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Cyclic Sulfonamides via the Ring-Closing Metathesis Reaction

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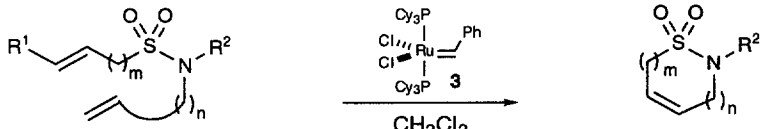
Abstract: The first examples of ring-closing metathesis (RCM) reactions on allyl- and vinylsulfonamide templates **1** and **2** catalyzed by the Grubbs ruthenium alkylidene **3** are described. The rate of cyclization of these reactions are sensitive to simple olefin substitution. These RCM reactions yield novel cyclic allyl- and vinylsultams **4** and **5** and represent our initial efforts toward the construction of novel sulfonamides.

Sulfonamide containing compounds have enormous potential as pharmaceutical and agricultural agents due to their diverse biological profiles. The ability to serve as amide surrogates, with unique physical properties, have made them ideal functional groups for the development of novel peptidomimetics.[1] In addition, sulfonamides have served as key functional groups in the development of: novel nonpeptidal HIV protease inhibitors,[2] matrix metalloproteinase inhibitors,[3] thrombin inhibitors,[4] fibrinogen receptor antagonists,[5] endothelin-A receptor antagonists,[6] and glycoprotein IIB/IIIA inhibitors.[7] They have also served as squalene epoxidase inhibitors[8] and sultam herbicides.[9] One attractive approach to the development of complex sultams, or conformationally restricted sulfonamide peptidomimetics, centers on the RCM reaction of allyl or vinylsulfonamides such as **1** and **2**.

Scheme 1



1a-d, m = 0
2a-d, m = 1

4a-d, m = 0
5a-d, m = 1

The RCM reaction[10] continues to be a powerful approach for the construction of complex organic molecules. A review has recently appeared which thoroughly categorizes the tolerance of both the Schrock and Grubbs catalysts to a vast array of functional groups.[11] Recently, we have shown that the RCM reaction catalyzed by the Grubbs ruthenium catalyst **3** is an effective method for the construction of phosphonate and phosphonamide P-heterocycles.[12] In addition, the more sensitive, but also more reactive, molybdenum catalysts have been shown to be effective for the RCM reaction of sulfides,[13] sulfones,[14] and highly substituted olefins.[15] As part of our program aimed at developing organometallic approaches[16] to diverse phosphorus and sulfur-containing compounds, we herein report the first examples of RCM reactions on sulfonamide templates **1** and **2** to derive novel allyl- and vinylsultams **4** and **5** (Scheme 1). This study represents our initial efforts toward the design of protease and matrix metalloproteinase inhibitors implicated in cancer, arthritis, AIDS, and other disease processes.[17]

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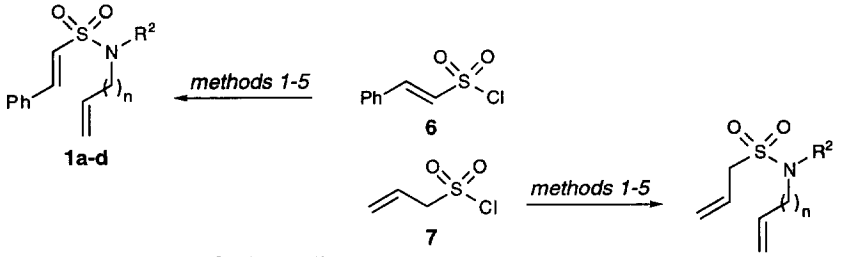
The vinylsulfonamides **1** and allylsulfonamides **2** were synthesized from the styrene derived sulfonyl chloride **6**[18] and allylsulfonyl chloride **7**[19] as outlined in Scheme 2. A minor problem arose in the synthesis of the allysulfonamides **2b-d**, in which the base promoted allylation protocols (methods 2, 3 and 5) gave minor amounts (~5-10%) of the corresponding vinylsulfonamides resulting from isomerization of the allylsulfonamide moiety. This problem could be circumvented via the use of benzylallylamine (method 4). Overall, all reactions proceeded in good to excellent yield and allowed us to derive the vinylsulfonamides **1** and the allylsulfonamides **2** in an expedient manner.

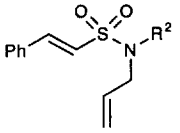
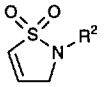
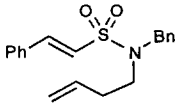
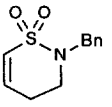
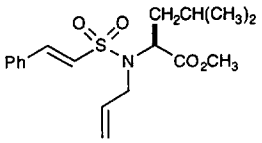
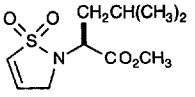
Scheme 2



Method 1: allylamine, CH_2Cl_2 (95-99%).
Method 2: i) benzylamine, CH_2Cl_2, ii) allyl bromide, K_2CO_3, acetone, reflux (95%).
Method 3: i) benzylamine, CH_2Cl_2, ii) homoallyl bromide, K_2CO_3, acetone, reflux (70-90%).
Method 4: Bn(allyl)NH, CH_2Cl_2 (95-99%).
Method 5: $H_2NCHR^3CO_2R^4$•HCl, Et_3N, CH_2Cl_2. ii) allyl bromide, K_2CO_3, acetone, reflux (82-90%).

The RCM reactions of vinylsulfonamides **1a-b** (R^2 = H and Bn, respectively) yielded the vinylsultams **4** (Table 1).[20] Though sluggish, all reactions proceeded cleanly in good to excellent yield. The smooth RCM of the vinylsulfonamide substrates **1** are noteworthy due to the fact that electron deficient olefins can be problematic in the RCM reaction with the Grubbs ruthenium alkylidene. Finally, the RCM of vinylsulfonamide **1d** gave excellent yields of the leucine-derived sultam **4d** (90%).

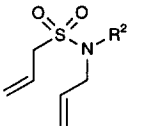
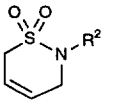
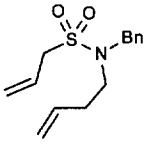
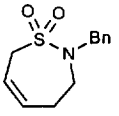
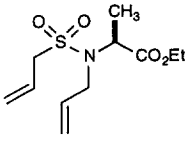
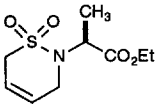
Table 1. RCM of Substrates **1a-1d**.

SM	SM	Conditions[a]	Pdt	Yield
1a R^2 = H		24h reflux, 6 mol% **3**[b]		**4a** R^2 = H, 90%
1b R^2 = Bn				**4b** R^2 = Bn, 88%
1c		24h reflux, 6 mol% **3**[b]		**4c**, 65%
1d		24h reflux, 6 mol% **3**[b]		**4d**, 90%

[a] substrate concentrations 0.01-0.02 M in CH_2Cl_2. [b] added in sequential portions of 3 mol%.

The RCM of allylsulfonamides **2** gave good to excellent yields of the allylsultams **5** (Table 2). Note that nitrogen substitution of allylsulfonamides **2a-b** is not required to attain good yields of the allylsultams **5**. These results are in opposition to our RCM results with the *bis*-allyl phosphonamide templates which require protection of the phosphonamide nitrogen to attain good yields in the six-membered series.[12b]

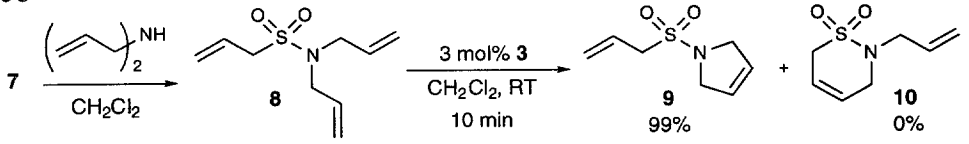
Table 2. RCM of Substrates **2a-2d**.

SM	SM	Conditions[a]	Pdt	Yield
2a $R^2 = H$		30 min, RT 3 mol% **3**		**5a** $R^2 = H$, 90%
2b $R^2 = Bn$		5h reflux, 1.5 mol% **3**		**5b** $R^2 = Bn$, 91%
2c		10 min reflux, 3 mol% **3**		**5c**, 91%
2d		2h reflux 3 mol% **3**		**5d**, 87%

[a] substrate concentrations 0.01-0.02 M in CH_2Cl_2.

Finally, we investigated the RCM of **8** which was derived from condensation of diallylamine and allylsulfonyl chloride **7** (Scheme 3). The RCM of **8** gave only the 5-membered heterocycle **9** and none of the 6-membered allylsultam **10**, thus implying electronic effects may be operative in the initial metathesis event.

Scheme 3



These preliminary results are encouraging and demonstrate the feasibility of the RCM strategy en route to complex sulfonamides. The rapid assembly, efficient cyclization, and the versatile nature of the resulting cyclic sultams provide ample opportunities for the construction of complex sulfonamides, including novel peptidomimetics. Efforts in this direction are currently underway in this laboratory.

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20. All new compounds have satisfactory ^{1}H, ^{13}C, and MS data.