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RESEARCH ARTICLE

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Synthesis of Amino-Benzothiaoxazepine-1,1-dioxides Utilizing a Microwave-Assisted, S_NAr Protocol

Alan Rolfe,[†] Farman Ullah,[§] Thiwanka B. Samarakoon,[†] Ryan D. Kurtz,[†] Patrick Porubsky,[‡] Benjamin Neuenswander,[‡] Gerald H. Lushington,[†,‡] Conrad Santini,[‡] Michael G. Organ,[*,§] and Paul R. Hanson[*,†,‡]

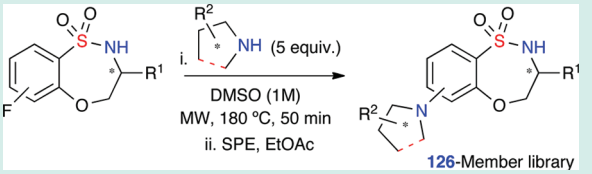
[†]Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045-7582, United States

[‡]The University of Kansas Center for Chemical Methodologies and Library Development (KU-CMLD), 2034 Becker Drive, Del Shankel Structural Biology Center, Lawrence, Kansas 66047, United States

[§]Department of Chemistry, York University, 4700 Keele Street, Toronto, ON, M3J 1P3, Canada

Supporting Information

ABSTRACT: The development of a microwave-assisted, intermolecular S_NAr protocol for the synthesis of a 126-member benzothiaoxazepine-1,1-dioxide library is reported. Diversification of 12 benzothiaoxazepine-1,1-dioxides was achieved in rapid fashion utilizing a variety of 2° amines and amino alcohols to generate an 80-member library. A second 48-member library was subsequently generated via a two-step alkylation, intermolecular S_NAr diversification protocol.



KEYWORDS: benzothiaoxazepine-1,1-dioxides, sultams, MACOS, S_NAr

INTRODUCTION

A key area of modern-day combinatorial science is the development and advancement of methodologies, protocols, and reaction platforms to enable the discovery of small-molecule probes to advance our understanding of chemical biology.[1] One aspect of this effort is the development of efficient methods to access collections of heterocycles for high-throughput screening (HTS). In this regard, the synthesis of core scaffolds on multigram scale, followed by efficient parallel diversification is one approach to generate diverse compound collections for HTS.

Sultams (cyclic sulfonamide analogues) have emerged as important targets in drug discovery due to their chemical and biological profiles.[2] Though not found in nature, sultams display activity across a wide variety of biological targets.[3,4] In particular, benzothiaoxazepine-1,1-dioxide-containing sultams, possessing a rich content of sp^3 amine functionality, have shown biological activity as antipsychotic agents,[5] modulators of histamine H3-recceptor,[6] and glucokinase activators (Figure 1).[7]

Despite these reports, methods to generate collections of benzofused sultams for HTS screening are limited.[8] In this regard, efforts have focused on the development of a variety of methodologies and protocols for the generation of diverse sultam collections.[9] These methodologies include the development of a variety of protocols namely, "Click-Click-Cyclize",[10] complementary ambiphile pairing (CAP),[11] and reagent-based diversity-oriented synthesis (DOS).[12] Building on these methods, we herein report the design and synthesis of a 126-member library of amino-benzothiaoxazepine-1,1-dioxides via a microwave-assisted, intermolecular S_NAr Diversification of core benzothiaoxazepine-1,1-dioxides scaffolds (Scheme 1).[13]

RESULTS AND DISCUSSION

The facilitated, scale-out synthesis of small molecules via microwave-assisted, continuous-flow organic synthesis (MACOS)[14] was previously reported for the generation of a number of core sultam scaffolds.[15] When this enabling technology is used, the generation of benzofused sultams via an intramolecular S_NAr cyclization was achieved on multigram scale.[15a] With this protocol in hand, we achieved the resynthesis of benzothiaoxazepine-1,1-dioxide scaffolds **1**−**12** possessing both functional and stereochemical diversity.

Initial investigation focused on the development and optimization of the corresponding intermolecular S_NAr reaction for the diversification of benzothiaoxazepine-1,1-dioxide **5** with amino alcohol {*8*}, chosen to probe chemoselectivity when utilizing amino alcohols (Table 1). We screened a variety of bases using 3 equiv of amino alcohol {*8*}, along with a control reaction without base (Table 1, entries, 1−4).[13b] It was observed that after heating under microwave irradiation at 150 °C for 30 min a 56% yield could be achieved when no base was present. Additional optimization of solvent (DMF, THF, DMSO), equivalents of {*8*}, temperature, and reaction time (Table 1, entries 6−9) revealed that 5 equivalents of amino alcohol {*8*} heated at 150 °C for 50 min provided the desired sultam **5**{*8*} now in 90% yield. It is of note that when only 1 equiv of {*8*} was used under optimized conditions, only a 40% yield was achieved. Further, it was found

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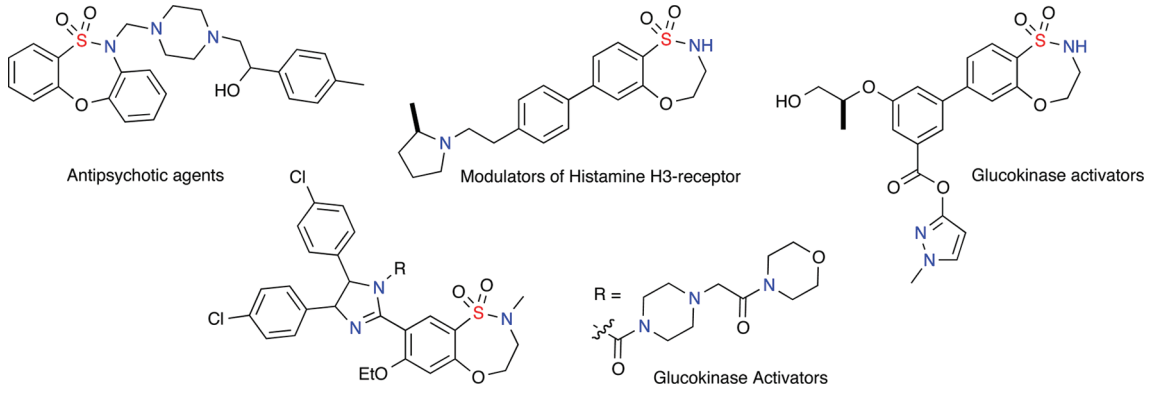
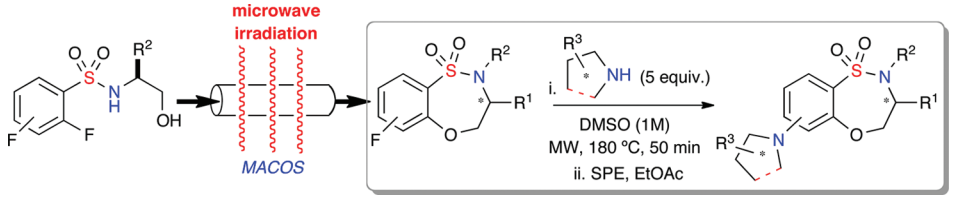


Figure 1. Biologically active benzothiaoxazepine-1,1-dioxide-containing sultams.

Scheme 1. Proposed Library Generation via Microwave-Assisted S_NAr Diversification to Access Benzofused Sultam Library



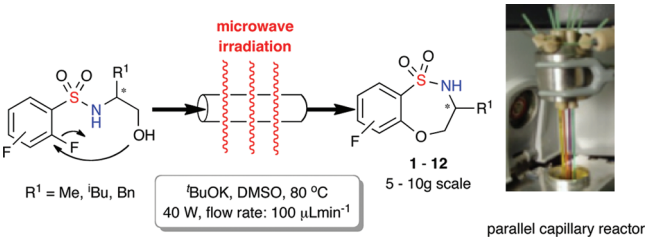
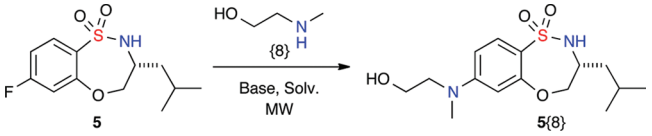


Figure 2. Synthesis of benzothiaoxazepine-1,1-dioxides **1**−**12** via MACOS scale-out.

that DBU (10 mol %) not only increased the yield to 95%, but also resulted in greater reproducibility (Table 1, entry 11).

Library Design. A 144-member, *full-matrix* library was designed using in silico analysis, literature precedence, and observed synthetic results.[16] Twelve benzothiaoxazepine-1,1-dioxide scaffolds **1**−**12** were designed, composed of two sets of enantiomers at R^1 thereby maintaining the ability to generate stereochemical SAR (SSAR) for each building block combination. Each set of enantiomers were varied at R^1 = Me, ^{i}Bu, or Ph with fluorine substitution on the benzofused ring at either 4- or 6-position. With the S_NAr derived core sultams in hand, a virtual library incorporating all possible building block combinations of 2° amine was constructed for each scaffold (Figure 3). Physicochemical property filters were applied, guiding the elimination of undesirable building blocks that led to products with undesirable in-silico properties.[17] These metric filters included standard Lipinski Rule of 5 parameters (molecular weight <500, ClogP <5.0, number of H-acceptors <10, and number of H-donors <5), in addition to consideration of the number of rotatable bonds (<5) and polar surface area. Absorption, distribution, metabolism and excretion (ADME) properties were calculated along with diversity analysis using standard H-aware 3D BCUT descriptors

Table 1. Optimization of Microwave-Assisted, S_NAr Reaction Conditions Utilizing Sultam E



entry	{8} (equiv)	base (equiv)	solv.	temp (°C)	time (min)	yield (%)[a]
1	3	Cs_2CO_3 (3)	DMF	150	30	20
2	3	NaO*t*Bu (3)	DMF	150	30	46
3	3	LiHMDS (3)	DMF	150	30	42
4	3	Et_3N (3)	DMF	150	30	47
5	3		DMF	150	30	56
6	5		DMF	150	30	68
7	5		THF	150	30	48
8	5		DMSO	150	30	86
9	5		DMSO	180	50	90
10	1		DMSO	180	50	40
11	5	DBU (1)	DMSO	180	50	94
12	5	DBU (0.1)	DMSO	180	50	95

[a] Yields are reported after flash column chromatography on silica gel.

comparing against the MLSMR screening set (~7/2010; ~330 000 unique chemical structures). Guided by this library design analysis, benzothiaoxazepine-1,1-dioxides (**1**−**36**) and amines {*1*−*9*} were chosen to generate the aforementioned 144-member library.

Validation and Library Generation. With these optimized conditions in hand, a 12-member validation library was prepared (General Procedure A) in 1 dram vials using the Anton Parr Synthos 3000 platform.[18] Upon completion, the crude reaction

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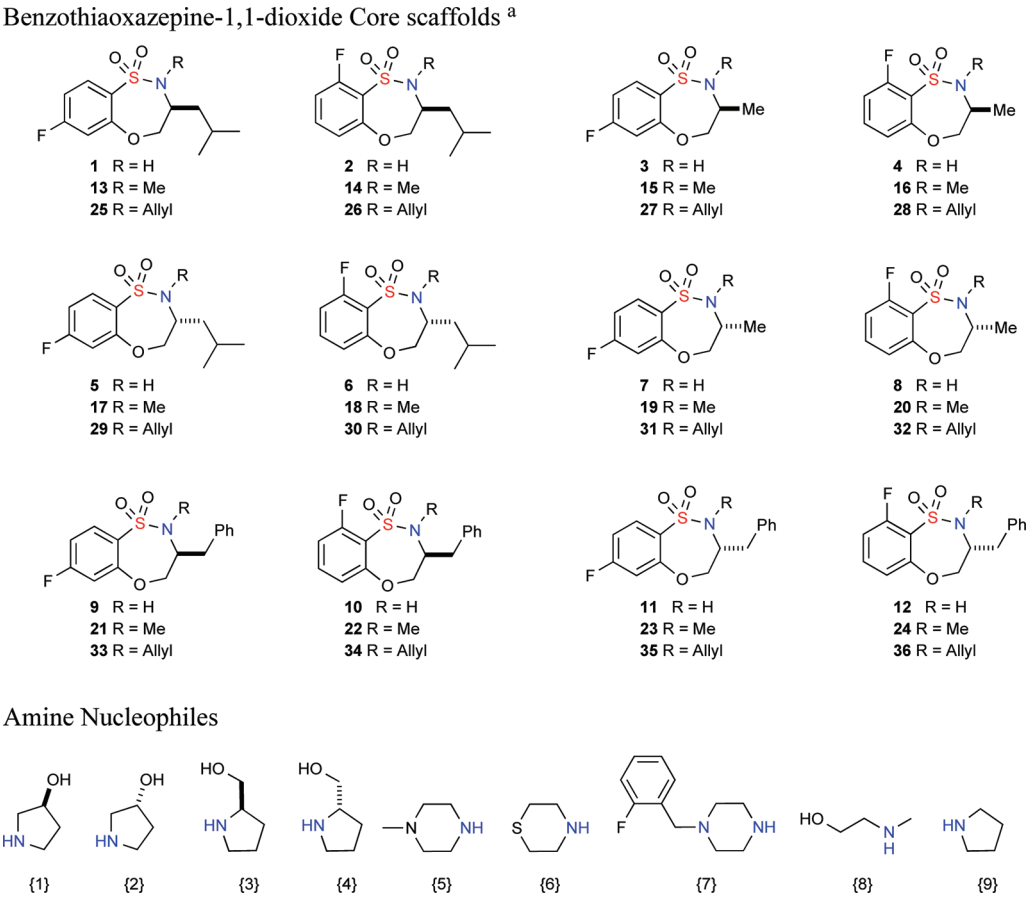
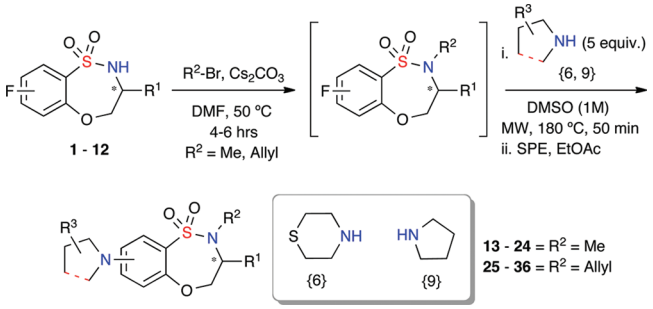


Figure 3. Benzothiaoxazepine-1,1-dioxides (**1**−**36**) and amines {*1*−*9*} library building blocks. (a) Benzothiaoxazepine-1,1-dioxide scaffolds **13**−**14** and **24**−**36**.

Table 2. 12-Member Validation Library Probing Reaction Scope



sultam[a]	purity (%)[b]	yield (%)[b]	quantity (mg)	sultam[a]	purity (%)[b]	yield (%)[b]	quantity(mg)
5{*2*}	83	45	69.0	**6**{*4*}	93	32	49.0
5{*4*}	97	51	77.6	**6**{*5*}	97	47	71.9
5{*5*}	99	30	42.5	**6**{*6*}	98	62	94.9
5{*6*}	97	44	66.9	**6**{*8*}	93	37	54.3
5{*7*}	74	36	69.0	**21**{*6*}	96	51	90.3
5{*8*}	91	51	71.5	**33**{*6*}	94	50	93.2

[a] Reaction conditions: Benzothiaoxazepine-1,1-dioxide **1**−**12** (1 equiv, 0.434 mmol), dry DMSO (434 μL, 1M), DBU (7 μL, 10 mol %), and amine (5 equiv.). [b] Purified by automated preparative reverse phase HPLC (detected by mass spectroscopy); purity was assessed by HPLC.

mixtures were diluted, filtered through silica SPE, and purified by automated mass-directed LCMS (Table 2). Library validation was essential to assess both substrate and reaction scope, along with evaluating the application of automated mass-directed LCMS as the final analysis and purification method. Key to successful library production was the synthesis of compounds in

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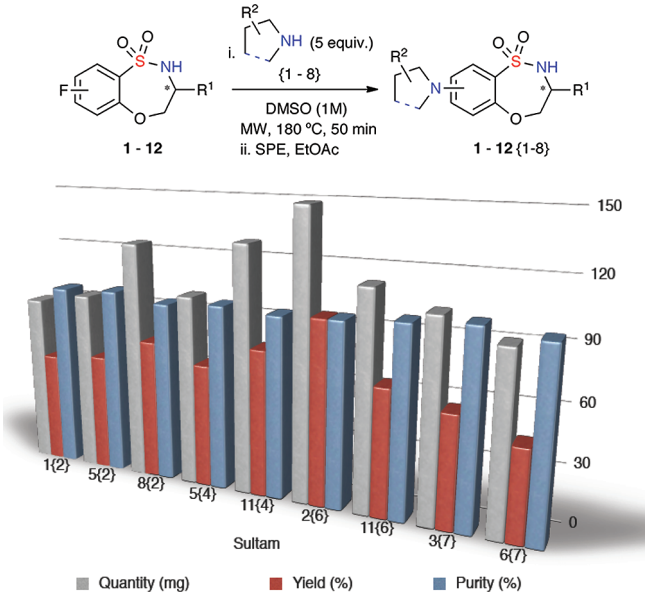
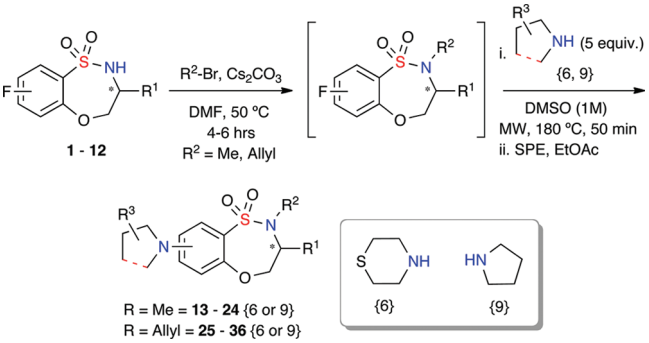
Chart 1. Library I: Representative Library Members Demonstrating Final Quantity, Purity, and Overall Yield



Scheme 2. Synthesis of Library II Utilizing a Two-Step Alkylation-S_NAr Protocol

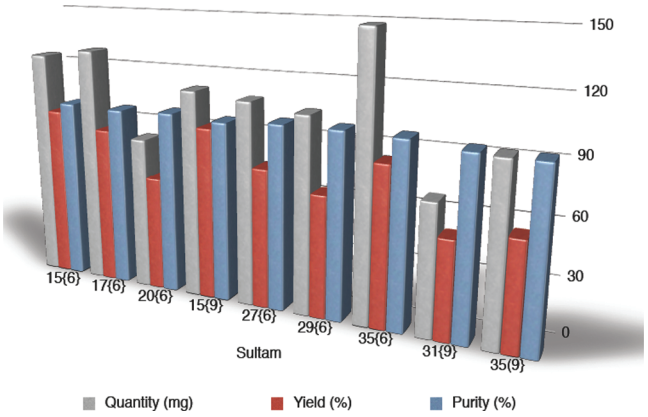


>90% purity in 40−50 mg quantities, which would be sufficient for HTS screening via the Molecular Library Probe Center Network (MLPCN) (20 mg), external biological outreach screening partners (20 mg), and to retain a sample (10 mg) for follow-up evaluation or to resupply the NIH MLPCN. Evaluation of this validation library demonstrated that all 12 members where successfully prepared (average purity = 92%, yield = 45%, quantity = 71 mg) in the desired sultams final masses, with 10/12 possessing a final purity >90%.

With the validation complete, a 96-membered library (library **I**) was proposed for the diversification of core benzothiaoxazepine-1,1-dioxide scaffolds **1**−**12** with amines {*1*−*9*}. Implementing the optimized S_NAr reaction conditions, Library **I** (96-member) was generated and purified by automated mass-directed LCMS. A total of 80 compounds were prepared, with amine enantiomers {*1*} and {*2*} excluded due to decomposition under reaction conditions; all products were isolated in good overall yield and quantity, with 78 compounds possessing a final purity >90% after automated purification (Chart 1).[19]

Upon completion of library **I** (80-member), a second 48-member compound set (library **II**) was investigated implementing

Chart 2. Library II: Representative Library Members Demonstrating Final Mass, Purity, and Overall Yield



a two-step alkylation-S_NAr procedure (General procedure B). Hence, benzothiaoxazepine-1,1-dioxides **1**−**12** were methylated (**13**−**24**) or allylated (**25**−**36**), concentrated, and submitted to the aforementioned microwave-assisted S_NAr diversification with amines {*6* and *9*} (Scheme 2). A total of 46 compounds from the proposed 48-membered library where prepared with 43 of the 48 possible products having a final purity >90% after automated purification (Chart 2).[19]

Final assessment of libraries I and II demonstrated that the primary objectives set out in the library design were achieved; final masses ranged between 8−158 mg and the average final mass was 68 mg (original target being 50 mg).

CONCLUSION

In conclusion, an efficient microwave-assisted intermolecular-S_NAr protocol for the synthesis of a 126-member collection (libraries **I** and **II**) of amino-benzothiaoxazepine-1,1-dioxides has been developed. Employing a variety of commercially available amines, a 126-member library was generated via the microwave assisted-S_NAr diversification at the 4-F and 6-F positions. These compounds have been submitted for evaluation of their biological activity in high-throughput screening assays at the NIH MLPCN and the results will be reported in due course.

EXPERIMENTAL PROCEDURES

General Procedure A: Microwave-Assisted Diversification of Benzothiaoxazepine-1,1-dioxides 1−12 Cores. Into a 1-dram vial was added benzothiaoxazepine-1,1-dioxide **1**−**12** (1 equiv, 0.43 mmol), dry DMSO (0.43 mL, 1M), DBU (7 μL, 10 mol %), and the corresponding amine (5 equiv). The reaction vessel was capped, placed in Anton Paar Synthos 3000 microwave and heated at 180 °C for 50 min [power =1200 W, 8 min ramp then 50 min hold]. After it was cooled to RT, the crude reaction mixture was diluted with EtOAc, filtered through a SiO_2 SPE and concentrated. The crude product was QC/purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy).

General Procedure B: 2-Step Alkylation-S_NAr Diversification of Benzothiaoxazepine-1,1-dioxides 13−24 and 25−36 Cores. Into a round-bottom flask, under Ar, was added benzothiaoxazepine-1,1-dioxide **1**−**12** (1 equiv.), Cs_2CO_3 (3 equiv.), dry DMF (0.5 M) and alkyl bromide (2 equiv.). The reaction was heated at

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50 °C and stirred for 4−6 h (TLC monitoring), after which time the reaction was cooled to RT, filtered through a SiO_2 SPE, washed with EtOAc and concentrated to remove solvent and excess alkylating reagent. To the crude reaction mixture was added dry DMSO (0.43 mL, 1M), DBU (7 μL, 10 mol %) and the corresponding amine (5 equiv.). The reaction vessel was capped, placed in Anton Paar Synthos 3000 microwave and heated at 180 °C for 50 min [power =1200 W, 8 min ramp then 50 min hold]. After it was cooled to room temperature the reaction was diluted in EtOAc, filtered through a SiO_2 SPE and concentrated. The crude reaction mixture was QC/purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy).

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, tabulated results for all libraries, and full characterization data for representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: phanson@ku.edu (P.K.H) and organ@yorku.ca(M.G.O.).

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(19) Representative compounds with full numeric data for each compound provided in Supporting Information.