

Synthesis of Sultam Scaffolds via Intramolecular Oxa-Michael and Diastereoselective Baylis–Hillman Reactions

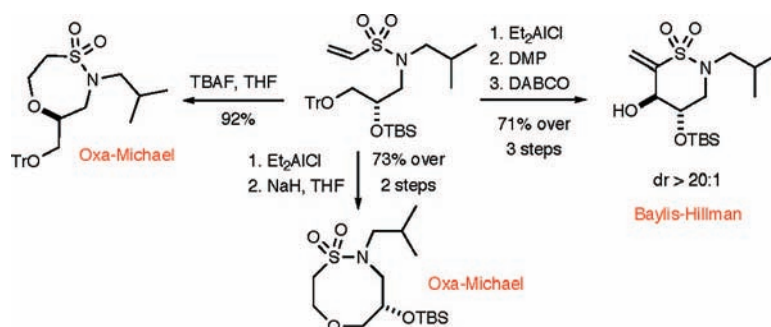
Aihua Zhou and Paul R. Hanson*

Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045-7582, and the Center for Chemical Methodologies and Library Development (CMLD) at the University of Kansas

phanson@ku.edu

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ABSTRACT



A divergent synthetic approach to new sultams utilizing intramolecular oxa-Michael and Baylis–Hillman reactions of readily prepared vinyl sulfonamides and suitably protected amino alcohols, is reported. A variety of seven- and eight-membered ring sultam scaffolds were synthesized using oxa-Michael pathways, whereas both five- and six-membered rings were synthesized using Baylis–Hillman methods. Baylis–Hillman reactions proceed with good to excellent levels of diastereoselectivity, and oxa-Michael reactions leading to eight-membered ring sultams provide empirical evidence validating 8-*endo-trig* cyclization pathways.

Sulfonamides and their analogs have a rich chemical and biological history and have emerged as a promising class of compounds in drug discovery.¹ Sultams (cyclic sulfonamides), although not found in nature, have also shown potent biological activity, including several displaying a wide spectrum of activities.² The more prominent include the antiepileptic agent Sulthiame³ (Figure 1), Brinzolamide⁴ for the treatment of glaucoma, the COX-2 inhibitors Ampiroxicam⁵ and S-2474,⁶ and selective inhibitors of cysteine proteases involved in the progression of malaria.⁷ In addition, a number of benzodithiazine dioxides and benzoxathiazepine

1,1-dioxides displaying anti-HIV-1 activity⁸ and the ability to activate glucokinase⁹ (type II diabetes), respectively, have been uncovered.

Traditionally, sultam syntheses have relied on classical cyclization protocols and a number of transition-metal-

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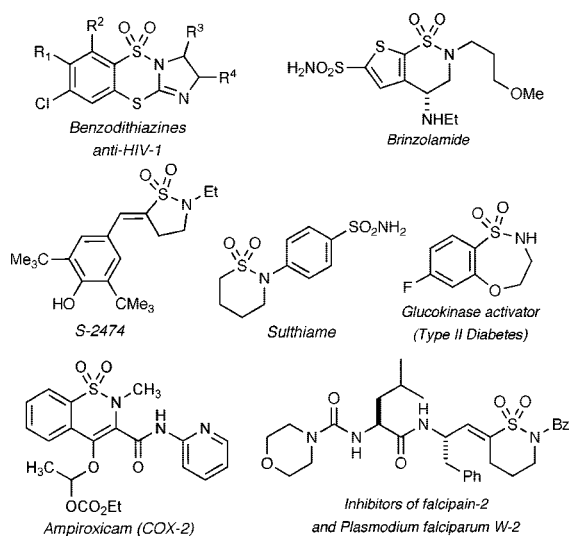


Figure 1. Biologically active sultams.

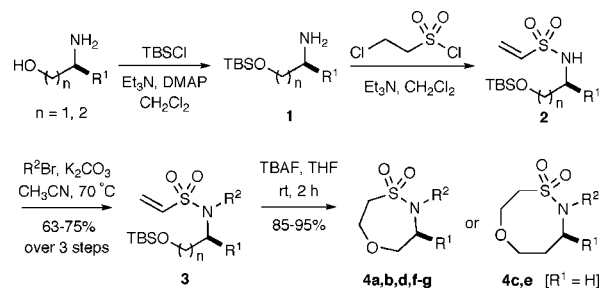
catalyzed processes that have recently been reported.¹⁰ Interest in the generation of new sultams for biological screening has provided impetus for exploring the Michael-accepting ability of vinyl sulfonamides. In particular, we aimed to study the titled intramolecular oxa-Michael and Baylis–Hillman approaches for the synthesis of chiral, nonracemic sultams.

The oxa-Michael¹¹ and Baylis–Hillman^{12,13} reactions have emerged as simple yet powerful methods for C–O and C–C bond formation. Both processes necessitate the presence of a competent electron-deficient Michael accepting moiety. The intermolecular oxa-Michael reaction has a long history dating back to its original discovery in 1878, roughly 5 years before the well-known Michael reaction was revealed.¹¹ The intramolecular version of the oxa-Michael reaction has seen a renaissance and has been extensively utilized in natural product synthesis for over 2 decades.¹⁴

In contrast, the Baylis–Hillman reaction was discovered in 1972.¹² Intramolecular versions of the Baylis–Hillman

reaction have only recently gained favor,¹³ where elegant work in this area has elevated the status of the intramolecular variant.¹⁵ Although the Michael accepting ability of vinyl sulfones is well-documented,¹⁶ their vinyl sulfonamide counterparts have assumed a far less prominent role as viable Michael acceptors.^{10,17} We herein report the first examples of intramolecular oxa-Michael and Baylis–Hillman reactions of vinyl sulfonamides to afford an array of novel five-, six-, seven-, and eight-membered ring sultam scaffolds in good to excellent yields. The Baylis–Hillman reactions proceed with good to excellent levels of diastereoselectivity, ultimately yielding interesting sultam scaffolds. Overall, this divergent route can be used to produce skeletally diverse scaffolds from a single precursor in excellent yields.

Scheme 1. Synthesis of Seven- and Eight-Membered Ring Sultams via Intramolecular Oxa-Michael Reactions



The titled route began with the assembly of TBS-protected amino alcohols, which represent cheap and versatile building blocks for sultam scaffold synthesis. These TBS-protected alcohols were reacted with 2-chloroethanesulfonyl chloride to produce vinyl sulfonamides **2** in good yields (Scheme 1). Subsequent benzylation/allylation reactions of vinyl sulfona-

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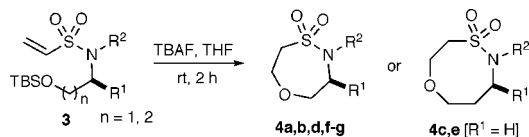
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mides **2** yielded vinyl sulfonamides **3** in good yields over three steps. The intramolecular oxa-Michael reaction was initiated by TBS-deprotection with TBAF in THF to afford the unique seven- and eight-membered ring sultams, respectively, in excellent yield under mild condition.

Several examples of this straightforward procedure were examined as outlined in Table 1. In all cases the cyclization

Table 1. Synthesis of Seven- and Eight-Membered Ring Sultams via Intramolecular Oxa-Michael Reactions



entry	product	<i>n</i>	R ¹	R ²	total yield ^a (%)
1	4a	1	<i>i</i> -Pr	CH ₂ CH=CH ₂	61
2	4b	1	CH ₂ Ph	CH ₂ Ph(<i>o</i> -Br)	60
3	4c	2	H	CH ₂ CH=CH ₂	54
4	4d	1	CH ₂ Ph	CH ₂ Ph(<i>o</i> -Me)	59 ^b
5	4e	2	H	CH ₂ Ph(<i>o</i> -F)	53 ^b
6	4f	1	<i>i</i> -Bu	CH ₂ Ph(<i>m</i> -Cl)	58 ^b
7	4g	1	<i>i</i> -Bu	CH ₂ Ph	61 ^b

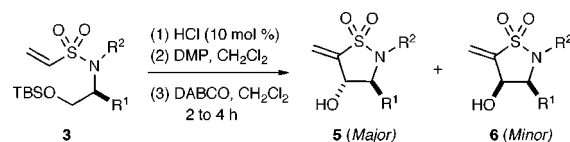
^a Total yield of all four steps. ^b Sultams **4d–g** were synthesized through chromatography-free linear synthesis; see Supporting Information for reaction procedure.

proceeded without incident. In several cases, the entire linear sequence could be run without the need for chromatography, ultimately resulting in the production of oxathiazepine- and oxathiazocine-dioxides, seven- and eight-membered ring systems, in excellent yields, respectively. To the best of our knowledge, this work represents the first report of using intramolecular oxa-Michael reactions to generate an eight-membered ring and enriches Baldwin's rules for ring closure.¹⁸

An orthogonal pathway leading to an intramolecular Baylis–Hillman reaction was next investigated. We observed that the intramolecular oxa-Michael reaction pathway was not operative under acidic conditions, and thus, a 10 mol % aqueous solution of HCl was implemented for TBS-deprotection of vinylsulfonamide **3**. Subsequent Dess–Martin oxidation yielded the aldehyde vinyl sulfonamide, which underwent smooth Baylis–Hillman reaction upon the addition of DABCO (10 mol %). Overall, the intramolecular Baylis–Hillman reaction was completed within 2–4 h, affording the vinyl sultam **5** in excellent yields and with moderate to good levels of diastereoselectivity (Table 2). Several other organocatalysts such as DMAP, DBU, quinine, quinidine, and brucine were also screened in this process. Overall, DABCO proved to be the most efficient for both yield and competitive diastereoselectivity.^{19,20}

The TBS-protected prolinol-derived vinyl sulfonamide **7** was next studied where treatment with TBAF resulted in the

Table 2. Intramolecular Baylis–Hillman Reactions

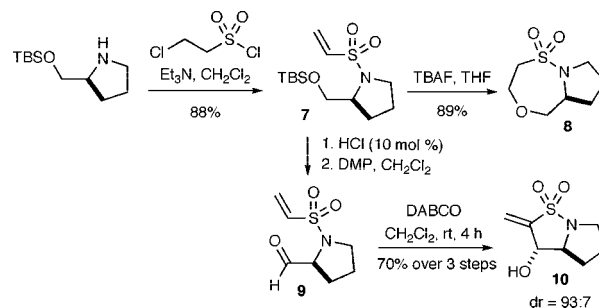


entry	product	R ¹	R ²	yield ^a (%)	dr (5/6)
1	5a/6a	<i>i</i> -Pr	CH ₂ CH=CH ₂	69	63:37
2	5b/6b	<i>i</i> -Bu	CH ₂ Ph(<i>o</i> -Br)	71	62:38
3	5c/6c	<i>i</i> -Bu	CH ₂ CH=CH ₂	67	76:24
4	5d/6d	CH ₂ Ph	CH ₂ CCH	69	77:23
5	5e/6e	CH ₂ Ph	CH ₂ Ph(<i>o</i> -Br)	72	88:12
6	5f/6f	CH ₂ Ph	CH ₂ Ph	71	90:10

^a Yield of three steps.

production of the bicyclic sultam **8** in excellent yields via an oxa-Michael pathway (Scheme 2). In contrast, treatment

Scheme 2. Synthesis of Bicyclic Sultam Scaffold



of **7** with the aforementioned orthogonal conditions involving acidic deprotection, oxidation, and addition of DABCO yielded the bicyclic sultam **10** with good yield and excellent diastereoselective ratio.

The method was extended to the readily prepared secondary alcohol, TBS-protected *trans*-2-amino-cyclohexanol (Scheme 3). Vinylsulfonylation and benzylation yielded the vinyl sulfonamide **12** in excellent yields. Treatment with TBAF yielded the bicyclic sultam **13** in excellent yield via an oxa-Michael pathway, and treatment with the orthogonal Baylis–Hillman conditions yielded the unique bicyclic vinyl sultam **15** in modest yield and extended reaction time (53%, 72 h) yet with excellent diastereoselectivity (dr > 95:5).

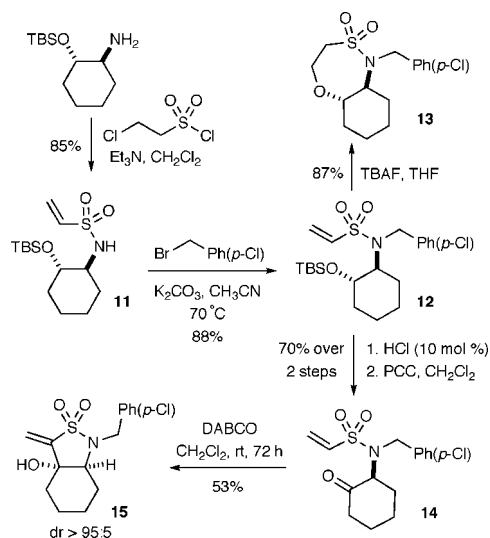
We next investigated the feasibility of extending the method to the generation of δ -sultams (Scheme 4). To address this question, chiral, nonracemic amino TBS-protected alcohol **16** was synthesized starting from (*S*)-glycidyl trityl ether.²¹ Subsequent TBS-protection and vinylsulfonylation with 2-chloroethanesulfonyl chloride af-

(18) Although Baldwin defined 7-*endo-trig* as favorable, 8-*endo-trig* pathways were not defined; see: Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 73, 4–736.

(19) The stereochemistry of major product **5** was determined by 1D-NOE and NOESY experiments; see Supporting Information.

(20) To the best of our knowledge, this work represents the first report of using an intramolecular Baylis–Hillman reaction to generate a sultam.

Scheme 3. Baylis–Hillman Reaction via Keto Vinyl Sulfonamide



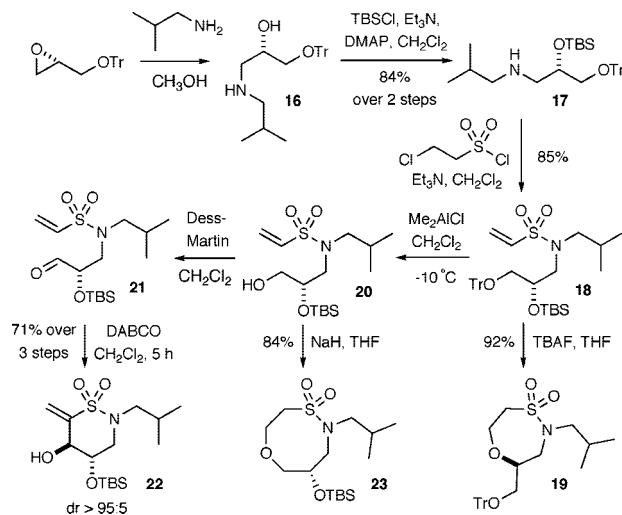
forded vinyl sulfonamide **18**. TBS-deprotection with TBAF afforded the δ -sultam **19** in excellent yield via an intramolecular oxa-Michael pathway. The Baylis–Hillman pathway was initiated by use of a selective, orthogonal deprotection of the trityl ether in **18** at -10°C using Me_2AlCl (CH_2Cl_2 solution) to yield vinylsulfonamide **20** in good yield. The resulting alcohol was oxidized to aldehyde **21** using the Dess–Martin agent as previously described. Treatment with DABCO afforded the δ -sultam scaffold **22** in excellent yield and diastereoselectivity ($\text{dr} > 95:5$).²² The intramolecular oxa-Michael reaction of **20** was also pursued to afford the eight-membered-ring sultam by using NaH in THF. This reaction proceeded quickly and gave a high yield of the eight-membered-ring sultam **23**.

In summary, the first examples of intramolecular oxa-Michael and Baylis–Hillman reactions to synthesize five-, six-, seven-, and eight-membered ring sultams have been attained. Moreover, empirical evidence validating *8-endo-trig* cyclization pathways in oxa-Michael reactions has been presented that enriches Baldwin's rules for ring closure. The titled oxa-Michael and Baylis–Hillman reactions are com-

(21) Regioselective ring-opening of glycidyl trityl ether with isobutylamine gave the amino alcohol **16** in excellent yield.

(22) Confirmed by ^1H measurements in different NMR solvents; see Supporting Information.

Scheme 4. Highly Diastereoselective Intramolecular Baylis–Hillman Reaction to Generate δ -Sultam



pleted within short order and occur with excellent yields. In addition, good to excellent levels of diastereoselectivity were achieved throughout the Baylis–Hillman study. Overall, these two reactions can be conveniently combined into one synthetic route to produce skeletally diverse scaffolds from a single precursor in excellent yields. In addition, the method is highly amenable to library generation and current efforts are currently engaged in this endeavor.

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Supporting Information Available: Experimental details and spectral characterization for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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