ACS Combinatorial Science

RESEARCH ARTICLE

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Automated Synthesis of a 184-Member Library of Thiadiazepan-1, 1-dioxide-4-ones

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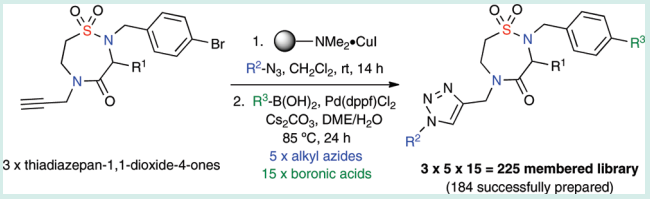
Supporting Information

ABSTRACT: The construction of a 225-member (3 × 5 × 15) library of thiadiazepan-1,1-dioxide-4-ones was performed on a Chemspeed Accelerator (SLT-100) automated parallel synthesis platform, culminating in the successful preparation of 184/225 sultams. Three sultam core scaffolds were prepared based upon the utilization of an aza-Michael reaction on a multifunctional vinyl sulfonamide linchpin. The library exploits peripheral diversity in the form of a sequential, two-step [3 + 2] Huisgen cycloaddition/Pd-catalyzed Suzuki−Miyaura coupling sequence.



KEYWORDS: thiadiazepan-1,1-dioxide-4-ones, parallel synthesis platform, aza-Michael reaction, Huisgen cycloaddition, Suzuki−Miyaura coupling

INTRODUCTION

Diversity-oriented synthesis (DOS) has emerged as a powerful strategy to produce large libraries of biologically relevant small-molecules for high throughput screening.[1,2] Various strategies in this area hinge on the ability to generate diverse collections of molecules in the fewest number of steps possible.[3] Among these, functional group pairing (FG-pairing) is a key concept that is at the heart of the "Build/Couple/Pair (BCP)" strategy pioneered by Schreiber and co-workers[4] and continues to be the impetus for DOS-based library efforts. Previously, the inherent chemistry of vinyl sulfonamides was employed in a "*Click, Click, Cyclize*" strategy for the facile construction of skeletally diverse sultam scaffolds via synthetic operations on a single sulfonamide-based linchpin as outlined in Figure 1.[5] In particular, thiadiazepan-1,1-dioxide-4-one scaffolds represent an under explored chemotype that was easy to access with the aforementioned strategy. We herein report the production of a 184-member library[6] using an automated sequential alkyl azide cycloaddition/Suzuki-Miyaura coupling sequence on three core thiadiazepan-1,1-dioxide-4-one scaffolds which were constructed using an aza-Michael variant of the "*Click, Click, Cyclize*" method.

Sulfonamides have long been valued for their rich biological and chemical profiles rendering them a promising class of compounds in drug discovery.[7] Cyclic sulfonamides (sultams), while not found in nature, exhibit a wide-array of potent biological activities[8] that has inspired the present study aimed at mining underrepresented chemical space of the titled peptidomimetic chemotype[9] in hopes of identifying new bioactive probes.

RESULTS AND DISCUSSION

Efforts toward the construction of the key thiadiazepan-1,1-dioxide-4-one scaffolds are outlined in Scheme 1. We envisioned utilizing two functional group handles in regions **A**/**B** on sultam scaffolds **5**{*1*−*3*} for the attachment of diverse appendages. The Huisgen [3 + 2] cycloaddition[10] and Suzuki−Miyaura coupling reactions[11] were chosen based upon their well-precedented efficiency[12] and use in library development.[13] The introduction of an alkyne group in quadrant **A** allows for facile diversification via the well-known Huisgen [3 + 2] cycloaddition, while installation of a bromophenyl group into quadrant **B** provides the necessary functionality for various Pd-catalyzed cross-couplings, such as the Suzuki−Miyaura reaction.

Each of the three sultam scaffolds **5**{*1*−*3*} were efficiently accessed using a FG-pairing strategy previously reported,[3b,5c] in which L-alanine/valine/leucine methyl ester hydrochlorides underwent sulfonylation to generate vinyl sulfonamides **2**{*1*−*3*}. Subsequent alkylation of sulfonamides **2**{*1*−*3*}, followed by aza-Michael addition of propargyl amine, yielded the desired tertiary sulfonamides **4**{*1*−*3*}. Initially, the direct intermolecular lactamization from sulfonamides **4** was investigated as a one-step route to **5**. However, despite similar intramolecular transformations in the literature,[9,14] little success was achieved. Efforts were next directed to a two-step hydrolysis/lactamization[15] sequence

Received: November 9, 2010
Revised: January 11, 2011
Published: February 10, 2011

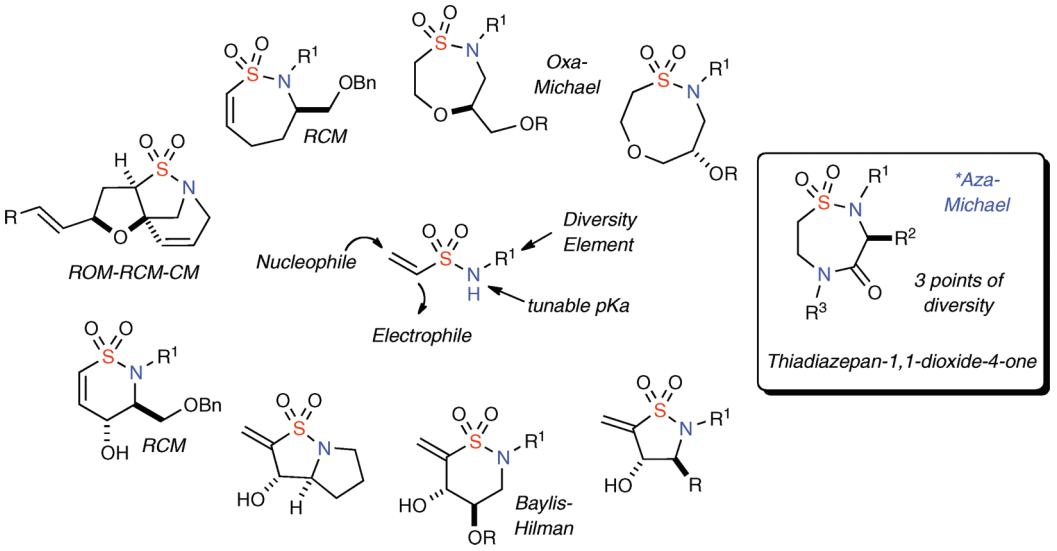
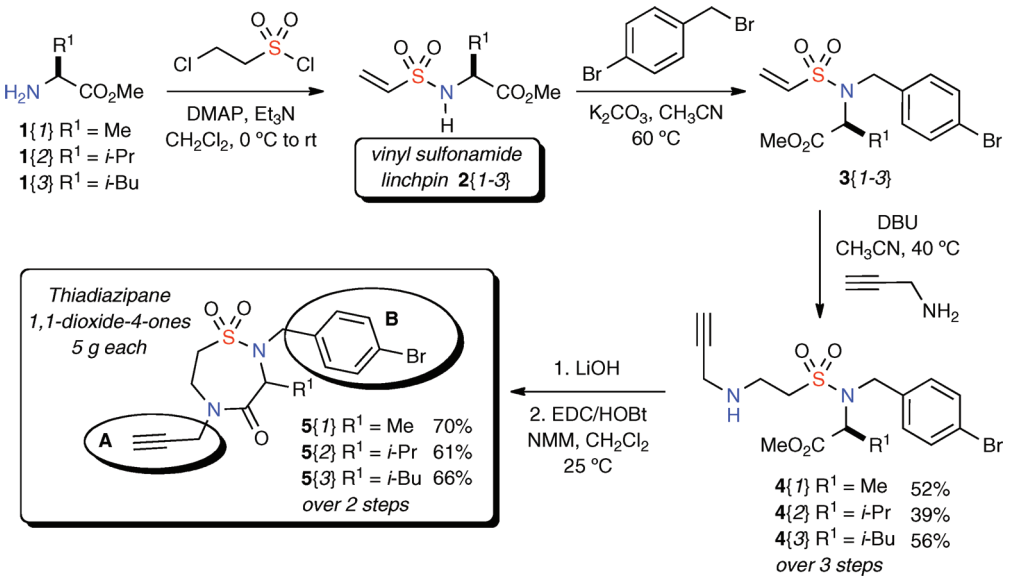


Figure 1. Use of a versatile vinyl sulfonamide linchpin to access skeletally diverse sultams.

Scheme 1. Synthesis of Substituted Thiadiazepan-1,1-dioxide-4-one Scaffolds 5{*1*−*3*}



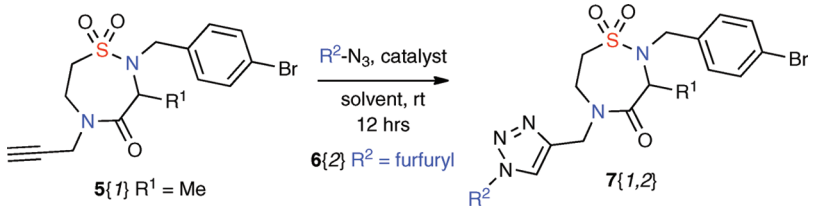
to produce scaffolds **5**{*1*−*3*} in good overall yields on multigram scale.[16,17]

With the desired scaffolds **5**{*1*−*3*} in hand, we next investigated the validation of the proposed library via diversification of regions **A** and **B**. The logical starting point relied on the noted selectivity and compatibility of the azide/alkyne [3 + 2] cycloaddition for its use in region **A**. In this regard, conditions employing Cu(I) catalysis (Table 1, entry 1) were initially explored and found to be high-yielding but unfortunately afforded an undesirable mixture of regioisomers. The use of Cu(II) catalysts in *t*-BuOH/H_2O, however, saw complete regioselectivity but suffered from poorer yields (Table 1, entry 2) attributed to poor substrate solubility. Additional optimization was achieved with the use of CH_2Cl_2 (Table 1, entry 3) or acetone (Table 1, entry 4) as cosolvents, which resulted in near quantitative yields. Use of lower catalyst/additive loadings was also explored to simplify library purification (Table 1, entries 4−6). Though catalyst loadings could be reduced to as low as 10 mol % without risking a substantial loss in yield, it was envisioned that an immobilized source of copper would be more amenable to parallel library synthesis. The use of copper immobilized on Amberlyst (A-21·CuI)[18] at 20 mol % in CH_2Cl_2, was found to afford the triazole-containing sultams 7{*1*,*2*} in excellent yield (Table 1, entry 7).

We began investigations into the Suzuki−Miyaura coupling reaction using Pd(dppf)Cl_2 and Cs_2CO_3 in DMF/H_2O (Table 2, entries 1−4). Near quantitative yields could be achieved with a catalyst loading of 5 mol % using relatively high temperatures and prolonged reaction times (Table 2, entry 4). However, these conditions resulted in difficult emulsions during the aqueous workups, a situation that renders the reaction impractical in a parallel platform. This problem was attributed to the choice of base/solvent combination utilized, and a number of alternative conditions were next explored (Table 2, entries 5−13). Ultimately, the combinations of Cs_2CO_3 in DME/H_2O provided the

dx.doi.org/10.1021/co100060x |*ACS Comb. Sci.* 2011, 13, 244–250

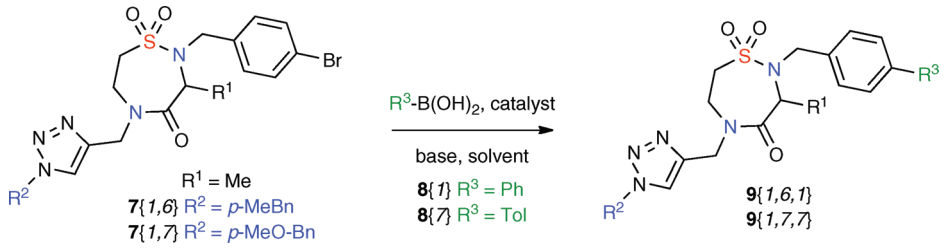
Table 1. Validation of Huisgen [3 + 2] Cycloaddition



entry	catalyst	loading (mol %)	additive	equiv	solvent	yield (%)
1	CuI	10	2,6-lutidine	1.2	$CHCl_3$	88[a]
2	$CuSO_4 \cdot 6H_2O$	10	Na ascorbate	0.1	*t*-BuOH/H_2O 1:2	45
3	$CuSO_4 \cdot 6H_2O$	20	Na ascorbate	0.3	*t*-BuOH/H_2O/CH_2Cl_2 1:1:1	97
4	$CuSO_4 \cdot 6H_2O$	20	Na ascorbate	0.3	*t*-BuOH/H_2O/acetone 3:4:1	96
5	$CuSO_4 \cdot 6H_2O$	10	Na ascorbate	0.2	*t*-BuOH/H_2O/acetone 3:4:1	95
6	$CuSO_4 \cdot 6H_2O$	5	Na ascorbate	0.1	*t*-BuOH/H_2O/acetone 3:4:1	78
7	A-21·CuI	20	none		CH_2Cl_2	90

[a] Resulted in a mixture of 1,4- and 1,5-regioisomers in 4:1 ratio.

Table 2. Validation of the Suzuki−Miyaura Coupling Reaction



entry	R^2	R^3	catalyst	loading (mol %)	base	solvent	temp (°C)	time (h)	yield (%)
1	*p*-Me-Bn	phenyl	$Pd(dppf)Cl_2$	1	Cs_2CO_3	DMF/H_2O	70	8	46
2	*p*-Me-Bn	phenyl	$Pd(dppf)Cl_2$	5	Cs_2CO_3	DMF/H_2O	70	8	51
3	*p*-Me-Bn	phenyl	$Pd(dppf)Cl_2$	10	Cs_2CO_3	DMF/H_2O	70	8	68
4	*p*-Me-Bn	phenyl	$Pd(dppf)Cl_2$	5	Cs_2CO_3	DMF/H_2O	85	24	98
5	*p*-MeO-Bn	*p*-tolyl	$Pd(dppf)Cl_2$	10	Cs_2CO_3	DMF/H_2O	70	14	85
6	*p*-MeO-Bn	*p*-tolyl	$Pd(dppf)Cl_2$	10	Na_2CO_3	DMF/H_2O	70	14	10
7	*p*-MeO-Bn	*p*-tolyl	$Pd(dppf)Cl_2$	10	K_3PO_4	DMF/H_2O	85	16	92
8	*p*-MeO-Bn	*p*-tolyl	$Pd(dppf)Cl_2$	10	K_3PO_4	dioxane/H_2O	90	16	90
9	*p*-MeO-Bn	*p*-tolyl	$Pd(dppf)Cl_2$	10	Cs_2CO_3	dioxane/H_2O	75	14	62
10	*p*-MeO-Bn	*p*-tolyl	$Pd(dppf)Cl_2$	10	Cs_2CO_3	dioxane/H_2O	90	16	94
11	*p*-MeO-Bn	*p*-tolyl	$Pd(dppf)Cl_2$	10	Cs_2CO_3	DME/H_2O	85	16	89
12	*p*-MeO-Bn	*p*-tolyl	$Pd(PPh_3)_4$	10	Cs_2CO_3	DME/H_2O	70	14	<5
13	*p*-MeO-Bn	*p*-tolyl	$Pd(PPh_3)_4$	10	CsF	DME/H_2O	80	14	61

most convenient workup while retaining high yields (Table 2, entry 11).[19]

On the basis of the optimal conditions chosen for both reactions, studies turned toward combining the two reactions into a single-step sequence for ease of use in parallel synthesis (Scheme 2). Sultam **5**{*1*} was first reacted for 14 h with excess *p*-methoxybenzyl azide **6**{*3*} in the presence of A-21·CuI, followed by filtration of the catalyst and concentration to yield crude, triazole-containing sultam **7**{*1,3*}.[20] Sultam **7**{*1,3*} was carried forward to the coupling event without further purification, upon which was sequentially added, DME, solid $Pd(dppf)Cl_2$, Cs_2CO_3 in H_2O, and excess boronic acid **8**{*2*} before heating at 85 °C for 14 h. After which time, a basic workup was performed to remove excess boronic acid and Cs_2CO_3 from the reaction mixture, followed by liquid−liquid extraction using CH_2Cl_2. The resulting solution was filtered via Si-SPE to remove residual Pd(0) and concentrated under reduced pressure to afford sultam **9**{*1,3,2*} in excellent yield over the combined two-step sequence. Overall, this sequence proved relevant in the transfer of chemistries to parallel methods in which both workup and purification were minimized.

The combined sequence was next attempted as a rehearsal 2 × 3 × 3 validation library using a Chemspeed Accelerator SLT-100 synthesizer[21] (Table 3). Azides **6**{*1*−*3*} were chosen as diverse representative members of the final library. A small substrate scope for the Suzuki−Miyaura coupling reaction was also explored with the choice of electron-deficient and electron-rich

dx.doi.org/10.1021/co100060x |*ACS Comb. Sci.* 2011, 13, 244–250

Scheme 2. Combined Two-Step Diversification Sequence

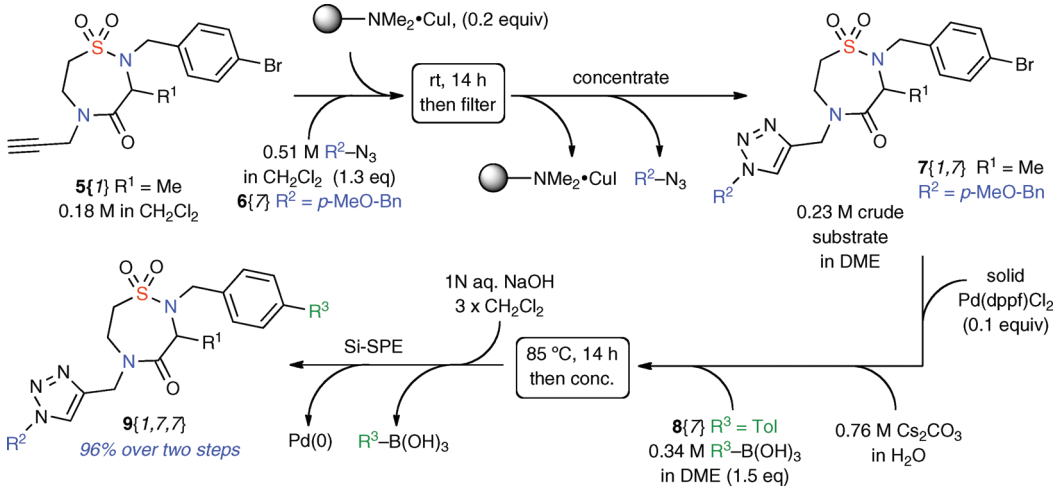
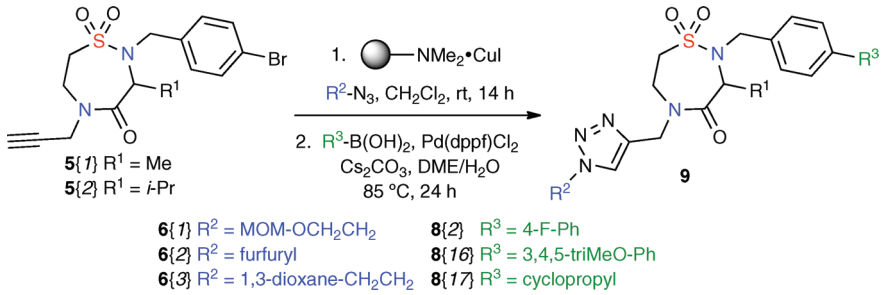


Table 3. Chemspeed Rehearsal 2 × 3 × 3 Library of Thiadiazepan-1,1-dioxide-4-ones



entry	sultam	azide	boronic acid	product	yield (%)[a]	purity (%)[b]
1	5{*1*}	6{*1*}	8{*2*}	9{*1,1,2*}	40	100
2	5{*1*}	6{*1*}	8{*16*}	9{*1,1,16*}	44	91
3	5{*1*}	6{*1*}	8{*17*}	9{*1,1,17*}	0	0
4	5{*1*}	6{*2*}	8{*2*}	9{*1,2,2*}	35	98
5	5{*1*}	6{*2*}	8{*16*}	9{*1,2,16*}	37	100
6	5{*1*}	6{*2*}	8{*17*}	9{*1,2,17*}	0	0
7	5{*1*}	6{*3*}	8{*2*}	9{*1,3,2*}	38	100
8	5{*1*}	6{*3*}	8{*16*}	9{*1,3,16*}	33	87
9	5{*1*}	6{*3*}	8{*17*}	9{*1,3,17*}	41	10
10	6{*1*}	6{*1*}	8{*2*}	9{*2,1,2*}	45	100
11	6{*1*}	6{*1*}	8{*16*}	9{*2,1,16*}	44	100
12	6{*1*}	6{*1*}	8{*17*}	9{*2,1,17*}	0	0
13	6{*1*}	6{*2*}	8{*2*}	9{*2,2,2*}	49	100
14	6{*1*}	6{*2*}	8{*16*}	9{*2,2,16*}	43	100
15	6{*1*}	6{*2*}	8{*17*}	9{*2,2,17*}	0	0
16	6{*1*}	6{*3*}	8{*2*}	9{*2,3,2*}	38	100
17	6{*1*}	6{*3*}	8{*16*}	9{*2,3,16*}	23	100
18	6{*1*}	6{*3*}	8{*17*}	9{*2,3,17*}	16	94

[a] Purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy). [b] Purity was determined by HPLC with peak area (UV) at 214 nm.

phenyl, and alkyl boronic acids **8**. Using the two-step sequence described above in the Chemspeed platform (0.150 mmol scale), the resulting 18 crude sultams **9** were subjected to preparative HPLC purification. In general, yields in the range of 16−49% were obtained with purities >87% (Figure 2). However, boronic acid **8**{*3*} (cyclopropyl), was significantly less reactive and resulted in either no yield or low yields as compared to both phenyl boronic acids in the sequence (Table 3, entries 3, 6, 9, 12,

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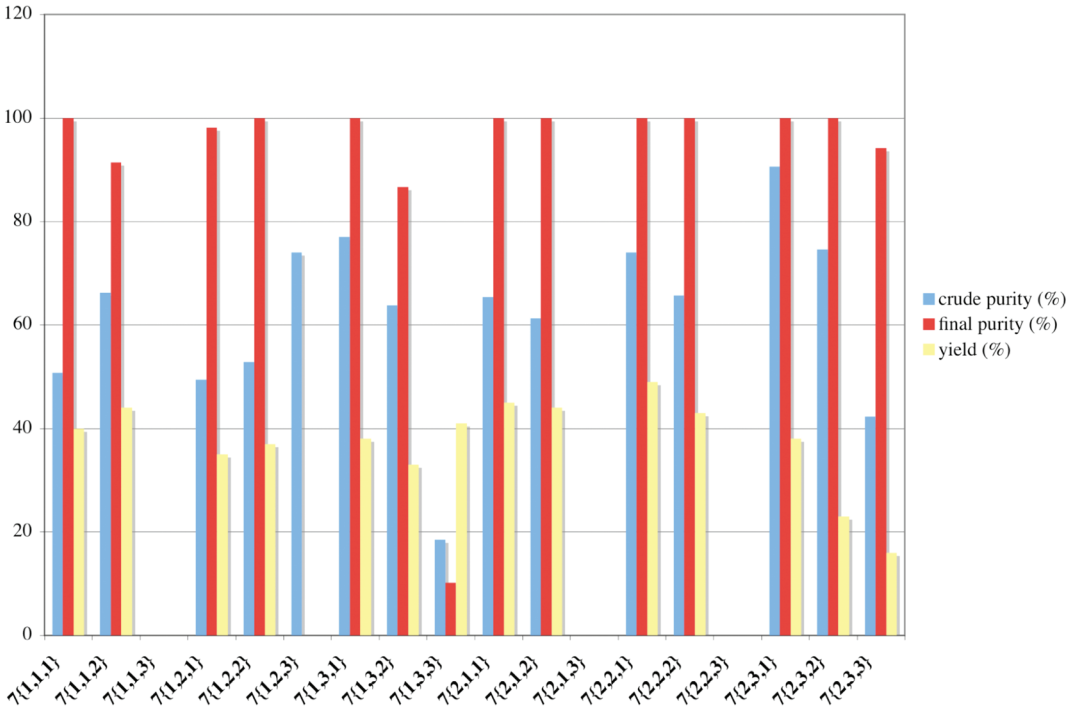
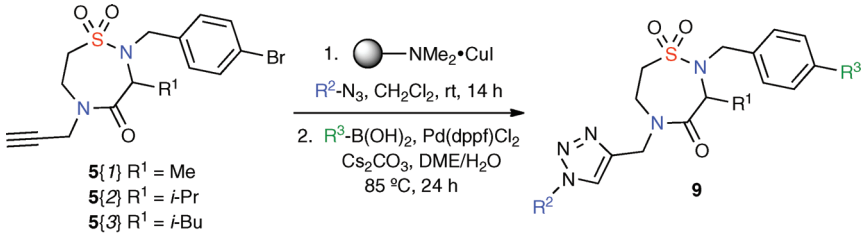


Figure 2. Crude purity, final purity, and yield from HPLC analysis of Chemspeed rehearsal 2 × 3 × 3 library of thiadiazepan-1,1-dioxide-4-ones.

Scheme 3. Building Blocks for the 3 × 5 × 15 Library of Thiadiazepan-1,1-dioxide-4-ones



6{*1*} R^2 = MOM-OCH_2CH_2
6{*2*} R^2 = furfuryl
6{*3*} R^2 = 1,3-dioxane-CH_2CH_2
6{*4*} R^2 = Cy-CH_2
6{*5*} R^2 = 1,3-dioxolane-CH_2CH_2

8{*1*} R^3 = Ph
8{*2*} R^3 = 4-F-Ph
8{*3*} R^3 = 4-Pyr
8{*4*} R^3 = 4-Cl-Ph
8{*5*} R^3 = 2-Thiophene
8{*6*} R^3 = 4-MeO-Ph
8{*7*} R^3 = 4-Me-Ph
8{*8*} R^3 = 3,4-diMeO-Ph

8{*9*} R^3 = 3-(NMe_2)-Ph
8{*10*} R^3 = 3,4-diCl-Ph
8{*11*} R^3 = $CH_3CH_2CH_2CHCH$
8{*12*} R^3 = 4-MeO-3-Pyr
8{*13*} R^3 = 4-F-3-Pyr
8{*14*} R^3 = 3-(CH_2OH)-Ph
8{*15*} R^3 = 4-Cl-3-Pyr

15, and 18). Overall, the results of the validation efforts demonstrated a successful two-step automated sequence.

With these results in hand, planning began for constructing the 225-member library using the Chemspeed platform with the conditions set in place during the rehearsal library. A number of azides and boronic acids were chosen (Scheme 3) based on differences in their structure and polarity. On the basis of the rehearsal library, alkyl boronic acids were excluded from the final library. Using the validated conditions, the Chemspeed was then programmed to run three consecutive 3 × 5 × 5 reactions (75 compounds each) for a total of 225 compounds.

Upon completion of the three 75-compound runs, a total of 225 reactions were purified via preparative/mass-directed HPLC in which 184 compounds were obtained with quantities ≥20 mg and with purity >90% starting from 0.150 mmol of sultams **5**{*1*−*3*}.[22] Further analysis of the data revealed no definitive trends in yields between substrates and reagents; however it was evident that thiophene boronic acid (R^3 = **5**) was the only reagent that yielded little or no material for the 15 reactions for which it was utilized.

In conclusion, we successfully completed the automated production of a 184/225-member library of thiadiazepan-1,1-dioxide-4-ones using a Chemspeed Accelerator platform in which a two-step diversification sequence was performed. The resulting compounds of this library are in the process of being distributed to a number of biological collaborators within the NIH Molecular Libraries Probe Center Network (MLPCN) and future efforts will focus on the production of targeted libraries of thiadiazepan-1,1-dioxide 4-ones and related chemotypes, as well as their anticipated biological evaluation.

dx.doi.org/10.1021/co100060x |*ACS Comb. Sci.* 2011, 13, 244–250

■ ASSOCIATED CONTENT

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

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Author Contributions

§Equally contributing authors.

Funding Sources

Financial support of this work was provided by the Institute of General Medical Sciences and is gratefully acknowledged (P50-GM069663 and P41-GM076302).

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(6) 184 out of 225 members were successfully produced in sufficient quantities and purities (>10 mg and >90% purity).

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(16) All three scaffolds were isolated as crystalline white foams with purity >95% as determined by ^{1}H NMR.

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(20) Note: Excess volatile azide/CH_2Cl_2 was removed during the process of concentrating the reaction mixture under reduced pressure.

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