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Selective Synthesis of Seven- and Eight-Membered Ring Sultams via Two Tandem Reaction Protocols from One Starting Material

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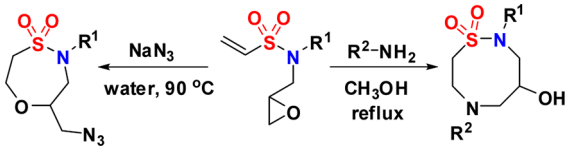
ABSTRACT



From one starting material, two tandem reaction protocols to synthesize seven- and eight-membered ring sultams were developed. One protocol employs intermolecular epoxide ring-opening by NaN_3, followed by an intramolecular 7-*endo-trig* oxa-Michael addition reaction. The second protocol applies to intermolecular aza-Michael addition of a primary amine, followed by 8-*endo-tet* intramolecular epoxide ring-opening of the resultant amine intermediate. Both protocols afforded the respective sultams in good yields under mild reaction conditions.

The growing demand for quick syntheses of small molecules for high-throughput screening has provided many opportunities and challenges for medicinal chemists. This is especially true for small molecules with privileged functional groups such as sulfonamides.[1] This category of compounds were well investigated before, but their analogues, the cyclic sulfonamide compounds (also called sultams), have been much less studied. Recently, sultams have attracted more attention because of their varieties of biological activities. Figure 1 shows six sultam derivatives that display different biological activities. These include an HIV integrase inhibitor,[2] a carbonic anhydrase inhibitor,[3] a cannabinoid-1 receptor (CB1R) inverse agonist for the treatment of obesity,[4] an MMP inhibitor,[5] an HIV-1 protease inhibitor,[6] and an inhibitor of both falcipain-2 and *Plasmodium falciparum* W-2.[7]

Some powerful synthetic methods for the generation of sultam derivatives have been developed. These methods include several transition metal-catalyzed reactions that

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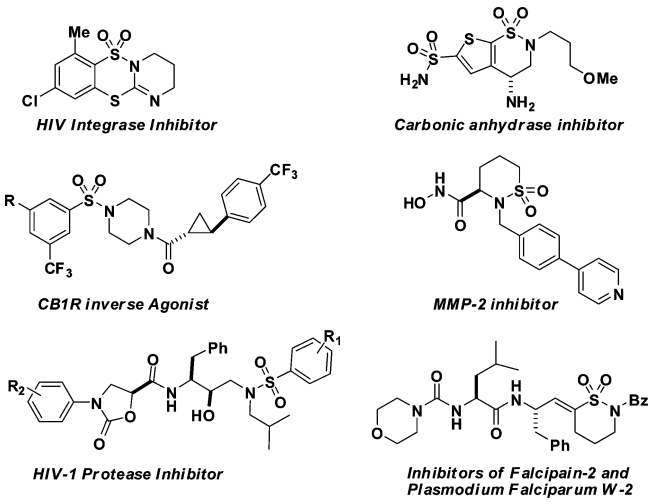
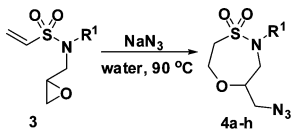


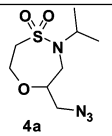
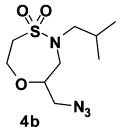
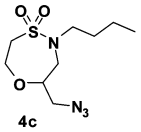
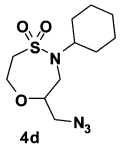
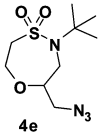
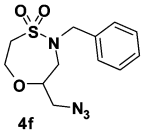
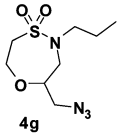
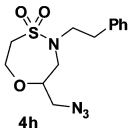
Figure 1. Biologically active sultams.

afforded sultams,[8] Friedel-Craft reactions,[9] Ring-Closing Metathesis (RCM),[10] cyclizations of aminosulfonyl chlorides,[11] [3 + 2] cycloadditions,[12] both Diels–Alder[13] and Heck reactions,[14] and intramolecular oxa-Michael and Baylis–Hillman reactions.[15] All of these reactions afforded sultams in a few step with good yields.

Scheme 1. Selective Epoxidation of Vinyl Sulfonamides

Table 1. Tandem Reactions Initiated by an Epoxide Ring Opening Using NaN_3, Followed by 7-*endo-trig* Intramolecular Oxa-Michael Addition



entry	R^1	7-membered ring sultams	yield (%)
1	$-CH(CH_3)_2$	 4a	67
2	$-CH_2CH(CH_3)_2$	 4b	61
3	$-(CH_2)_3CH_3$	 4c	63
4	$-CH(CH_2)_5$	 4d	56
5	$-C(CH_3)_3$	 4e	62
6	$-CH_2Ph$	 4f	65
7	$-CH_2CH_2CH_3$	 4g	60
8	$-CH_2CH_2Ph$	 4h	56

In this paper, two tandem reactions are reported that use the same vinyl sulfonamide epoxide starting material

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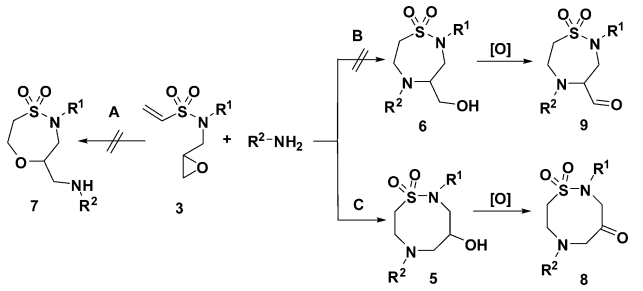
(14) Vinyl sulfonamide Heck reaction: Merten, S.; Frohlich, R.; Kataeva, O.; Metz, P. *Adv. Synth. Catal.* **2005**, *347*, 754–758.

(15) (a) Zhou, A.; Hanson, R. P. *Org. Lett.* **2008**, *10*, 2951–2954. (b) Zhou, A.; Rayabarapu, D.; Hanson, R. P. *Org. Lett.* **2009**, *11*, 531–534.

Scheme 2. Possible Tandem Reaction Routes



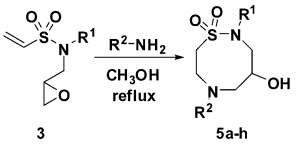
to make both seven- and eight-membered ring sultams. This vinyl sulfonamide epoxide was produced in three effective steps presented in Scheme 1.[15]

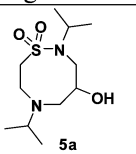
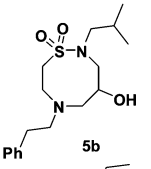
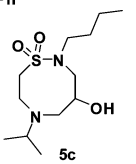
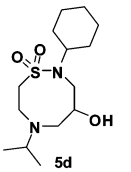
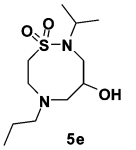
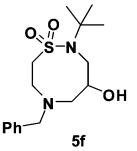
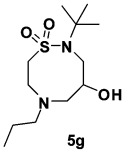
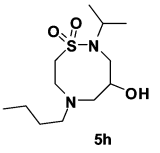
The synthesis started by reacting a primary amine with 2-chloroethanesulfonyl chloride in DCM solvent in the presence of triethylamine to generate an α,β-unsaturated sulfonamide **1**. Alkylation of **1** with allyl bromide in the presence of K_2CO_3 afforded product **2** with an electron-poor and an electron-rich double bond.[10,15] The latter was selectively epoxidized by *m*-CPBA to give vinyl sulfonamide epoxides **3** (see Scheme 1) in good yield under mild conditions (totally eight different amines were used).

A tandem intermolecular ring-opening reaction of the epoxide followed by intramolecular oxa-Michael reaction to the electron-deficient double bond was planned and developed. NaN_3 was used as a nucleophile for this reaction first. Experiments proved that NaN_3 was not a good nucleophile for intermolecular aza-Michael addition reaction of vinyl sulfonamide in water. However a facile intermolecular epoxide ring-opening reaction by NaN_3 occurred in water solution (pH around 9). Furthermore, this reaction did not stop at the epoxide ring-opening stage, but the neucleophilic oxygen anion intermediate that resulted from epoxide ring-opening by NaN_3 initiated an intramolecular *7-endotrig* oxa-Michael reaction. This tandem sequence afforded seven-membered ring sultams **4a**–**h** in good yields under mild conditions (see Table 1).

Besides NaN_3, several other nucleophiles can also be used for epoxide ring-opening of vinyl sulfonamide epoxides **3a**–**h**. Primary amines were among the top choices for this tandem reaction. Interestingly, when the reaction was initiated by a primary amine, it did not follow the NaN_3-initiated route shown in Table 1. Instead, the primary amine became the nucleophile in an initial Michael-addition to the vinyl sulfonamide epoxides first, followed by subsequent 8-*endo-tet* intramolecular epoxide ring-opening reaction to give eight-membered-ring sultams **5a**–**h** in good yields within 5 h. Theoretically, there are three possible tandem reaction routes (see Scheme 2). Route A was ruled out by ^{1}H NMR spectra of products. Further experiments also proved that primary amines underwent aza-Michael addition faster than epoxide ring-opening reaction. In order to make sure the sturcture of the tandem reaction product was **5** (Scheme 2, Table 2), the reaction product was oxidized by PCC, PDC, and

Table 2. Tandem Reactions Initiated by an R^2-NH_2 Intermolecular Aza-Michael Addition Followed by an 8-*endo-tet* Intramolecular Ring-Opening of an Epoxide



entry	R^1	R^2	8-membered ring sultams	yield (%)
1	$-CH(CH_3)_2$	$-CH(CH_3)_2$	 **5a**	87
2	$-CH_2CH(CH_3)_2$	$-(CH_2)_2Ph$	 **5b**	78
3	$-(CH_2)_3CH_3$	$-CH(CH_3)_2$	 **5c**	85
4	$-CH(CH_2)_5$	$-CH(CH_3)_2$	 **5d**	79
5	$-CH(CH_3)_2$	$-(CH_2)_2CH_3$	 **5e**	88
6	$-C(CH_3)_3$	$-CH_2Ph$	 **5f**	80
7	$-C(CH_3)_3$	$-(CH_2)_2CH_3$	 **5g**	79
8	$-CH(CH_3)_2$	$-(CH_2)_3CH_3$	 **5h**	79

Jones agent, respectively, and no aldehyde or acid was isolated. Only keto sultam **8** was obtained as a major product. Because of steric factors, the resultant secondary amine from the Michael addition attacked the epoxide ring only at the least substituted (CH_2) end, so no

seven-membered ring sultams were found in the reaction products. The results are shown in Table 2.

In summary, two tandem reaction protocols to synthesize seven- and eight-membered ring sultams from one starting material were developed. One protocol employed intermolecular epoxide ring-opening of α,β-unsaturated sulfonamide epoxides by NaN_3 followed by intramolecular 7-*endo*-*trig* oxa-Michael addition reaction to give seven-membered ring sultams exclusively. The second protocol applies an amine nucleophile to the same starting material to induce intermolecular aza-Michael addition reaction, followed by an *8*-*endo*-*tet* intramolecular selective epoxide ring-opening of the resultant amine intermediate. Eight-membered ring sultams were mainly formed. Ovreall, these two reactions can be conveniently combined into one synthetic route to produce skeletally diverse scaffolds from a single starting material in excellent yields. In addition, the method is highly amenable to library generation and current efforts are engaged in this direction.

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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.

The authors declare no competing financial interest.