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Synthesis of a Unique Isoindoline/Tetrahydroisoquinoline-based Tricyclic Sultam Library Utilizing a Heck-aza-Michael Strategy

Qin Zang,[†] Salim Javed,[†,‡] Patrick Porubsky,[§] Farman Ullah,[∥] Benjamin Neuenswander,[§] Gerald H. Lushington,[†,§] Fatima Z. Basha,[‡] Michael G. Organ,[∥] and Paul R. Hanson[†,§,*]

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

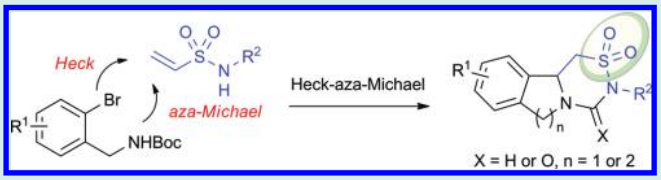
[‡]H. E. J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Pakistan

[§]The University of Kansas Center for Chemical Methodologies and Library Development (KU-CMLD), 2034 Becker Drive, Del Shankel Structural Biology Center, Lawrence, Kansas 66047-3761, United States

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

S *Supporting Information*

ABSTRACT: The synthesis of a unique isoindoline- and tetrahydroisoquinoline (THIQ)-containing tricyclic sultam library, utilizing a Heck-aza-Michael (HaM) strategy is reported. Both isoindoline and THIQ rings are installed through a Heck reaction on a vinylsulfonamide, followed by one-pot deprotection and intramolecular aza-Michael reaction. Subsequent cyclization with either paraformaldehyde condensation or 1,1′-carbonyldiimidazole coupling generates a variety of tricyclic sultams. Overall, a 160-member library of these sultams, together with their isoindolines/THIQ and secondary sulfonamides precursors, were constructed using this strategy.



KEYWORDS: *isoindoline/tetrahydroisoquinoline, tricyclic sultam library, Heck-aza-Michael*

INTRODUCTION

The growing demand for diverse small molecule libraries for the development of therapeutic agents requires efficient methodologies to provide access to structurally unique drug-like molecules.[1,2] Substituted isoindolines and THIQ are heterocyclic motifs presented in numerous natural products and bioactive small molecules displaying a wide array of biological activity. In particular, isoindolines have been shown to exhibit a number of potent properties, including: (i) modulation of the dopamine D_3 receptor and hence potential as antipsychotic agents (**A**, Figure 1),[3] (ii) inhibition of amyloid protein aggregation indicating a potential capacity in the treatment of Alzheimer's disease (**B**),[4] (iii) selective antagonism of the ET_A receptor and thus may play a pathophysiological role in a large number of diseases related to the heart and lungs (**C**),[5] and (iv) ligand affinity for the melanocortin subtype-4 receptor (MC4R) (**D**).[6] Additional disparate activities have also been seen in a family of THIQ-containing antitumor antibiotics, including a number of naturally occurring alkaloids such as quinocarcin (**E**) and quinocarcinol (**F**).[7] (−)-Tetrahydroberberine (**G**) also shows a variety of bioactivities such as insecticidal activity against *Drosophila melanogaster*,[8] antitumor promoter (inhibitory effect on Epstein−Barr virus),[9] while (+)-laudanosine (**H**), which occurs naturally in opium, has been shown to interact with GABA receptors, opioid receptors, and nicotinic acetylcholine receptors.[10] THIQ **I** was discovered as a potent and selective inhibitor of prolyl dipeptidase DPP8 and therefore has potential in the treatment of Type II diabetes.[11] As a final note, compound **J** displays histamine H_3 receptor antagonism and thus may be useful in the treatment of a variety of CNS disorder.[12] Taken collectively, isoindolines and THIQ-containing compounds have emerged as attractive targets in organic and medicinal chemistry, thus spurring on methods development for their synthesis.[13,14]

The generation of a variety of substituted isoindolines and THIQs,[6,15] isoindolinones and isoquinolinones[16] utilizing both transition metal-catalyzed coupling and aza-Michael cyclization steps in domino or sequential Heck-aza-Michael (HaM) cascades has emerged in a number of highly efficient pathways (Figure 2). In spite of the prevalent usage of acrylate, the utilization of vinylsulfonamide derivatives in HaM strategies leading to isoindolines/THIQ-based tricyclic sultam products is void in the literature. More interestingly, a brief literature survey shows 4 compounds containing isoindoline-pyrimidine substructure **K** and roughly 250 compounds with THIQ-pyrimidine substructure **L**, while isoindoline/THIQ-thiadiazinane substructures **M** and **N** represent completely new molecular chemotypes (Figure 2). As part of a larger program aimed at DOS strategies toward sultam libraries and their comparison with amides, we herein report the facile synthesis of a library of tricyclic sultam heterocycles containing isoindolines/THIQ motifs utilizing a HaM reaction protocol.

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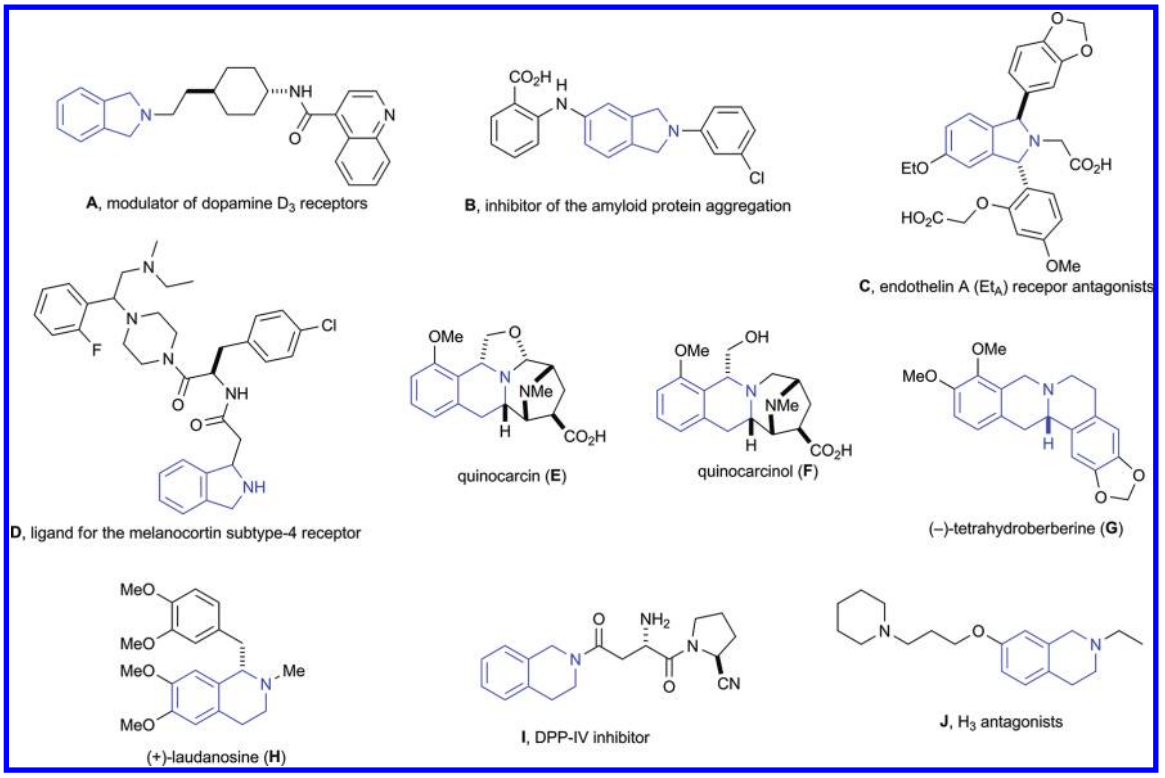


Figure 1. Biologically active compounds containing isoindolines and THIQs.

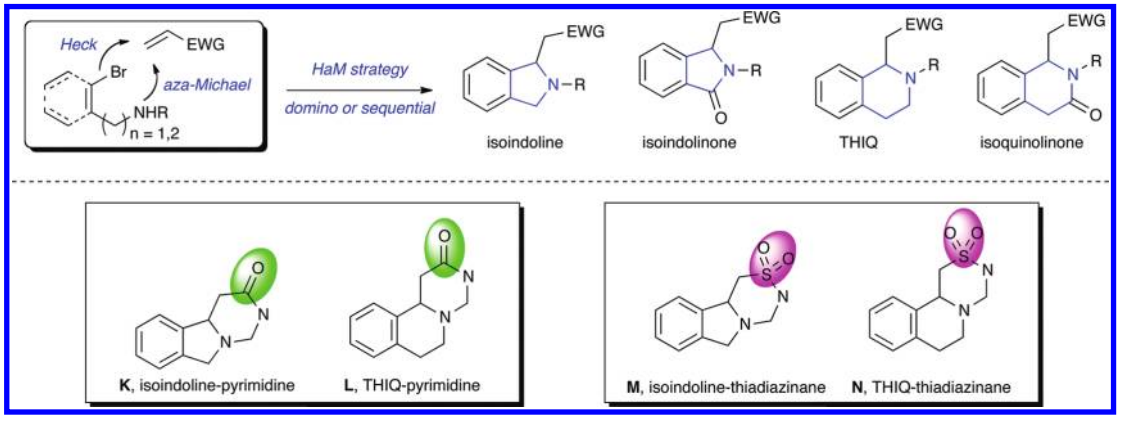
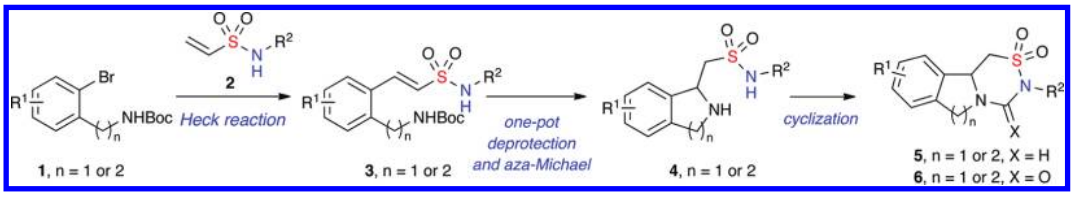


Figure 2. HaM strategy in the synthesis of isoindolines and THIQ, isoindolinones, and isoquinolinones.

Scheme 1. Library Outline



RESULTS AND DISCUSSION

We recently reported the synthesis of sultams using vinylsulfonamides as reliable and efficient precursors, which undergo facile hetero-Michael reactions and intramolecular Diels–Alder reaction.[17] In addition, domino HaM protocols have been developed in our laboratory for the synthesis of a library of functionalized 1,1-dioxido-1,2-benzisothiazolines.[18] In this regard, we envisioned the construction of a tricyclic sultam library via integration of a HaM protocol with vinylsulfonamides, as outlined in Scheme 1. In this approach, the secondary sulfonamide linchpin **3** can easily be synthesized via a Heck reaction of substituted bromobenzene **1** and vinylsulfonamide **2**. Subsequent one-pot, sequential deprotection and intramolecular aza-Michael reaction on **3** results in generation of the central alkaloid ring bearing a secondary amine and a proximal secondary sulfonamide, which can be utilized for further transformation into tricyclic ring systems **5** and **6**.

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Scheme 2. Preparation of Heck Reaction Precursors 1 and 2

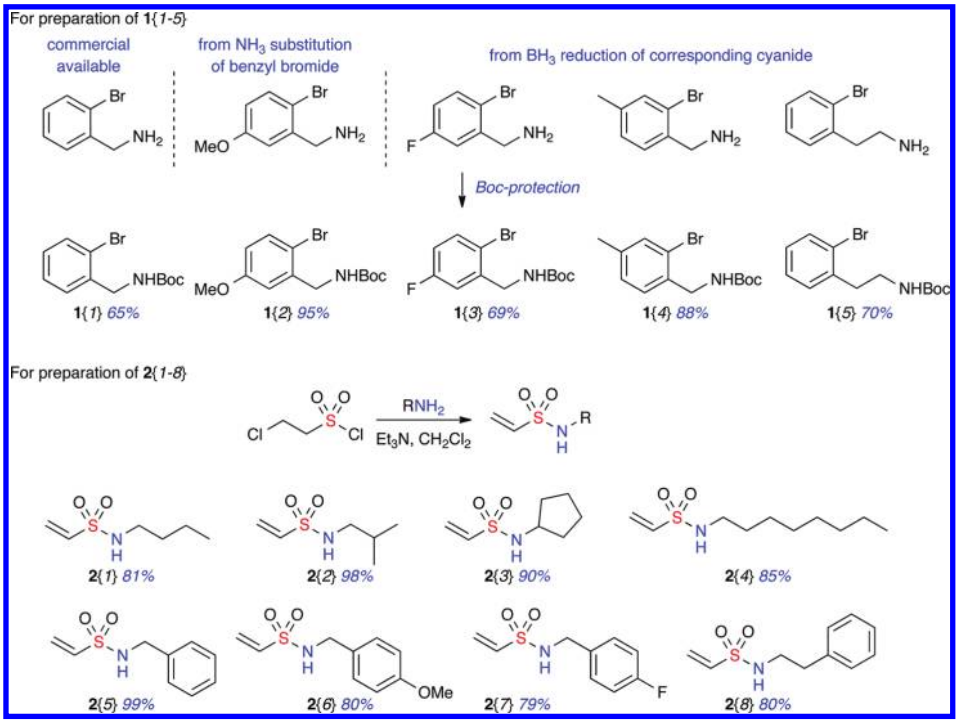
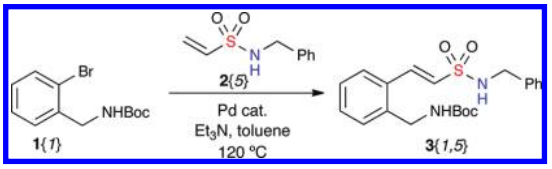


Table 1. Optimization of the Heck Reaction[a]



entry	catalyst	loading (mol %)	additive	equiv	solvent	yield (%)[b]
1	$Pd(OAc)_2$	10	PPh_3	0.2	toluene	30
2	$PdCl_2$	10	PPh_3	0.2	toluene	42
3	$Pd(PPh_3)_4$	10			toluene	40
4	$Pd(dppf)Cl_2$	10			toluene	47
5	**$Pd(PPh_3)_2Cl_2$**	**10**			**toluene**	**80**
6	$Pd(PPh_3)_2Cl_2$	10			DMF	40
7	$Pd(PPh_3)_2Cl_2$	5			toluene	57

[a]General procedure: A mixture of 1.1 equiv of **1**{*1*}, 1.0 equiv of **2**{*5*}, Pd catalyst, additive, 3 equiv of Et_3N in toluene (0.1 M) was heated in a sealed tube at 120 °C for 14 h. [b]Isolated yield.

Library Design. A full matrix library was designed using in silico analysis, literature precedence, and observed synthetic results for compounds **5** and **6**, together with their precursors **3** and **4**.[19] A virtual library incorporating all possible building block combinations of bromobenzene **1** and vinylsulfonamide **2** was constructed for each scaffold (**3**, **4**, **5**, and **6**) (Scheme 2). Physicochemical property filters were applied, guiding the elimination of undesirable building blocks that led to products with undesirable in silico properties.[20] 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 a diversity analysis using standard H-aware 3D BCUT descriptors comparing against the MLSMR screening set (~7/2010; ~330 000 unique chemical structures). Guided by this library design analysis, the corresponding bromobenzene **1** and vinylsulfonamide **2** were chosen to generate the proposed sultam libraries.

Library Construction. We started from the preparation of substituted (2-bromophenyl)methanamine and 2-(2-bromophenyl)ethanamine, which are either commercially available, obtained through NH_3 substitution of substituted benzyl bromide,[21] or through BH_3 reduction of the corresponding cyanides[22] (Scheme 2). Without further purification, the resulting primary amines were Boc-protected thus generating the desired substituted *t*-butyl 2-bromobenzylcarbamates **1**{*1*–*4*} and *t*-butyl 2-bromophenethylcarbamate **1**{*5*}. With these substituted bromobenzenes in hand, we were able to form unsubstituted isoindolines (from **1**{*1*}), isoindolines with electron donating (from **1**{*2*}, **1**{*4*}) and electron withdrawing groups (from **1**{*3*}), as well as THIQ derivatives (from **1**{*5*}).

Vinylsulfonamides **2**{*1*–*8*} were synthesized from 2-chloroethanesulfonyl chloride and the corresponding primary

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Scheme 3. One-Pot Deprotection, Intramolecular Aza-Michael Reaction, and Cyclization

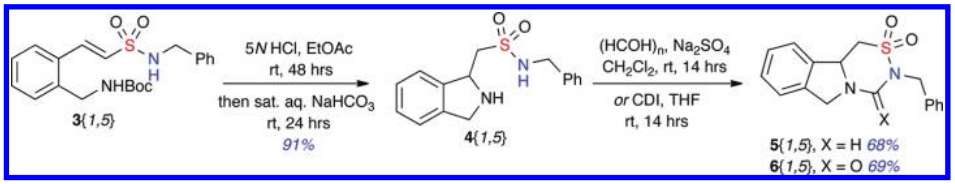
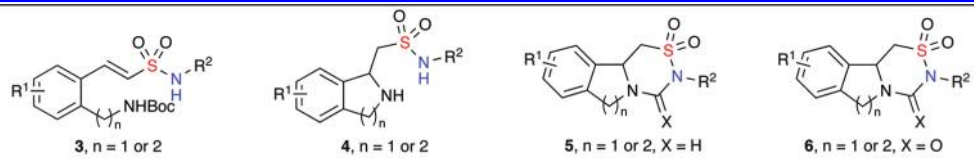


Table 2. Yield of 3{1−5,1−8}, 4{1−5,1−8}, 5{1−5,1−8}, 6{1−5,1−8}



1{1-5} / 2{1-8}	1{1}	1{2}	1{3}	1{4}	1{5}
2{1}	92, 73, 98, 58[a,b]	51, 98, 80, 56	80, 96, 84, 56	66, 99, 70, 55	67, 95, 56, 60
2{2}	83, 98, 99, 60	74, 93, 77, 67	51, 98, 64, 40	81, 94, 72, 43	66, 82, 88, 60
2{3}	90, 74, 76, 46	67, 94, 35, 70	63, 97, 86, 70	75, 97, 93, 40	58, 92, 93, 57
2{4}	86, 74, 82, 63	58, 94, 71, 62	62, 99, 73, 58	82, 53, 45, 35	71, 98, 58, 52
2{5}	80, 99, 63, 48	47, 92, 58, 70	50, 97, 64, 57	71, 99, 59, 57	66, 92, 94, 61
2{6}	65, 98, 84, 65	55, 98, 67, 62	75, 64, 46, 81	75, 81, 76, 39	69, 84, 93, 22
2{7}	70, 94, 68, 58	88, 79, 69, 50	75, 60, 78, 71	99, 99, 92, 32	75, 86, 76, 74
2{8}	58, 99, 72, 88	59, 95, 88, 30	76, 94, 86, 65	92, 92, 74, 66	72, 92, 98, 60

[a]Numbers refer to the respective stepwise yield of 3{X,Y}, 4{X,Y}, 5{X,Y}, 6{X,Y} from corresponding starting materials. [b]Isolated yield for **3**, **5** and **6**; crude yield for **4**.

amines through sulfonylation and in situ β-elimination of HCl (Scheme 2). The scope of substituents on 2{1−8} includes linear, branched and cyclic alkyl groups 2{1−4}, as well as unsaturated groups 2{5−8}, all of which were prepared in one-step on multigram scale with good yield. The validation of the Heck reaction was performed using *tert*-butyl 2-bromobenzyl-carbamate 1{1} and *N*-benzylethenesulfonamide 2{5} (Table 1). The initial screening of Pd-catalysts found Pd(PPh3)2Cl2 to give optimal yield (entries 1−5), by switching solvent from low polarity (toluene) to high polarity (DMF), no improvement in the yield was observed (entry 5). Furthermore, when the catalyst loading was reduced to 5 mol% using toluene, again, no improvement in yield was seen (entry 6). Microwave conditions were also attempted, and although they reduced the reaction time the yield was comparable to conventional oil bath conditions. With these parameters in hand, the library was synthesized employing optimized oil bath conditions as outlined in entry 5, using 10 mol % of $Pd(PPh_3)_2Cl_2$ in

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toluene. Using these conditions, no regioisomer was observed and the products were of exclusively *E*-configuration as evident by a ^{1}H NMR coupling constant (15.3 Hz, which was in agreement with literature reports).[23]

With optimized Heck reaction conditions being developed, the one-pot, deprotection and intramolecular aza-Michael reaction was next examined by treating **3**{*1,5*} with 5N HCl in EtOAc, followed by neutralizing to pH 8 with addition of $NaHCO_3$ (saturated aqueous, Scheme 3). Isoindoline product **4**{*1,5*} was obtained in 91% yield, and was clean enough to go through next step without further purification. Cyclization was accomplished through paraformaldehyde condensation and 1,1′-carbonyldiimidazole (CDI) coupling between the secondary amine and sulfonamide presented in **4**{*1,5*}, and provided the desired products **5**{*1,5*} and **6**{*1,5*} with satisfactory yield.

After the preparation of starting materials **1**{*1*−*5*} and **2**{*1*−*8*} and development of an optimized route toward tricyclic sultams **5** and **6**, the proposed library was generated according to plan. The results of the synthesis of **3**{*1*−*5,1*−*8*}, **4**{*1*−*5,1*−*8*}, **5**{*1*−*5,1*−*8*}, **6**{*1*−*5,1*−*8*} are summarized in Table 2. The Heck reaction was carried out in a Radley Carousel parallel synthesizer where the yield of products **3**{*1*−*5,1*−*8*} ranged from 51% to 99%, with an average yield of 71%. The aza-Michael reactions were run in 1-dram vials on an aluminum reaction block. Yields were generally good, as the average yield for compounds **4**{*1*−*5,1*−*8*} as high as 90%. Although the intermediate products were not purified by flash chromatography, they were pure enough as shown in NMR and used in the next step without purification. The formaldehyde condensation and CDI couplings were also run in 1-dram vials on an aluminum reaction block and provided moderate to good yield, with average yields of 57% and 75%, respectively. The structure of **5**{*2,8*} was confirmed via X-ray crystallography (Figure 4). Overall, a total of 80 tricyclic sultams **5**{*1*−*5,1*−*8*}

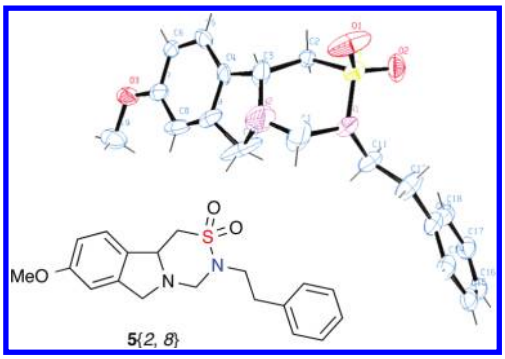

Figure 4. ORTEP diagram of **5**{*2,8*}.

and **6**{*1*−*5,1*−*8*}, 40 isoindolines and THIQs **4**{*1*−*5,1*−*8*}, as well as 40 secondary sulfonamides **3**{*1*−*5,1*−*8*}, were successfully synthesized and samples of each compound with quantities ≥60 mg and with purity >90% (determination by UV area percent from HPLC analysis) were submitted to the KU-CMLD.

In conclusion, we successfully completed the production of an 80-member library of unique tricyclic sultams through a HaM pathway with variable substituents. These compounds, together with their isoindolines/THIQ and secondary sulfonamides precursors, are in the process of being distributed to a number of biological collaborators within the NIH Molecular Libraries Probe Center Network (MLPCN). Further development and improvement of this strategy using flow technology is currently in progress, and will be reported in due course.

EXPERIMENTAL PROCEDURES

General Procedure for the Heck Reaction to Synthesize Sulfonamide 3. To pressure tube containing substituted bromobenzene **1** (2.2 mmol, 1.1 equiv) was added sulfonamide linchpin **2** (2.0 mmol, 1.0 equiv) and toluene (20 mL, 0.1 M). To this solution was added Et_3N (6.0 mmol, 3.0 equiv) and $Pd(PPh_3)_2Cl_2$ (0.2 mmol, 0.1 equiv) and the mixture was stirred at 120 °C for 6−12 h. The reaction mixture was concentrated and the residue was purified using flash chromatography.

General Procedure for One-Pot Deprotection, Intramolecular Aza-Michael Reaction to Synthesize Sulfonamide 4. To a solution of sulfonamide **3** (1.4 mmol, 1.0 equiv) in EtOAc (14 mL, 0.1 M) was added 5N HCl (1.4 mL, 5.0 equiv), and the reaction mixture was stirred at room temperature for 48 h. Aqueous $NaHCO_3$ was carefully added to the reaction mixture until pH 8. The mixture was stirred for another 24 h, and then extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 to afford the crude product, which is used in next step without further purification.

General Procedure for Paraformaldehyde Cyclization to Synthesize Sultam 5. To a solution of sulfonamide **4** (0.3 mmol, 1.0 equiv) in CH_2Cl_2 (1.5 mL, 0.2 M) was added paraformaldehyde (0.9 mmol, 3.0 equiv) and Na_2SO_4 (0.9 mmol, 3.0 equiv), and the reaction mixture was stirred at 40 °C for overnight. The solid was removed by filtration, and filtrate was concentrated under reduced pressure to afford the crude product, which was purified using flash chromatography.

General Procedure for CDI Cyclization to Synthesize Sultam 6. To a solution of sulfonamide **4** (0.3 mmol, 1.0 equiv) in THF (3 mL, 0.1 M) was added Cs_2CO_3 (0.6 mmol, 2.0 equiv) followed by CDI (0.36 mmol, 1.2 equiv) and the reaction mixture was stirred at 40 °C for overnight. The solid was removed through filtration, and filtrate was concentrated under reduced pressure to afford the crude product, which was purified using flash chromatography.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full characterization 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. Phone: (785) 864-3094. Fax: (785) 864-5396.

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