2S$, MH^+ requires 334.1589, found 334.1595.

10{***3,8***}**.** 10.9 mg, 90%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.39 (6H, d, J = 1.5 Hz), 2.29 (6H, s), 4.44 (H, m), 4.52 (2H s), 6.91 (H, s), 7.01 (2H s), 7.49 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$): 21.19 (2C), 21.27 (2C), 38.35, 48.92, 127.01 (2C), 127.73, 128.76 (2C), 129.46, 129.47 (2C), 130.10, 135.95, 138.30 (2C), 150.24, 155.66. HPLC (254 nm): t_R = 5.31 min (100%). LC/MS (ESI): t_R = 3.46 min (*m*/*z* 337.3, M^+). HRMS: $C_{20}H_{23}N_3S$, MH^+ requires 338.1691, found 338.1688.

10{***3,9***}**.** 8 mg, 86%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.51 (6H, d, J = 1.5 Hz), 4.21 (2H s), 4.53 (H, m), 7.51 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$): 18.75, 21.70 (2C), 49.18, 115.61, 127.08, 128.93 (2C), 129.43 (2C), 130.45, 146.25, 156.76. HPLC (254 nm): t_R = 3.50 min (100%). LC/MS (ESI): t_R = 2.58 min (*m*/*z* 258.3, M^+). HRMS: $C_{13}H_{14}N_4S$, MH^+ requires 259.1017, found 259.1019.

10{***3,10***}**.** 9.7 mg, 75%; white solid; HPLC (254 nm): t_R = 5.40 min (98%); LC/MS (ESI): t_R = 3.46 min (*m*/*z* 359.3, M^+).

10{***3,11***}**.** 11.2 mg, 88%; colorless oil; HPLC (254 nm): t_R = 4.74 min (100%); LC/MS (ESI): t_R = 3.16 min (*m*/*z* 345.3, M^+).

10{***4,1***}**.** 7.2 mg, 81%; white solid; HPLC (254 nm): t_R = 6.14 min (100%); LC/MS (ESI): t_R = 3.67 min (*m*/*z* 248.9, M^+).

10{***4,2***}**.** 10.3 mg, 92%; colorless oil; HPLC (254 nm): t_R = 6.66 min (100%); LC/MS (ESI): t_R = 3.86 min (*m*/*z* 310.9, M^+).

10{***4,3***}**.** 9.2 mg, 87%; colorless oil; HPLC (254 nm): t_R = 5.02 min (100%); LC/MS (ESI): t_R = 3.32 min (*m*/*z* 292.9, M^+).

10{***4,4***}**.** 7.9 mg, 84%; yellow oil; HPLC (254 nm): t_R = 6.21 min (100%); LC/MS (ESI): t_R = 3.72 min (*m*/*z* 260.9, M^+).

10{***4,5***}**.** 13.2 mg, 100%; colorless oil; HPLC (254 nm): t_R = 6.43 min (100%); LC/MS (ESI): t_R = 3.75 min (*m*/*z* 368.9, M^+).

10{***4,6***}**.** 12.5 mg, 94%; colorless oil; HPLC (254 nm): t_R = 6.56 min (100%); LC/MS (ESI): t_R = 3.78 min (*m*/*z* 370.9, M^+).

10{***4,7***}**.** 10.6 mg, 88%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.46 (9H, s), 1.67 (6H, d, J = 1.5 Hz), 3.89 (2H s), 4.66 (H, brs), 7.33 (H, td, J = 0.5, 2 Hz), 7.45 (H, d, J = 2 Hz), 7.63 (H, td, J = 0.5, 2 Hz), 8.14 (H, dd, J = 0.5, 2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 19.46 (2C), 28.02 (3C), 36.05, 53.38, 82.15, 120.60, 125.68, 125.69, 126.60, 134.02, 146.68, 155.33, 162.03, 167.55. HPLC (254 nm): t_R = 6.09 min (100%). LC/MS (ESI): t_R = 3.70 min (*m*/*z* 334.9, M^+). HRMS: $C_{17}H_{22}N_2O_3S$, $(M - C_4H_9)H^+$ requires 279.0803, found 279.0800.

10{***4,8***}**.** 10.8 mg, 89%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.63 (6H, d, J = 1.5 Hz), 2.31 (6H, s), 4.44 (2H s), 4.66 (H, brs), 6.91 (H, s), 7.47 (2H s), 7.35 (H, td, J = 0.5, 2 Hz), 7.56 (H, d, J = 2 Hz), 7.67 (H, td, J = 0.5, 2 Hz), 8.16 (H, dd, J = 0.5, 2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 19.42 (2C), 21.23 (2C), 37.39, 52.87, 120.65, 125.53, 125.66, 126.59, 127.28 (2C), 129.34, 134.04, 135.71, 138.23 (2C), 146.92, 156.43, 162.15. HPLC (254 nm): t_R = 7.36 min (100%). LC/MS (ESI): t_R = 4.07 min (*m*/*z*

338.9, M^+); HRMS: $C_{20}H_{22}N_2OS$, MH^+ requires 339.1531, found 339.1532.

10{***4,9***}**.** 7.6 mg, 81%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.68 (6H, d, $J = 1.5$ Hz), 4.06 (2H s), 4.48 (H, br), 7.40 (H, td, $J = 0.5$, 2 Hz), 7.58 (H, d, 2 Hz), 7.69 (H, td, $J = 0.5$, 2 Hz), 8.17 (H, dd, $J = 0.5$, 2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 18.28, 19.54 (2C), 53.89, 116.03, 120.63, 126.05, 126.48, 126.70, 134.43, 146.26, 152.25, 161.79. HPLC (254 nm): $t_R = 4.88$ min (100%). LC/MS (ESI): $t_R = 3.29$ min (*m*/*z* 259.9, M^+). HRMS: $C_{13}H_{13}N_3OS$, MH^+ requires 260.0858, found 260.0856.

10{***4,10***}**.** 10.7 mg, 83%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.64 (6H, d, $J = 1.5$ Hz), 4.67 (3H, br s), 7.35 (H, td, $J = 0.5$, 2 Hz), 7.46 (2H m), 7.57 (H, dd, $J = 0.5$, 2 Hz), 7.60 (H, d, $J = 2$ Hz), 7.68 (H, td, $J = 0.5$, 2 Hz), 7.81 (3H, m), 7.94 (H, s), 8.17 (H, dd, $J = 0.5$, 2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 19.43 (2C), 37.51, 53.41, 120.68, 125.61, 125.68, 126.06, 126.29, 126.63, 127.28, 127.69, 127.70, 128.36, 128.40, 132.72, 133.29, 133.70, 134.09, 146.88, 156.11, 162.15. HPLC (254 nm): $t_R = 7.43$ min (100%). LC/MS (ESI): $t_R = 4.05$ min (*m*/*z* 360.9, M^+). HRMS: $C_{22}H_{20}N_2OS$, MH^+ requires 361.1374, found 361.1373.

10{***4,11***}**.** 11.4 mg, 89%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.61 (6H, d, $J = 1.5$ Hz), 4.64 (H, brs), 4.88 (2H s), 7.35 (H, td, $J = 0.5$, 2 Hz), 7.41 (H, td, $J = 0.5$, 2 Hz), 7.55 (2H t, $J = 2$ Hz), 7.67 (H, td, $J = 0.5$, 2 Hz), 7.88 (H, dd, $J = 0.5$, 2 Hz), 8.03 (H, dd, $J = 0.5$, 2 Hz), 8.14 (H, dd, $J = 0.5$, 2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 19.40 (2C), 33.51, 53.41, 120.61, 125.10, 125.50, 125.73, 126.65, 128.55, 132.86, 133.29, 133.52, 134.14, 146.59, 148.61, 155.55, 162.05. HPLC (254 nm): $t_R = 6.41$ min (100%). LC/MS (ESI): $t_R = 3.78$ min (*m*/*z* 355.9, M^+). HRMS: $C_{18}H_{17}N_3O_3S$, MH^+ requires 356.1069, found 356.1068.

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Supporting Information Available. ^{1}H NMR and ^{13}C NMR spectra for 20 representative library members are reproduced. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Although in principle, slope detection can also be used to control the fraction collector, this method was found to be unreliable in this case.
(18) In principle, according to the flow-through paradigm we have exploited, compounds with high purities should also be associated with high isolated yields. Lower yields would be expected to correlate to products that were contaminated with unreacted alkylating agent, particularly for nonvolatile electrophiles. However, this was not observed in practice, and all purities were uniformly high. The lower yields are most likely to be attributable to nonoptimal sample collection in some cases, which arises as a consequence of using a generic set of parameters to trigger the fraction collector.
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