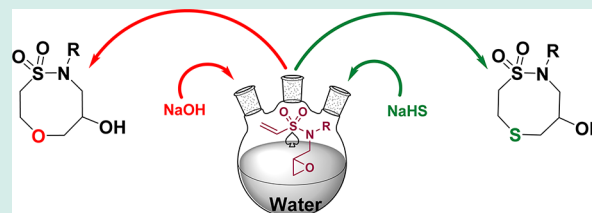


Parallel Syntheses of Eight-Membered Ring Sultams via Two Cascade Reactions in Water

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Supporting Information

ABSTRACT: From vinyl sulfonamides as precursors to vinyl sulfonamide epoxides, two cascade reaction protocols were developed to synthesize eight-membered ring sultams in water. These protocols employ intermolecular Michael addition by NaOH or NaHS in water, followed by rapid proton transfer and intramolecular 8-endo-tet epoxide ring-opening to give medium-size sultams selectively in one-pot. Novel core structures and high synthetic efficiency make these cascade reactions highly suitable for sultam library production. Both reactions proceeded well and



afforded the respective sultams in good yields under environmentally friendly conditions.

KEYWORDS: Michael addition, sultam, sulfonamide, parallel synthesis, eight-membered ring compound

Sulfonamides are known to possess broad-spectrum bioactivity.¹ These compounds have gradually become favorite compounds for drug discovery. Until now, some powerful synthetic methods for the generation of sultam derivatives have been developed. These routes include several transition metal-catalyzed reactions that afforded sultams,² Friedel–Craft reactions,³ ring-closing metathesis (RCM),⁴ cyclizations of aminosulfonyl chlorides,⁵ [3 + 2] cycloadditions,⁶ both Diels–Alder⁷ and Heck reactions,⁸ and both intramolecular oxa-Michael and Baylis–Hillman reactions.⁹ However, most sultam cyclization reactions above have been carried out in toxic organic solvents and complex procedures are needed to make compound libraries. Until now, no explorations of using water as a solvent for sultam synthesis has appeared, let alone the use of efficient cascade reactions to synthesize medium-sized ring sultams. Using water as a reaction solvent not only avoids toxic organic solvents and a tiresome solvent recovery but also prevents environmental pollution. Water is a polar and universal solvent suitable for reactions employing inorganic salt reactants, making water a reaction solvent of choice for most people.

Linear sulfonamides have been well studied,¹⁰ but their cyclic analogs, sultams, are far less explored in the respect of synthetic methods and biological activities.¹¹ Figure 1 presents several sulfonamide derivatives which display various potent biological activities. These include a H4 receptor inverse agonist,¹² a carbonic anhydrase inhibitor,¹³ a cannabinoid-1 receptor (CB1R) inverse agonist for the treatment of obesity,¹⁴ an MMP inhibitor,¹⁵ an HIV-1 protease inhibitor,¹⁶ or an antagonist for the EP1 receptor.¹⁷ Here, we've developed two efficient cascade ring-forming sultam synthesis reactions which were carried out in water. Water is a polar, protic solvent,

inorganic NaOH and NaHS can be easily dissolved in it. Sulfonamides are also slightly soluble in water. Here NaOH and NaHS were used as nucleophiles for initiating these two reaction sequences, both of which proceeded well under environmentally friendly conditions.

Vinyl sulfonamide is an important type of precursor for making sultams. It embodies a potent Michael acceptor with an electron-deficient double bond, which can be used for many different Michael-addition reactions.¹⁸ Vinyl sulfonamides were prepared by reacting 2-chloroethanesulfonyl chloride with primary amines in DCM containing triethylamine (Scheme 1). These reactions with a variety of amines afforded a series of vinyl sulfonamides **1a–h** in good yields. Alkylation of the resultant sulfonamides with allyl bromide in CH₃CN in the presence of K₂CO₃ at 95 °C afforded a series of secondary vinyl sulfonamides **2a–h** (Scheme 1), also in high yields.¹⁹ Compounds **2a–h** have two carbon–carbon double bonds of different reactivity. One is electron-rich, and other is electron-poor. Thus, selective epoxidations of the electron-rich double bond of vinyl sulfonamides **2a–h** with *m*-CPBA were carried out and the expected vinyl sulfonamide epoxides **3a–h** were obtained in good yields.²⁰

With both a potent Michael acceptor and an epoxide function present in the molecule, several cyclization reactions to generate sultams can be envisioned. Here, two cascade reactions were designed, one using NaOH and the other using NaHS as the triggering nucleophile. NaOH and NaHS can

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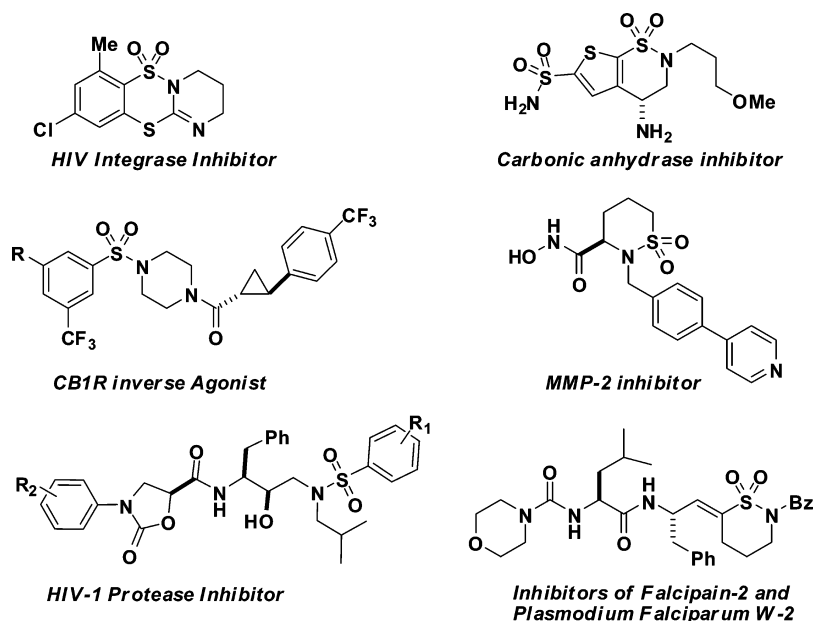
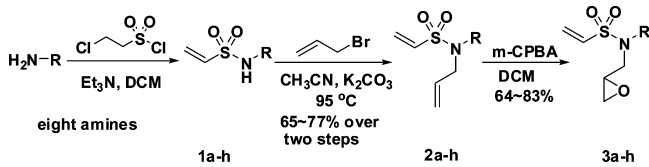


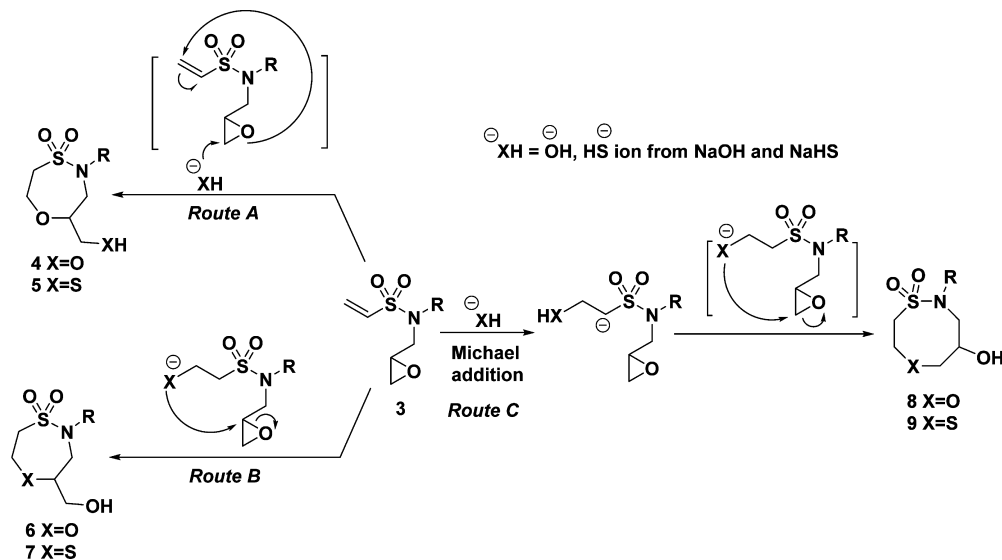
Figure 1. Representative biologically active sulfonamides and sultams.

Scheme 1. Selective Epoxidations of Vinyl Sulfonamides



easily provide OH^- and SH^- ions in water. Both of which are good nucleophiles, which participate in Michael addition reactions easily, and theoretically can also react with an epoxide. NaOH and NaHS reacted with vinyl sulfonamide epoxides very slowly in water at room temperature. However, when the temperature increased to 90 °C, these reactions became much faster. TLC analysis demonstrated both reactions afforded a single major product after overnight.

Scheme 2. Three Possible Reaction Routes Using NaOH or NaHS



Scheme 3. Representative Example Using NaOH as a Nucleophile

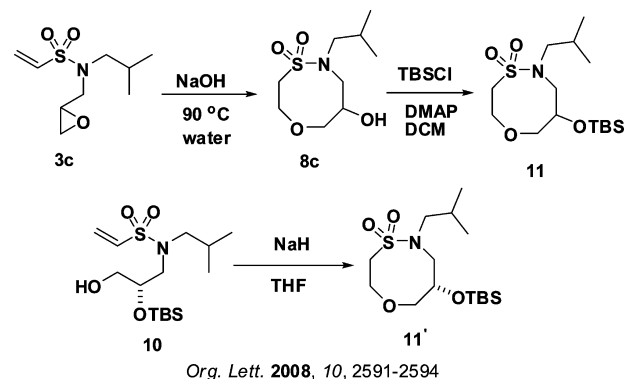


Table 1. Cascade Reactions of Vinyl Sulfonamide Epoxides with NaOH in Water

Reaction scheme showing the conversion of vinyl sulfonamide epoxide **3a-h** to sultam **8a-h** using NaOH in water at 90 °C.

entry	reactant 3	product 8	yield %
1			68.9
2			66.3
3			77.8
4			69.6
5			75.8
6			82.4
7			62.6

There are three possible reaction routes (Scheme 2). In Route A, NaOH or NaHS attacks epoxide ring from the less hindered side first, which then could be followed by intramolecular *7-endo-trig* oxa-Michael addition to give the seven-membered ring sultams **4/5**. In route B, NaOH, or NaHS undergo intermolecular Michael-addition first, followed by *7-exo-tet* epoxide ring-opening to give seven-membered ring sultams **6/7**. Finally, in route C, NaOH or NaHS again first initiate intermolecular Michael-addition, which is followed by *8-endo-tet* epoxide ring-opening to produce eight-membered ring sultams **8/9**.²¹ Each of these three cascade routes afford different reaction products.

The reaction of vinyl sulfonamide epoxide with NaOH conducted in hot 90 °C water only afforded one major product, so it was easy to isolate the product and verify its structure. Here the major product **8c** from the reaction of vinyl

sulfonamide epoxide **3c** with NaOH was used as a representative example (Scheme 3). After the reaction, **8c** was obtained in 77.8% yield. Then **8c** was reacted with TBSCl in the presence of DMAP and triethylamine to give compound **11**. The ¹H NMR of compound **11** exactly matched those of eight-membered ring compound **11'** which was synthesized by us previously from **10**.¹¹ This proved that the cascade reactions triggered by NaOH in hot water afforded eight-membered ring sultam (Route C). The aqueous OH⁻ ion underwent Michael-addition first. Then the resulting alkoxy ion intermediate attacked the epoxide ring at the least substituted end opening the epoxide while closing system to the eight-membered ring sultam **8c** (Route C).

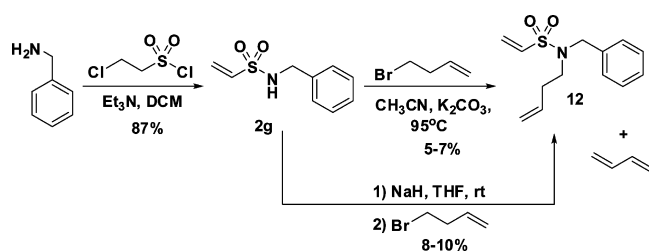
Seven different vinyl sulfonamide epoxides were reacted with NaOH in hot water, affording eight-membered ring sultams **8a-g**, as presented in the Table 1. When the more nucleophilic

Table 2. Cascade Reactions of Vinyl Sulfonamide Epoxide with NaHS in Water

$$\text{3b-h} \xrightarrow[\text{Water, 90}^\circ\text{C}]{\text{NaHS}} \text{9b-h}$$

entry	reactant 3	product 9	yield %
1			63.9
2			65.0
3			73.2
4			75.1
5			66.2
6			77.0
7			69.3

Scheme 4. Synthesis of Reaction Precursor for Making Nine-Membered Ring Sultam



HS^- was used as the nucleophile to react with the vinyl sulfonamide epoxide, one major product was again readily generated in hot water based on TLC analysis. Scheme 2 illustrates the three possible reaction routes. Route A was ruled

out because the reaction product's IR spectra did not exhibit any S–H absorption at $2400\text{--}2600\text{ cm}^{-1}$.²² This ruled out the presence of the –SH function in the final product, which means the HS^- ion did not attack epoxide ring from the less hindered side first. Instead, this nucleophile first induced intermolecular Michael-addition and then the resultant thiol ion intermediate attacked epoxide ring via the 8-endo-tet process to give the eight-membered ring sultams **9b–h** (Route C). Table 2 summarizes the reactions of seven vinyl sulfonamide epoxides with NaSH in hot water. All reactions produced eight-membered ring sultams **9b–h** in yields of 63–77%.

To further investigate a modified protocol to possibly make nine-membered ring sultams, benzylamine was reacted with 2-chloroethylsulfonamide chloride and vinyl sulfonamide **2g** was obtained in a good yield. However, alkylation of **2g** by 4-bromobut-1-ene in acetonitrile solvent in the presence of

K_2CO_3 at 95 °C afforded only a very small amount of **12**. The majority of **2g** still remained unreacted after 48 h, even when 2–3 equivalent excesses of 4-bromide-1-butene were used. Instead, 4-bromide-1-butene was converted into butadiene instead of reacting with sulfonamide **2g**. Another base, NaH, was also tried, but the yield was also low so not further tests were made to produce nine-membered ring sultams in water were conducted.

Compared to what is known about cyclic sultam syntheses, the advantages of these two cascade protocols are their high synthetic efficiency, novel core structures, and the use of water as a reaction solvent. Both reactions are suitable for synthetic Auto-Robot application. Within a short reaction time, a series of novel medium-sized ring core structures can be produced in good yields, and they are good scaffolds for sultam libraries.

In conclusion, we have discovered two cascade reactions which were triggered by NaOH or NaHS in hot water to synthesize eight-membered ring sultams in one pot. This is the first report of using water as a convenient and environmentally friendly solvent for sultam parallel synthesis. Both cascade reactions followed the same reaction route, in which an initial intermolecular Michael addition reaction was followed by proton transfer and then an 8-endo-tet intramolecular epoxide ring-opening which then closed the eight-membered sultam ring. Both reaction sequences afforded the respective sultams in moderate to good yields under mild conditions. These resultant novel sultams can be directly used as scaffolds for large sultam libraries.

■ ASSOCIATED CONTENT

📄 Supporting Information

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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Notes

The authors declare no competing financial interest.

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