Synthesis of Sultams by Ring-Closing Metathesis

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Abstract: Synthesis of a series of five-membered sultams containing different hetero- or carbocycles were obtained in good to excellent yields by ring-closing metathesis (RCM) reaction. Many sultams were precipitated from the reaction mixture and they were easily separated by filtration without further purification.

Keywords: sulfonamides, sultams, sulfonylation, ring-closing metathesis, Grubbs II catalyst

Sulfonamide-containing compounds are rarely found in nature, but they are extremely familiar because of their chemical and biological utility.[1–3] Recently, there has been great interest directed towards sultams, the cyclic counterpart of sulfonamides, as pharmaceuticals and agricultural agents.[4,5] Three biologically active sultams are shown in Figure 1.

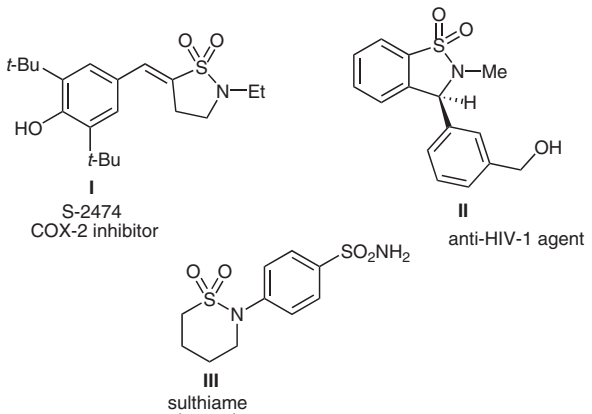

Figure 1 Selected biologically active sultams

The sultam S-2474[6] (**I**) is used as a COX-2 inhibitor whereas the compound **II**[7] acts as an anti-HIV agent. Sulthiame (**III**) is popular as a carbonic anhydrase inhibitor and used as an anticonvulsant.[8] In addition to their application as pharmaceuticals, sultams are also used as key intermediates for the total synthesis of many natural products. For example, Ley and co-workers reported[9] the total synthesis of epothilone C (a potent cytotoxic antitumor agent) via a sultam intermediate. Holmes and co-workers developed[10] the total synthesis of (–)-histrionicotoxin, (+)-histrionicotoxin, and (–)-histrionicotoxin 235A employing sultams.

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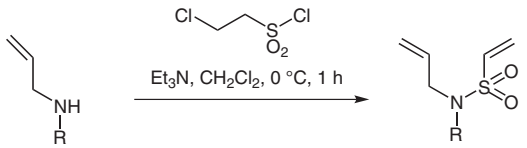
In the literature, a number of classical cyclization protocols such as Friedel–Craft,[11] dianion,[12] [3+2] cycloadditions,[13] Diels–Alder reactions,[14] etc., are reported to have been used for the synthesis of sultams. However, recently, transition-metal-catalyzed reactions like palladium-,[15] gold-,[16] copper-,[17] and rhodium-catalyzed[18] cyclization been developed for the synthesis of sultam frameworks. Ring-closing metathesis (RCM) is a very well-known method for the construction of small- to large-ring sized carbo- and heterocycles. A few sultams have also been synthesized by ring-closing metathesis. For example, an application of RCM in the synthesis of enantiopure sultams was reported[19] by Hanessian and co-workers in 2003. Subsequently, the synthesis of β-lactam-fused sultams using an RCM reaction was developed by Metz and co-workers in 2004.[20] The synthesis of a sultam with a pyramidal nitrogen at the bridgehead and a sulfur atom at the apex position was reported by Paquette and co-workers by RCM methodology.[21] A cascade ring-closure metathesis/isomerization followed by radical cyclization was utilized to synthesize sultams by Piva and co-workers.[22] The development of a ring-opening metathesis/ring-closing metathesis/cross-metathesis (ROM–RCM–CM) cascade strategy for the synthesis of diverse sultams was reported by Hanson and co-workers.[23] In our continued effort in sultam chemistry,[4a,24,25] we have now investigated the synthesis of carbo- or heterocycle-containing sultams using the RCM reaction. Here we report our results.

For the synthesis of sultams, the monoallylamine compounds **1a**–**k** (Table 1), which are common starting materials, were prepared according to standard literature procedures.[26] For example, compound **1a** was prepared by the tosylation of allylamine whereas compounds **1b**–**e**,**g**,**h** were prepared by tosylation of the corresponding amines followed by reaction with allyl bromide and finally deprotection of the tosyl group. Sometimes in the treatment of allyl bromide with the free amine, the monoallyl product appears as the major compound. We chose this method for the synthesis of monoallylamine derivatives as in the case of **1f** and **1i**. Compounds **1j** and **1k** were synthesized by the treatment of allylamine with 5-bromouracil derivatives.

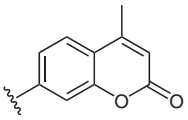
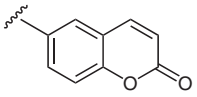
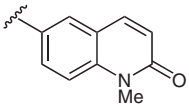
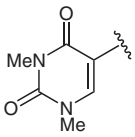
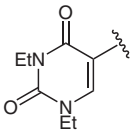
To a solution of the monoallylamines **1a**–**k** in dichloromethane, triethylamine was added and the mixture was stirred for 15 minutes at room temperature. Then 2-chloroethanesulfonyl chloride was added dropwise to the reaction mixture at 0 °C and the mixture was stirred for one hour at this temperature to give the ethenesulfonamides

2a–k in excellent yields, which are the precursors in this study of the synthesis of five-membered sultams (Table 1).

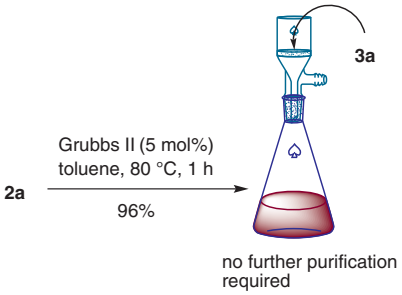
Table 1 Synthesis of Ethenesulfonamides



1a–k **2a–k**

Entry	Substrate	R	Sulfonamide	Yield (%)
1	**1a**	Ts	**2a**	85
2	**1b**	4-$O_2NC_6H_4$	**2b**	80
3	**1c**		**2c**	86
4	**1d**		**2d**	90
5	**1e**		**2e**	92
6	**1f**	3-$MeOC_6H_4$	**2f**	88
7	**1g**	Ph	**2g**	85
8	**1h**	4-MeC_6H_4	**2h**	83
9	**1i**	2-pyridyl	**2i**	85
10	**1j**		**2j**	95
11	**1k**		**2k**	92

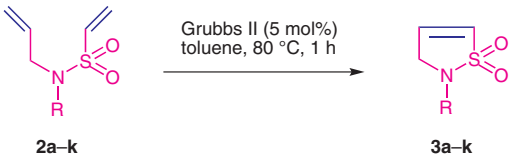
To reach the final goal, i.e. the synthesis of sultams by RCM, the RCM of *N*-allyl-*N*-tosylethenesulfonamide (**2a**) was examine. Initially, compound **2a** was treated with Grubbs I catalyst in dichloromethane at room temperature, but no conversion was shown by TLC. The same reaction was then performed under reflux for 24 hours and it also showed no reaction by TLC. Next the use of Grubbs II catalyst was examined. When compound **2a** was reacted in with 5 mol% Grubbs II catalyst in toluene at 80 °C for 1 h, interestingly, the cyclized product **3a** precipitated out of the reaction mixture. The precipitate was filtered off to give **3a** in 96% yield (100% conversion) as a white solid (Scheme 1). No further purification was needed.



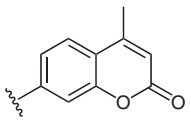
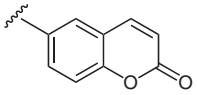
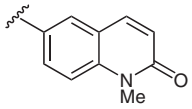
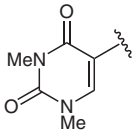
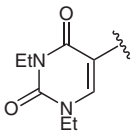
Scheme 1 Synthesis of sultam **3a**

After this satisfactory result, sultam precursors **2b–k** were reacted under the same reaction conditions, i.e., 5 mol% Grubbs II catalyst in toluene at 80 °C for one hour, and they gave the sultams **3b–k** in 60–95% yields (Table 2). Sultams **3b–e** precipitated from the reaction mixture as in the case of sultam **3a** and they were isolated by simple fil-

Table 2 RCM Reaction To Give Sultams



2a–k **3a–k**

Entry	R	Sultam	Yield (%)
1	Ts	**3a**	96
2	4-$O_2NC_6H_4$	**3b**	90
3		**3c**	92
4		**3d**	95
5		**3e**	95
6	3-$MeOC_6H_4$	**3f**	93
7	Ph	**3g**	90
8	4-MeC_6H_4	**3h**	88
9	2-pyridyl	**3i**	60
10		**3j**	92
11		**3k**	91

tration, whereas sultams **3f–k** were purified by column chromatography through a small bed of silica gel. The comparatively low yield of **3i** can be explained by the coordination of the pyridine nitrogen, which might interrupt the catalytic system of the metathesis reaction.

In conclusion, we have successfully demonstrated the synthesis of a series of five-membered sultams containing different hetero- or carbocycles via ring-closing metathesis (RCM) reaction in 60–96% yields. Our next endeavor is to study the biological activity of the newly synthesized sultams and this will be reported in due course.

Column chromatography was performed on silica gel, Merck grade 60–120 mesh. Petroleum ether = PE. Reactions were monitored by TLC (visualized: UV and iodine chamber). TLC was not performed on **3a–e** due to solubility problems. Melting points were recorded in open capillaries and are uncorrected. IR spectra were recorded on a Shimadzu FT-IR 8400S spectrophotometer using KBr discs. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ascend spectrometer (400 MHz and 100 MHz, for ^{1}H and ^{13}C, respectively) relative to the solvent [^{1}H: δ = 7.26 ($CHCl_3$) and δ = 2.50 (DMSO-d_5); ^{13}C: δ = 77.16 ($CDCl_3$) and δ = 39.52 (DMSO-d_6)]. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. CHN analyses were recorded on a 2400 series II CHN analyzer (Perkin-Elmer). All reactions were performed under a N_2 atmosphere using freshly dried solvents unless noted.

***N*-Allyl-*N*-tosylethenesulfonamide (2a); Typical Procedure**

To a solution of **1a** (250 mg, 1.18 mmol) in anhyd CH_2Cl_2 (10 mL), Et_3N (0.63 mL, 4.73 mmol) was added under a N_2 atmosphere and the mixture was stirred for 15 min at r.t. Then 2-chloroethanesulfonyl chloride (0.2 mL, 1.77 mmol) was added dropwise to the mixture at 0 °C and it was stirred for a further 1 h at the same temperature. The residual solvent was evaporated under reduced pressure and the crude product obtained was purified by column chromatography (silica gel, 20% EtOAc–PE) to afford **2a** (305 mg, 85%) as a colorless liquid; R_f = 0.55 (20% EtOAc–PE).

IR (KBr): 1620, 1365, 1164 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, J = 8.4 Hz, 2 H, H_{Ar}), 7.31 (d, J = 8.2 Hz, 2 H, H_{Ar}), 6.92 (dd, J = 16.6, 9.9 Hz, 1 H, $CHSO_2$), 6.35 (d, J = 16.6 Hz, 1 H, H_aH_bC=$CHSO_2$), 6.07 (d, J = 9.5 Hz, 1 H, H_aH_bC=$CHSO_2$), 5.87–5.78 (m, 1 H, CH_2CH=CH_aH_b), 5.28 (dd, J = 17.1, 1.1 Hz, 1 H, CH_2CH=CH_aH_b), 5.20 (dd, J = 10.2, 0.9 Hz, 1 H, CH_2CH=CH_aH_b), 4.27–4.25 (m, 2 H, CH_2CH=CH_aH_b), 2.43 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.2, 137.3, 136.8, 132.5, 129.8, 128.6, 128.4, 120.1, 51.3, 21.8.

MS (ESI): m/z = 302 [M + H]$^+$.

Anal. Calcd for $C_{12}H_{15}NO_4S_2$: C, 47.82; H, 5.02; N, 4.65. Found: C, 47.67; H, 5.14; N, 4.69.

***N*-Allyl-*N*-(4-nitrophenyl)ethenesulfonamide (2b)**

Following the typical procedure for **2a** using **1b** (250 mg, 1.40 mmol), Et_3N (0.75 mL, 5.61 mmol), and 2-chloroethanesulfonyl chloride (0.22 mL, 2.10 mmol) in anhyd CH_2Cl_2 (10 mL). The crude product was purified by column chromatography (silica gel, 20% EtOAc–PE) to afford **2b** (300 mg, 80%) as a yellowish liquid; R_f = 0.40 (20% EtOAc–PE).

IR (KBr): 1599, 1514, 1344, 1153 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (dt, J = 9.0, 1.9 Hz, 2 H, H_{Ar}), 7.47 (dt, J = 9.0, 2.0 Hz, 2 H, H_{Ar}), 6.53 (dd, J = 16.5, 9.9 Hz, 1 H, $CHSO_2$), 6.25 (d, J = 16.5 Hz, 1 H, H_aH_bC=$CHSO_2$), 6.05 (d, J = 9.8 Hz, 1 H, H_aH_bC=$CHSO_2$), 5.85–5.75 (m, 1 H, CH_2CH=CH_aH_b), 5.23–5.18 (m, 2 H, CH_2CH=CH_aH_b), 4.33–4.31 (m, 2 H, CH_2CH=CH_aH_b).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.2, 145.2, 134.1, 132.1, 129.0, 127.6, 124.6, 120.0, 53.2.

MS (ESI): m/z = 269 [M + H]$^+$.

Anal. Calcd for $C_{11}H_{12}N_2O_4S$: C, 49.24; H, 4.51; N, 10.44. Found: C, 49.33; H, 4.56; N, 10.32.

***N*-Allyl-*N*-(4-methyl-2-oxo-2*H*-1-benzopyran-7-yl)ethenesulfonamide (2c)**

Following the typical procedure for **2a** using **1c** (300 mg, 1.39 mmol), Et_3N (0.74 mL, 5.57 mmol), and 2-chloroethanesulfonyl chloride (0.22 mL, 2.10 mmol) in anhyd CH_2Cl_2 (10 mL). The crude product was purified by column chromatography (silica gel, 70% EtOAc–PE) to afford **2c** (367 mg, 86%) as a colorless liquid; R_f = 0.55 (80% EtOAc–PE).

IR (KBr): 2341, 1604, 1338, 1149 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, J = 8.5 Hz, 1 H, H_{Ar}), 7.34–7.26 (m, 2 H, H_{Ar}), 6.57 (dd, J = 16.5, 9.9Hz, 1 H, $CHSO_2$), 6.32 (s, 1 H, COCH), 6.26 (d, J = 16.5 Hz, 1 H, H_aH_bC=$CHSO_2$), 6.06 (d, J = 9.9 Hz, 1 H, H_aH_bC=$CHSO_2$), 5.87–5.80 (m, 1 H, CH_2CH=CH_aH_b), 5.22 (d, J = 16.7 Hz, 1 H, CH_2CH=CH_aH_b), 5.19 (d, J = 9.9 Hz, 1 H, CH_2CH=CH_aH_b), 4.30 (d, J = 6.0 Hz, 2 H, CH_2CH=CH_aH_b), 2.45 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4, 153.7, 151.9, 142.3, 134.1, 132.2, 128.6, 125.2, 124.1, 119.7, 119.1, 115.4, 115.2, 53.3, 18.7.

MS (ESI): m/z = 306 [M + H]$^+$.

Anal. Calcd for $C_{15}H_{15}NO_4S$: C, 59.00; H, 4.95; N, 4.59. Found: C, 59.17; H, 4.99; N, 4.51.

***N*-Allyl-*N*-(2-oxo-2*H*-1-benzopyran-6-yl)ethenesulfonamide (2d)**

Following the typical procedure for **2a** using **1d** (350 mg, 1.74 mmol), Et_3N (0.93 mL, 6.96 mmol), and 2-chloroethanesulfonyl chloride (0.27 mL, 2.61 mmol) in anhyd CH_2Cl_2 (10 mL). The crude product was purified by column chromatography (silica gel, 30% EtOAc–PE) to afford **2d** (455 mg, 90%) as a colorless liquid; R_f = 0.30 (30% EtOAc–PE).

IR (KBr): 2353, 1737, 1342, 1163 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 9.6 Hz, 1 H, COCH=C*H*), 7.44 (d, J = 2.4 Hz, 1 H, H_{Ar}), 7.39 (dd, J = 8.8, 2.5 Hz, 1 H, H_{Ar}), 7.28 (d, J = 8.8 Hz, 1 H, H_{Ar}), 6.54 (dd, J = 16.5, 9.9 Hz, 1 H, $CHSO_2$), 6.43 (d, J = 9.6 Hz, 1 H, COC*H*=CH), 6.16 (d, J = 16.5 Hz, 1 H, H_aH_bC=$CHSO_2$), 5.99 (d, J = 9.8 Hz, 1 H, H_aH_bC=$CHSO_2$), 5.82–5.72 (m, 1 H, CH_2CH=CH_aH_b), 5.14–5.10 (m, 2 H, CH_2CH=CH_aH_b), 4.19 (d, J = 6.4 Hz, 2 H, CH_2CH=CH_aH_b).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2, 153.2, 143.0, 135.1, 134.0, 132.4, 131.8, 128.7, 128.5, 119.8, 119.3, 117.8, 117.5, 53.9.

MS (ESI): m/z = 292 [M + H]$^+$.

Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50; N, 4.81. Found: C, 57.59; H, 4.61; N, 4.88.

***N*-Allyl-*N*-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yl)ethenesulfonamide (2e)**

Following the typical procedure for **2a** using **1e** (300 mg, 1.40 mmol), Et_3N (0.75 mL, 5.60 mmol), and 2-chloroethanesulfonyl chloride (0.22 mL, 2.10 mmol) in anhyd CH_2Cl_2 (10 mL). The crude product was purified by column chromatography (silica gel, 70% EtOAc–PE) to afford **2e** (395 mg, 92%) as a light yellowish liquid; R_f = 0.50 (70% EtOAc–PE).

IR (KBr): 2339, 1741, 1654, 1344 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, J = 9.5 Hz, 1 H, COCH=C*H*), 7.47–7.45 (m, 2 H, H_{Ar}), 7.33 (d, J = 9.8 Hz, 1 H,

H_{Ar}), 6.72 (d, J = 9.5 Hz, 1 H, COC*H*=CH), 6.55 (dd, J = 16.5, 9.8 Hz, 1 H, $CHSO_2$), 6.17 (d, J = 16.6 Hz, 1 H, H_aH_bC=$CHSO_2$), 5.99 (d, J = 9.9 Hz, 1 H, H_aH_bC=$CHSO_2$), 5.86–5.76 (m, 1 H, CH_2CH=CH_aH_b), 5.16–5.11 (m, 2 H, CH_2CH=CH_aH_b), 4.22 (d, J = 6.4 Hz, 2 H, CH_2CH=CH_aH_b), 3.69 (s, 3 H, NCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 139.6, 138.6, 134.3, 133.1, 132.7, 131.1, 128.9, 128.2, 122.8, 121.1, 119.7, 115.2, 54.0, 29.7.

MS (ESI): m/z = 305 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.20. Found: C, 59.01; H, 5.22; N, 9.29.

***N*-Allyl-*N*-(3-methoxyphenyl)ethenesulfonamide (2f)**
Following the typical procedure for **2a** using **1f** (300 mg, 1.84 mmol), Et_3N (1 mL, 7.35 mmol), and 2-chloroethanesulfonyl chloride (0.30 mL, 2.76 mmol) in anhyd CH_2Cl_2 (10 mL). The crude product was purified by column chromatography (silica gel, 30% EtOAc–PE) to afford **2f** (410 mg, 88%) as a light greenish liquid; R_f = 0.50 (30% EtOAc–PE).

IR (KBr): 2354, 1735, 1598, 1340 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.25 (m, 1 H, H_{Ar}), 6.89–6.85 (m, 3 H, H_{Ar}), 6.56 (dd, J = 16.6, 9.9 Hz, 1 H, $CHSO_2$), 6.20 (d, J = 16.6 Hz, 1 H, H_aH_bC=$CHSO_2$), 5.98 (d, J = 9.9 Hz, 1 H, H_aH_bC=$CHSO_2$), 5.88–5.78 (m, 1 H, CH_2CH=CH_aH_b), 5.20–5.12 (m, 2 H, CH_2CH=CH_aH_b), 4.20 (d, J = 6.3 Hz, 2 H, CH_2CH=CH_aH_b), 3.81 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 140.3, 134.4, 132.9, 129.8, 127.6, 120.7, 119.1, 115.0, 113.5, 55.5, 53.9.

MS (ESI): m/z = 254 $[M + H]^+$.

Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 56.99; H, 5.91; N, 5.62.

***N*-Allyl-*N*-phenylethenesulfonamide (2g)**
Following the typical procedure for **2a** using **1g** (350 mg, 2.63 mmol), Et_3N (1.40 mL, 10.51 mmol), and 2-chloroethanesulfonyl chloride (0.42 mL, 3.94 mmol) in anhyd CH_2Cl_2 (10 mL). The crude product was purified by column chromatography (silica gel, 10% EtOAc–PE) to afford **2g** (500 mg, 85%) as a colorless liquid; R_f = 0.45 (10% EtOAc–PE).

IR (KBr): 2337, 1593, 1338 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.29 (m, 5 H, H_{Ar}), 6.56 (dd, J = 16.5, 9.9 Hz, 1 H, $CHSO_2$), 6.16 (d, J = 16.5 Hz, 1 H, H_aH_bC=$CHSO_2$), 5.97 (d, J = 9.9 Hz, 1 H, H_aH_bC=$CHSO_2$), 5.87–5.77 (m, 1 H, CH_2CH=CH_aH_b), 5.18–5.11 (m, 2 H, CH_2CH=CH_aH_b), 4.22 (d, J = 6.3 Hz, 2 H, CH_2CH=CH_aH_b).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.0, 134.3, 132.8, 129.2, 128.8, 128.0, 127.6, 119.0, 53.8.

MS (ESI): m/z = 224 $[M + H]^+$.

Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27. Found: C, 59.26; H, 5.94; N, 6.19.

***N*-Allyl-*N*-(4-methylphenyl)ethenesulfonamide (2h)**
Following the typical procedure for **2a** using **1h** (350 mg, 2.38 mmol), Et_3N (1.27 mL, 9.51 mmol), and 2-chloroethanesulfonyl chloride (0.38 mL, 3.57 mmol) in anhyd CH_2Cl_2 (10 mL). The crude product was purified by column chromatography (silica gel, 10% EtOAc–PE) to afford **2h** (470 mg, 83%) as a light orange liquid; R_f = 0.30 (10% EtOAc–PE).

IR (KBr): 2354, 1915, 1514, 1338 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (s, 4 H, H_{Ar}), 6.56 (dd, J = 16.5, 9.9 Hz, 1 H, $CHSO_2$), 6.16 (d, J = 16.5 Hz, 1 H, H_aH_bC=$CHSO_2$), 5.96 (d, J = 10.0 Hz, 1 H, H_aH_bC=$CHSO_2$), 5.86–5.77 (m, 1 H, CH_2CH=CH_aH_b), 5.18–5.11 (m, 2 H, CH_2CH=CH_aH_b), 4.19 (dt, J = 6.2, 1.1 Hz, 2 H, CH_2CH=CH_aH_b), 2.35 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1, 136.4, 134.4, 133.0, 129.9, 128.7, 127.4, 118.9, 53.9, 21.1.

MS (ESI): m/z = 238 $[M + H]^+$.

Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90. Found: C, 60.82; H, 6.29; N, 5.79.

***N*-Allyl-*N*-(2-pyridyl)ethenesulfonamide (2i)**
Following the typical procedure for **2a** using **1i** (250 mg, 1.86 mmol), Et_3N (1 mL, 7.45 mmol), and 2-chloroethanesulfonyl chloride (0.30 mL, 2.79 mmol) in anhyd CH_2Cl_2 (10 mL). The crude product was purified by column chromatography (silica gel, 20% EtOAc–PE) to afford **2i** (358 mg, 85%) as a yellowish liquid; R_f = 0.60 (20% EtOAc–PE).

IR (KBr): 2337, 1587, 1151 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40–8.39 (m, 1 H, H_{Ar}), 7.68 (td, J = 7.7, 2.0 Hz, 1 H, H_{Ar}), 7.39 (d, J = 8.1 Hz, 1 H, H_{Ar}), 7.15–7.12 (m, 1 H, H_{Ar}), 6.67 (dd, J = 16.6, 9.9 Hz, 1 H, $CHSO_2$), 6.25 (d, J = 16.6 Hz, 1 H, H_aH_bC=$CHSO_2$), 5.96 (d, J = 9.9 Hz, 1 H, H_aH_bC=$CHSO_2$), 5.90–5.80 (m, 1 H, CH_2CH=CH_aH_b), 5.21 (dd, J = 17.2, 1.4 Hz, 1 H, CH_2CH=CH_aH_b), 5.10 (dd, J = 10.2, 1.3 Hz, 1 H, CH_2CH=CH_aH_b), 4.43 (dt, J = 5.9, 1.3 Hz, 2 H, CH_2CH=CH_aH_b).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.6, 148.4, 138.1, 135.2, 133.1, 127.5, 121.7, 121.3, 118.5, 51.1.

MS (ESI): m/z = 225 $[M + H]^+$.

Anal. Calcd for $C_{10}H_{12}N_2O_2S$: C, 53.55; H, 5.39; N, 12.49. Found: C, 53.59; H, 5.44; N, 12.41.

***N*-Allyl-*N*-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethenesulfonamide (2j)**
Following the typical procedure for **2a** using **1j** (300 mg, 1.54 mmol), Et_3N (0.82 mL, 6.15 mmol), and 2-chloroethanesulfonyl chloride (0.24 mL, 2.30 mmol) in anhyd CH_2Cl_2 (10 mL). The crude product was purified by column chromatography (silica gel, 50% EtOAc–PE) to afford **2j** (415 mg, 95%) as a white solid; mp 112–115 °C; R_f = 0.60 (50% EtOAc–PE).

IR (KBr): 2333, 1668, 1157 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (s, 1 H, CH), 6.62 (dd, J = 16.5, 9.9 Hz, 1 H, $CHSO_2$), 6.23 (d, J = 16.5 Hz, 1 H, H_aH_bC=$CHSO_2$), 5.98 (d, J = 9.9 Hz, 1 H, H_aH_bC=$CHSO_2$), 5.80–5.70 (m, 1 H, CH_2CH=CH_aH_b), 5.16–5.11 (m, 2 H, CH_2CH=CH_aH_b), 3.99 (d, J = 5.2 Hz, 2 H, CH_2CH=CH_aH_b), 3.39 (s, 3 H, NCH_3), 3.30 (s, 3 H, NCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 151.0, 147.0, 135.3, 133.0, 127.6, 119.6, 111.8, 51.4, 37.6, 28.4.

MS (ESI): m/z = 286 $[M + H]^+$.

Anal. Calcd for $C_{11}H_{15}N_3O_4S$: C, 46.31; H, 5.30; N, 14.73. Found: C, 46.41; H, 5.37; N, 14.79.

***N*-Allyl-*N*-(1,3-diethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethenesulfonamide (2k)**
Following the typical procedure for **2a** using **1k** (300 mg, 1.34 mmol), Et_3N (0.72 mL, 5.37 mmol), and 2-chloroethanesulfonyl chloride (0.21 mL, 2.01 mmol) in anhyd CH_2Cl_2 (10 mL). The crude product was purified by column chromatography (silica gel, 20% EtOAc–PE) to afford **2k** (389 mg, 92%) as a white solid; mp 92–95 °C; R_f = 0.50 (20% EtOAc–PE).

IR (KBr): 2333, 1649, 1452, 1139 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (s, 1 H, CH), 6.64 (dd, J = 16.5, 9.9 Hz, 1 H, $CHSO_2$), 6.24 (d, J = 16.5 Hz, 1 H, H_aH_bC=$CHSO_2$), 5.98 (d, J = 9.9 Hz, 1 H, H_aH_bC=$CHSO_2$), 5.81–5.72 (m, 1 H, CH_2CH=CH_aH_b), 5.17–5.12 (m, 2 H, CH_2CH=CH_aH_b), 4.00 (d, J = 6.0 Hz, 2 H, CH_2CH=CH_aH_b), 3.99–3.94 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 3.83–3.78 (q, J = 7.3 Hz, 2 H, CH_2CH_3), 1.31 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.19 (t, J = 7.1 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 150.2, 145.9, 135.4, 133.1, 127.4, 119.6, 112.1, 51.4, 45.4, 37.2, 14.3, 12.8.

MS (ESI): *m*/*z* = 314 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{19}N_3O_4S$: C, 49.83; H, 6.11; N, 13.41. Found: C, 49.77; H, 6.18; N, 13.36.

2-Tosyl-2,3-dihydroisothiazole 1,1-Dioxide (3a); Typical Procedure

N_2 gas was bubbled through a solution of **2a** (100 mg, 0.33 mmol) in distilled toluene (5 mL) for 10 min (substrate solution). A solution of Grubbs II catalyst (14 mg, 5 mol%) in distilled toluene (5 mL) was also degassed with N_2 for 10 min (catalyst solution). Then the catalyst solution was added dropwise to the substrate solution and the mixture was heated for 1 h at 80 °C under N_2. The product was precipitated out and it was filtered off to afford **3a** (87 mg, 96%) as a white solid; mp >250 °C.

IR (KBr): 3091, 2331, 1348, 1174 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (d, *J* = 8.3 Hz, 2 H, H_{Ar}), 6.57 (d, *J* = 8.1 Hz, 2 H, H_{Ar}), 6.40 (dt, *J* = 7.1, 2.1 Hz, 1 H, SO_2CH), 6.20 (dt, *J* = 7.1, 2.1 Hz, 1 H, CH_2CH), 3.46 (t, *J* = 2.2 Hz, 2 H, CH_2CH), 2.47 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 145.6, 135.4, 133.4, 130.1, 128.1, 126.4, 50.6, 21.4.

MS (ESI): *m*/*z* = 296 $[M + Na]^+$.

Anal. Calcd for $C_{10}H_{11}NO_4S_2$: C, 43.94; H, 4.06; N, 5.12. Found: C, 44.02; H, 3.99; N, 5.18.

2-(4-Nitrophenyl)-2,3-dihydroisothiazole 1,1-Dioxide (3b)

Following the typical procedure for **3a** using **2b** (100 mg, 0.37 mmol), Grubbs II catalyst (16 mg, 5 mol%), and distilled toluene (10 mL). The product was precipitated out and filtered off to afford **3b** (81 mg, 90%) as a white solid; mp >250 °C.

IR (KBr): 3093, 2339, 1298, 1122 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 9.2 Hz, 2 H, H_{Ar}), 6.51–6.46 (m, 4 H, H_{Ar}, SO_2CH, CH_2CH), 3.76 (d, *J* = 2.0 Hz, 2 H, CH_2CH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 143.0, 141.8, 136.5, 126.5, 125.6, 115.7, 50.5.

MS (ESI): *m*/*z* = 263 $[M + Na]^+$.

Anal. Calcd for $C_9H_8N_2O_4S$: C, 45.00; H, 3.36; N, 11.66. Found: C, 45.12; H, 3.43; N, 11.59.

2-(4-Methyl-2-oxo-2*H*-1-benzopyran-7-yl)-2,3-dihydroisothiazole 1,1-Dioxide (3c)

Following the typical procedure for **3a** using **2c** (100 mg, 0.33 mmol), Grubbs II catalyst (14 mg, 5 mol%), and distilled toluene (10 mL). The product was precipitated out and filtered off to afford **3c** (84 mg, 92%) as a white solid; mp >250 °C.

IR (KBr): 3056, 2331, 1685, 1135 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (d, *J* = 8.8 Hz, 1 H, H_{Ar}), 6.60–6.56 (m, 2 H, H_{Ar}), 6.50 (dd, *J* = 8.7, 1.7 Hz, 1 H, SO_2CH), 6.31 (d, *J* = 1.4 Hz, 1 H, COCH), 5.43 (s, 1 H, CH_2CH), 3.85 (s, 2 H, CH_2CH), 1.56 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.8, 154.1, 153.1, 140.3, 136.3, 126.6, 126.6, 114.5, 112.3, 103.2, 50.4, 18.0.

MS (ESI): *m*/*z* = 278 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; N, 5.05. Found: C, 56.22; H, 3.92; N, 5.13.

2-(2-Oxo-2*H*-1-benzopyran-6-yl)-2,3-dihydroisothiazole 1,1-Dioxide (3d)

Following the typical procedure for **3a** using **2d** (100 mg, 0.34 mmol), Grubbs II catalyst (15 mg, 5 mol%), and distilled toluene (10 mL). The product was precipitated out and filtered off to afford **3d** (86 mg, 95%) as a white solid; mp >250 °C.

IR (KBr): 3070, 2335, 1728, 1182 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (d, *J* = 9.6 Hz, 1 H, COCH=C*H*), 6.60–6.57 (m, 2 H, H_{Ar}), 6.46 (d, *J* = 8.8 Hz, 1 H, H_{Ar}), 6.37 (s, 2 H, SO_2CH, CH_2CH), 5.50 (d, *J* = 9.5 Hz, 1 H, COC*H*=CH), 3.62 (s, 2 H, CH_2CH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.1, 149.9, 144.0, 136.5, 133.5, 126.7, 122.3, 119.5, 117.7, 117.3, 117.2, 51.1.

MS (ESI): *m*/*z* = 264 $[M + H]^+$.

Anal. Calcd for $C_{12}H_9NO_4S$: C, 54.75; H, 3.45; N, 5.32. Found: C, 54.84; H, 3.51; N, 5.37.

2-(1-Methyl-2-oxo-1,2-dihydroquinolin-6-yl)-2,3-dihydroisothiazole 1,1-Dioxide (3e)

Following the typical procedure for **3a** using **2e** (100 mg, 0.33 mmol), Grubbs II catalyst (14 mg, 5 mol%), and distilled toluene (10 mL). The product was precipitated out and filtered off to afford **3e** (87 mg, 95%) as a white solid; mp >250 °C.

IR (KBr): 3074, 2337, 1652, 1280 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.96 (d, *J* = 9.5 Hz, 1 H, COCH=C*H*), 6.74–6.65 (m, 3 H, H_{Ar}), 6.46 (s, 2 H, SO_2CH, CH_2CH), 5.72 (d, *J* = 9.6 Hz, 1 H, COC*H*=CH), 3.71 (s, 2 H, CH_2CH), 2.68 (s, 3 H, NCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.9, 138.8, 136.4, 131.3, 126.8, 122.2, 122.1, 120.8, 117.9, 116.0, 51.1, 29.2.

MS (ESI): *m*/*z* = 277 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{12}N_2O_3S$: C, 56.51; H, 4.38; N, 10.14. Found: C, 56.62; H, 4.44; N, 10.07.

2-(3-Methoxyphenyl)-2,3-dihydroisothiazole 1,1-Dioxide (3f)

Following the typical procedure for **3a** using **2f** (100 mg, 0.39 mmol), Grubbs II catalyst (17 mg, 5 mol%), and distilled toluene (10 mL). The crude product was purified by column chromatography (silica gel, 50% EtOAc–PE) to afford **3f** (83 mg, 93%) as a white solid; mp 83–86 °C; R_f = 0.45 (50% EtOAc–PE).

IR (KBr): 3085, 2335, 1604, 1290 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (t, *J* = 8.2 Hz, 1 H, H_{Ar}), 6.88 (d, *J* = 7.1 Hz, 1 H, H_{Ar}), 6.83–6.79 (m, 2 H, H_{Ar}), 6.66 (d, *J* = 7.0 Hz, 1 H, SO_2CH), 6.60 (dd, *J* = 8.4, 1.9 Hz, 1 H, CH_2CH), 4.34 (s, 2 H, CH_2CH), 3.72 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 137.8, 134.0, 130.5, 127.6, 110.5, 109.6, 104.6, 55.5, 50.8.

MS (ESI): *m*/*z* = 226 $[M + H]^+$.

Anal. Calcd for $C_{10}H_{11}NO_3S$: C, 53.32; H, 4.92; N, 6.22. Found: C, 53.44; H, 4.88; N, 6.28.

2-Phenyl-2,3-dihydroisothiazole 1,1-Dioxide (3g)

Following the typical procedure for **3a** using **2g** (100 mg, 0.45 mmol), Grubbs II catalyst (19 mg, 5 mol%), and distilled toluene (10 mL). The crude product was purified by column chromatography (silica gel, 50% EtOAc–PE) to afford **3g** (78 mg, 90%) as a white solid; mp 145–148 °C; R_f = 0.30 (30% EtOAc–PE).

IR (KBr): 3072, 2572, 1496, 1282 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (t, *J* = 8.5 Hz, 2 H, H_{Ar}), 7.31 (d, *J* = 7.7 Hz, 2 H, H_{Ar}), 7.15 (t, *J* = 7.2 Hz, 1 H, H_{Ar}), 6.97 (dt, *J* = 7.1, 2.4 Hz, 1 H, SO_2CH), 6.75 (dt, *J* = 7.1, 2.0 Hz, 1 H, CH_2CH), 4.44 (t, *J* = 2.2 Hz, 2 H, CH_2CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.6, 133.9, 129.8, 127.7, 124.5, 118.6, 50.8.

MS (ESI): *m*/*z* = 196 $[M + H]^+$.

Anal. Calcd for $C_9H_9NO_2S$: C, 55.37; H, 4.65; N, 7.17. Found: C, 55.46; H, 4.59; N, 7.28.

2-(4-Methylphenyl)-2,3-dihydroisothiazole 1,1-Dioxide (3h)
Following the typical procedure for **3a** using **2h** (100 mg, 0.42 mmol), Grubbs II catalyst (18 mg, 5 mol%), and distilled toluene (10 mL). The crude product was purified by column chromatography (silica gel, 50% EtOAc–PE) to afford **3h** (78 mg, 88%) as a white solid; mp 158–161 °C; R_f = 0.50 (50% EtOAc–PE).

IR (KBr): 3083, 2339, 1610, 1284 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.17 (m, 4 H, H_{Ar}), 6.96 (dt, *J* = 7.1, 3.1 Hz, 1 H, SO_2CH), 6.74 (dt, *J* = 7.1, 1.9 Hz, 1 H, CH_2CH), 4.41 (t, *J* = 2.4 Hz, 2 H, CH_2CH), 2.32 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.8, 134.1, 133.8, 130.3, 127.6, 119.9, 51.4, 20.9.

MS (ESI): *m*/*z* = 232 $[M + Na]^+$.

Anal. Calcd for $C_{10}H_{11}NO_2S$: C, 57.39; H, 5.30; N, 6.69. Found: C, 57.28; H, 5.38; N, 6.65.

2-(2-Pyridyl)-2,3-dihydroisothiazole 1,1-Dioxide (3i)
Following the typical procedure for **3a** using **2i** (100 mg, 0.45 mmol), Grubbs II catalyst (19 mg, 5 mol%), and distilled toluene (10 mL). The crude product was purified by column chromatography (silica gel, 70% EtOAc–PE) to afford **3i** (52 mg, 60%) as a white solid; mp 103–106 °C; R_f = 0.45 (70% EtOAc–PE).

IR (KBr): 2923, 2339, 1290, 1139 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 4.2 Hz, 1 H, H_{Ar}), 7.69 (td, *J* = 8.6, 1.6 Hz, 1 H, H_{Ar}), 7.43(d, *J* = 8.4 Hz, 1 H, H_{Ar}), 7.04–7.00 (m, 2 H, H_{Ar}, SO_2CH), 6.76 (d, *J* = 7.0 Hz, 1 H, CH_2CH), 4.74 (s, 2 H, CH_2CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.5, 148.4, 138.4, 134.6, 127.4, 118.8, 111.3, 49.6.

MS (ESI): *m*/*z* = 197 $[M + H]^+$.

Anal. Calcd for $C_8H_8N_2O_2S$: C, 48.97; H, 4.11; N, 14.28. Found: C, 49.09; H, 4.16; N, 14.21.

2-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2,3-dihydroisothiazole 1,1-Dioxide (3j)
Following the typical procedure for **3a** using **2j** (100 mg, 0.35 mmol), Grubbs II catalyst (15 mg, 5 mol%), and distilled toluene (10 mL). The crude product was purified by column chromatography (silica gel, 70% EtOAc–PE) to afford **3j** (83 mg, 92%) as a white solid; mp 149–152 °C; R_f = 0.30 (70% EtOAc–PE).

IR (KBr): 3074, 1660, 1448, 1288 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.60 (s, 1 H, CH), 6.98 (d, *J* = 6.8 Hz, 1 H, SO_2CH), 6.80 (d, *J* = 7.2 Hz, 1 H, CH_2CH), 4.46 (s, 2 H, CH_2CH), 3.40 (s, 3 H, NCH_3), 3.30 (s, 3 H, NCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.0, 151.0, 144.5, 136.2, 126.3, 108.0, 51.9, 37.4, 28.3.

MS (ESI): *m*/*z* = 258 $[M + H]^+$.

Anal. Calcd for $C_9H_{11}N_3O_4S$: C, 42.02; H, 4.31; N, 16.33. Found: C, 42.12; H, 4.22; N, 16.39.

2-(1,3-Diethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2,3-dihydroisothiazole 1,1-Dioxide (3k)
Following the typical procedure for **3a** using **2k** (100 mg, 0.32 mmol), Grubbs II catalyst (14 mg, 5 mol%), and distilled toluene (10 mL). The crude product was purified by column chromatography (silica gel, 70% EtOAc–PE) to afford **3k** (83 mg, 91%) as a colorless liquid; R_f = 0.40 (70% EtOAc–PE).

IR (KBr): 3074, 2327, 1652, 1288 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (s, 1 H, CH), 6.99 (dt, *J* = 7.1, 2.3 Hz, 1 H, SO_2CH), 6.81 (dt, *J* = 7.1, 2.3 Hz, 1 H, CH_2CH), 4.49 (t, *J* = 2.4 Hz, 2 H, CH_2CH), 4.00–3.95 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 3.85–3.79 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 1.32 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.20 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 150.2, 143.2, 136.1, 126.4, 108.5, 52.0, 45.4, 37.2, 14.4, 12.8.

MS (ESI): *m*/*z* = 286 $[M + H]^+$.

Anal. Calcd for $C_{11}H_{15}N_3O_4S$: C, 46.31; H, 5.30; N, 14.73. Found: C, 46.44; H, 5.39; N, 14.69.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are copies of ^1H and ^{13}C NMR spectra of all new compounds.

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