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Ring-closing metathesis in the synthesis of fused sultones

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ABSTRACT

Synthesis of seven-membered sultones fused with different carbo- and heterocycles have been developed using ring closing metathesis as the key operation. The required substrates have been easily synthesized from their commercially available corresponding phenols.

Sultones, the internal esters of hydroxyl sulfonic acids, are synthetically very useful heterocycles in organic synthesis since they can be manipulated in a flexible fashion.[1] Many natural products have been synthesized using sultones as the key intermediates. For example, Metz et al. developed the total synthesis of 1, 10-seco-eudesmanolides ivangulin,[2] eriolanin, and eriolangin[3–5] using the sultone chemistry. Metz and co-workers also demonstrated the application of the sultone route in the total synthesis of pamamycin-607.[6] By applying the sultone chemistry, Metz et al. were also able to synthesize the monomeric subunits, methyl nonactate, of naturally occurring macrotetrolides.[7–9] A further synthetic application employing a sultone as a key intermediate in an enantioselective synthesis of the unusual sesquiterpenoid alcohol (−)-myltaylenol has been described by Winterfeldt and co-workers.[10,11] Recently, Novikov and co-workers developed[12] the enantioselective synthesis of bakuchiol by the desulfonation of δ-sultone as the key step. Cossy and co-workers also described the racemic synthesis of the originally-proposed structure of marine natural product, mycothiazole (**5**) via an unsaturated sultone intermediate (**3**), generated by ring-closing metathesis of compound **1** (Scheme 1).[13–15] Besides their synthetic application, sultone scaffolds are in great demand in medicinal chemistry research.[16] Biological studies on sultones are mainly concerned with their toxicological, skin sensitization, and antiviral activities.[17–23]

The earlier literatures for sultone synthesis involved either carbanion-mediated sulfonate intermolecular or intramolecular coupling reactions (CSIC reaction)[24] or sulfonation of olefins with dioxane-sulfur trioxide. Recently, many powerful methodologies have been developed for the synthesis of the sultones, such as intramolecular Diels–Alder reactions,[25] Pd-catalyzed intramolecular coupling reactions,[26] Rh-catalyzed C–H insertion,[27] etc. Ring-closing metathesis (RCM) is a very well known method for the construction of small to large ring size carbo- and heterocycles. The olefin metathesis reaction of sulfur-containing alkenes and dienes is a challenging area in synthetic organic chemistry research.[28] A few numbers of sultones have also been synthesized by ring-closing metathesis. For example, Metz and co-workers reported the preparation of a series of normal (five-, six- and seven-membered), medium (eight- and nine-membered), and large (15-membered) ring size sultones by ring closing metathesis (RCM).[29,30] In our continuous effort on sultone chemistry,[1a,26a] we now want to make an investigation on the synthesis of carbo- or heterocycle fused sultones using the RCM reaction. Here we report our results.

For the synthesis of sultones, the *ortho*-allylphenol derivatives **1a–g**, which are the common starting materials, were prepared according to the standard literature procedures[31] via Claisen rearrangement of their corresponding aryl allyl ether derivatives. The required precursors **2a–g** for the synthesis of seven-membered fused sultams, were prepared in 81–95% yields by the sulfonylation of **1a–g** with 2-chloroethylsulfonyl chloride. In a dichloromethane solution of the *ortho*-allylphenol derivatives **1a–g**, triethyl amine was added and stirred for 15 min at room temperature. Then the dropwise addition of 2-chloroethylsulfonyl chloride to the reaction mixture at 0 °C and stirring for 1 h at the same temperature gave the vinyl sulfonates **2a–g** in excellent yields (Table 1).

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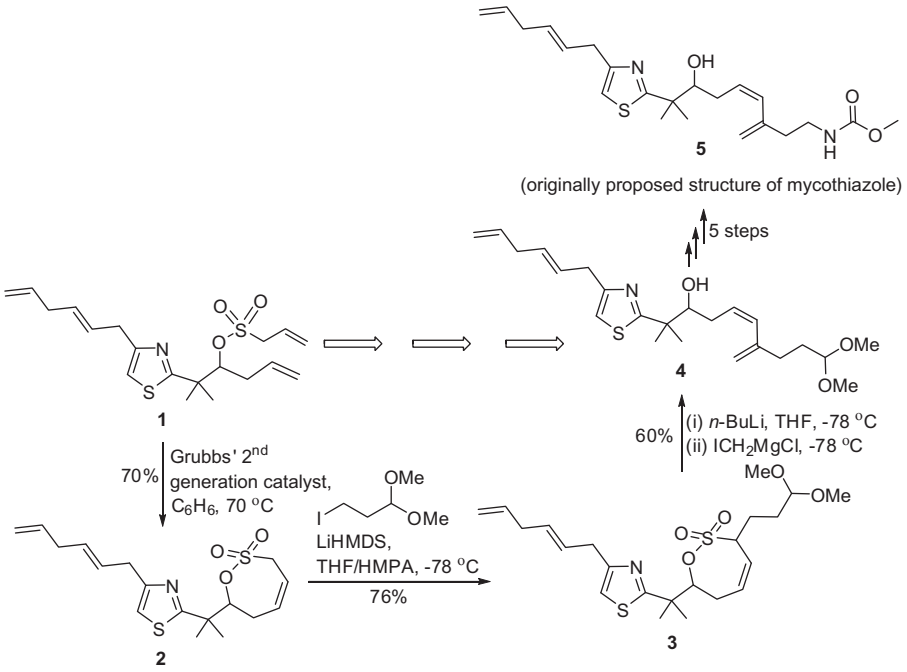
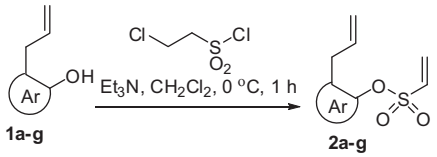


Scheme 1. Synthesis of mycothiazole via sultone intermediate.

Table 1
Synthesis of vinyl sulfonates **2a–g**



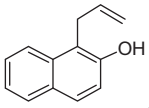
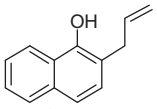
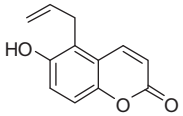
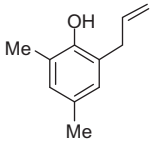
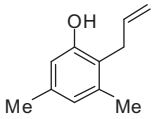
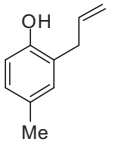
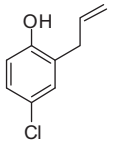
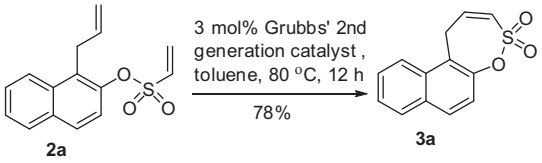
Entry	Substrate	Molecular structure of substrate	Sulfonate	Yield (%)
1	**1a**		**2a**	92
2	**1b**		**2b**	90
3	**1c**		**2c**	95
4	**1d**		**2d**	88
5	**1e**		**2e**	85
6	**1f**		**2f**	85

Table 1 (*continued*)

Entry	Substrate	Molecular structure of substrate	Sulfonate	Yield (%)
7	**1g**		**2g**	81

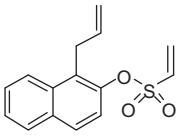
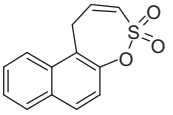
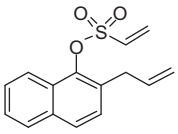
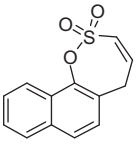
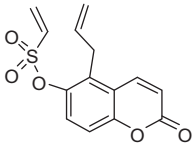
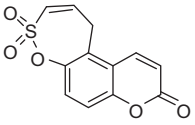
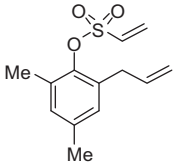
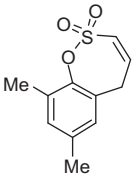
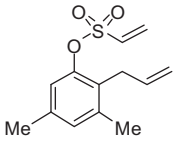
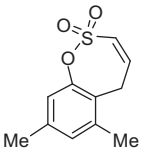


Scheme 2. Synthesis of sultone **3a**.

Now to reach the final goal that is, the synthesis of sultones by RCM, we started our experiment with the compound **2a**. At first, the compound **2a** was treated with the 5 mol % 1st generation Grubbs' catalyst in dichloromethane at room temperature. But no conversion was shown in TLC. After that we performed the same reaction in dichloromethane at a refluxing condition for 24 h and it also showed no evolution in TLC. Then we tried the above mentioned reaction with 10 mol % 1st generation Grubbs' catalyst in toluene at 80 °C for 12 h but still no cyclized product was obtained. We then went for Grubbs' 2nd generation catalyst. When the compound **2a** was subjected with 3 mol % Grubbs' 2nd generation catalyst in toluene and heated for 12 h at 80 °C, the cyclized product, that is, the sultone **3a**,[32] was obtained in 78% yield (Scheme 2).

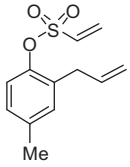
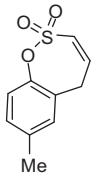
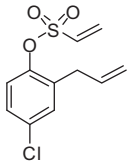
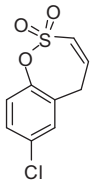
After getting satisfactory results, we treated the other sultone precursors **2b–g** with the optimized reaction conditions, that is,

Table 2
Summarized results of sultones

Entry	Sultone Precursor	Time (h)	Sultone	Yield (%)
1	 **2a**	12	 **3a**	78
2	 **2b**	12	 **3b**	80
3	 **2c**	15	 **3c**	71
4	 **2d**	12	 **3d**	79
5	 **2e**	12	 **3e**	75

(*continued on next page*)

Table 2 (*continued*)

Entry	Sultone Precursor	Time (h)	Sultone	Yield (%)
6	 **2f**	24	 **3f**	73
7	 **2g**	15	 **3g**	70

3 mol % Grubbs' 2nd generation in toluene at 80 °C for 12–24 h and obtained the sultones **3b**–**g** in 70–80% yields. All the results for the synthesis of sultones are summarized in Table 2.

In conclusion, we have successfully demonstrated the synthesis of a series of seven-membered sultones fused with different hetero- or carbocycles via ring-closing metathesis (RCM) reaction in 70–80% yields. Our next endevour, which is to study the biological activities of the newly synthesized sultones is underway and will be published in due course.

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.074.

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32. *Preparation of sultone* ***3a****:* Nitrogen gas was bubbled through a solution of compound **2a** (100 mg, 0.36 mmol) in distilled toluene (5 mL) for 10 min. Another solution of 2nd generation Grubbs' catalyst (9 mg, 3 mol %) in distilled toluene (5 mL) was also degassed by nitrogen for 10 min. Then the catalyst solution was drop-wise added to the compound solution and heated for 1 h at 80 °C under nitrogen atmosphere. The crude product was purified by silica gel column chromatography (10% ethyl acetate/pet. ether) to afford the compound **3a** (70 mg, 78%) as a white solid. mp 148–151 °C; IR (KBr,cm^{-1}) ν_{max}: 2341, 1348, 1161; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.02 (1H, d, J = 8.4 Hz), 7.92 (1H, d, J = 8.4 Hz), 7.87 (1H, d, J = 8.8 Hz), 7.61 (1H, td, J = 6.8, 1.2 Hz), 7.55 (1H, td, J = 8.0, 0.8 Hz), 7.50 (1H, d, J = 9.2 Hz), 6.78–6.72 (1H, m), 6.40 (1H, d, J = 11.2 Hz), 4.15 (2H, dd, J = 6.4, 0.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 146.3, 138.4, 132.7, 131.1, 129.9, 129.2, 128.4, 127.9, 127.6, 126.5, 122.9, 121.6, 24.3; ESI-MS: m/z: 247 (M^++H); Anal. Calcd for $C_{13}H_{10}O_3S$: C, 63.40; H, 4.09. Found: C, 63.51; H, 4.01.