Ring-Closing Enyne Metathesis (RCEYM) for the Synthesis of Cyclic Sulfoximines

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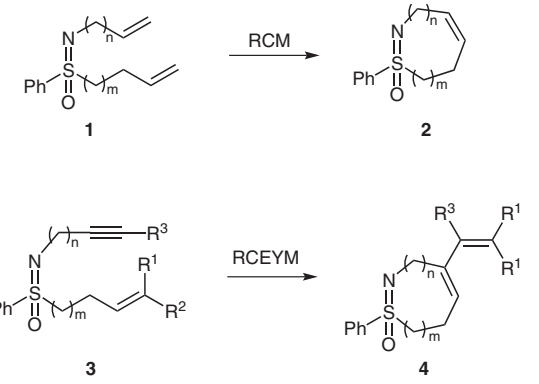
Abstract: Heterocyclic sulfoximines have been synthesized by RCEYM reactions starting from *N*-alkynyl-*S*-alkenyl sulfoximines in up to 79% yield. The products can be converted to tricyclic derivatives by a domino Diels–Alder/aromatization reaction sequence.

Key words: enynes, heterocycles, ring-closing metathesis, sulfoximines, tricycles

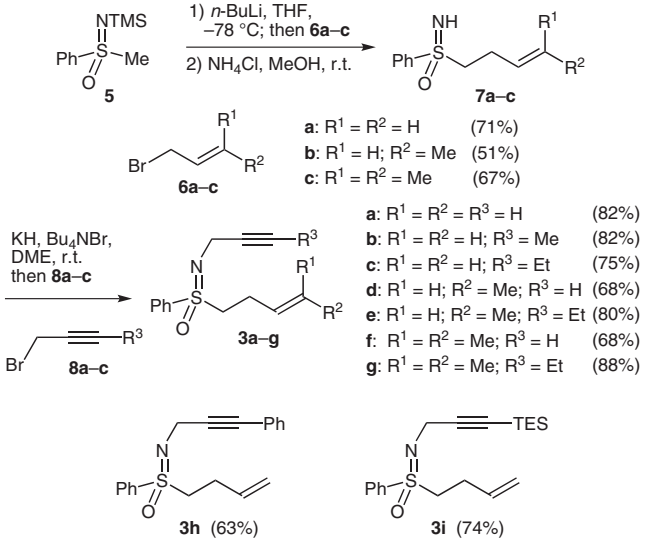
Sulfoximines are valuable sulfur reagents, which have been used in asymmetric synthesis[1] and as building blocks for pseudopeptides.[2] Various strategies for the synthesis of heterocyclic derivatives have been described,[3–6] and among them metathesis reactions are particularly attractive, because they open access to macrocyclic products, which are difficult to synthesize by other means.

In 2005 we reported ring-closing olefin metathesis (RCM) reactions of *N*,*S*-dialkenyl sulfoximines **1** affording heterocyclic sulfoximines **2** in yields up to 97%.[5] We now envisaged to expand this concept. If analogous enyne metathesis (RCEYM) reactions[7] were applicable, sulfoximines **4** should result starting from *N*-alkynyl-*S*-alkenyl sulfoximines **3**. Subsequent conversions of **4** involving the 1,3-diene moiety would then allow further variations of the heterocyclic motif (Scheme 1).

Doubly unsaturated sulfoximines **3a–i** were synthesized starting from *N*-TMS-protected *S*-methyl-*S*-phenyl sulfoximine **5**. Deprotonation of **5** with *n*-BuLi in THF and treatment of the resulting anion with allyl bromides **6a–c** at –78 °C led, after N-deprotection, to *N*(*H*)-*S*-alkenyl-*S*-phenyl sulfoximines **7a–c** in yields ranging from 51–71%. Even with only 1.0 equivalent of *n*-BuLi double α-alkylation of **5** was observed (at –78 °C), when the addition of the alkenyl bromide was slow. The best results were obtained when either an excess of **6** was rapidly added to the preformed carbanion or when the latter was slowly transferred into a solution of the alkenyl bromide by syringe pump. The subsequent N-functionalizations were easily performed following a standard protocol.[8] Thus, deprotonation of **7a–c** with KH and treatment of the resulting anion with the corresponding bromoalkynes **8a–c** under phase-transfer conditions at room temperature in DME led to doubly unsaturated sulfoximines **3a–g** in good yields (68–88%). Sonogashira coupling of **3a** with phenyl iodide afforded phenyl-substituted derivative **3h** in 63% yield,[9] and silylation of **3a** with TESCl gave TES-protected alkyne **3i** in 74% yield (Scheme 2).[10]



Scheme 1 Approaches to heterocyclic sulfoximines by RCM and RCEYM reactions



Scheme 2 Synthesis of *N*-alkynyl-*S*-alkenyl sulfoximines

The search for the optimal reaction conditions to convert **3a** efficiently to its cyclized product **9a** started with testing Grubbs I (G1) and Grubbs II (G2) metathesis catalysts (10 mol%). Whereas G1 proved to be unsuitable leading to a low yield of **9a** due to only partial conversion of **3a** (Table 1, entries 1–3), the application of G2 (in toluene under reflux) afforded **9a** in 45% yield (with full conversion of **3a** after 1 h; Table 1, entry 4). Reducing the reac-

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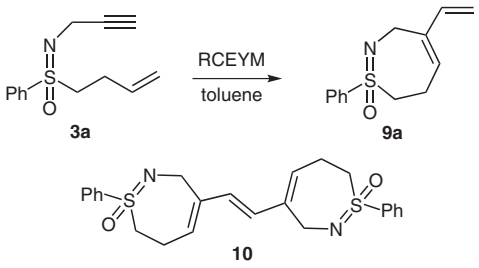
Table 1 Optimization of the RCEYM Reaction Conditions

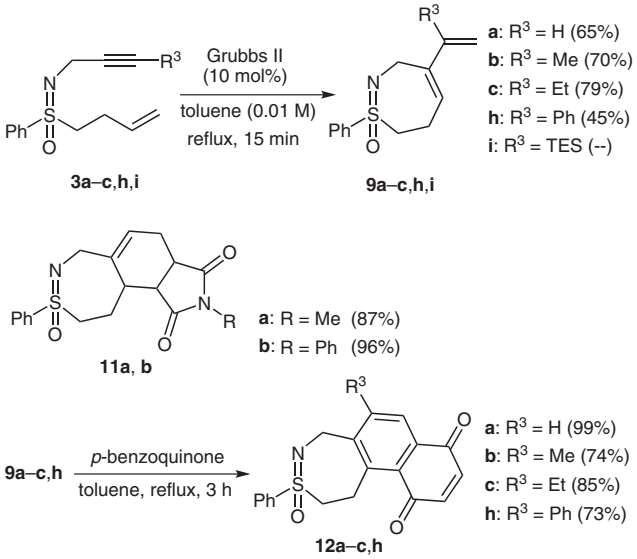


Entry	Cat.	Cat. amount (mol%)	Concn of **3a**	Temp (°C)	Time (h)	Yield of **9a** (%)
1[a]	G1	10	0.01	50	24	0[b]
2	G1	10	0.01	120	96	12[b]
3	G1	10	0.01	120	1	11[b]
4	G2	10	0.01	120	1	45
5	G2	10	0.01	120	0.25	65
6	G2	10	0.01	120	0,0167	41
7	G2	10	0.01	80	0.25	36[b]
8[c]	G2	10	0.01	120	0.25	45
9	G2	5	0.01	120	0.25	33[b]
10	G2	20	0.01	120	0.25	39
11	G2	3.3 (3×)	0.01	120	0.25	50
12	G2	10	0.003	120	0.25	57
13	G2	10	0.001	120	0.25	39
14[c]	G2	10	0.003	120	0.25	49
15	G2	3.3 (3×)	0.003	120	0.25	47

[a] Use of CH_2Cl_2 instead of toluene.
[b] Incomplete conversion, **3a** remaining.
[c] Under an atmosphere of ethylene (1 atm).

tion time to 15 minutes led to an increased yield of 65% (entry 5). After one minute reaction time **9a** was obtained in a remarkable 41% yield (entry 6). Lowering the reaction temperature from 120 °C to 80 °C resulted in incomplete conversion of the substrate affording **9a** in 36% yield (entry 7). When the reaction was performed under an atmosphere of ethylene **9a** was obtained in 45% yield (entry 8). Neither varying the catalyst amount from 10 mol% to 5 mol% or 20 mol% nor applying sequential catalyst additions (three times 3.3 mol% each of G2 with 5 min intervals) led to an improvement in the yield of **9a** (Table 1, entries 9–11). Because in all reactions 10–20% of byproduct **10** (stemming from a homocoupling of **9a**) was detected, substrate concentration effects were studied. However, even when the reaction mixture was diluted by a factor of 3 or 10, the yield of **9a** did not increase and a small amount of **10** remained detectable (entries 12 and 13). Also performing these high dilution experiments under an atmosphere of ethylene or applying multiple catalyst additions did not substantially change the yield of **9a** (Table 1, entries 14 and 15).

Next, the substrate scope was investigated (Scheme 3).[11] Compared to **3a**, having an unsubstituted alkynyl group, methyl-substituted sulfoximine **3b** delivered the corresponding product **9b** with a slightly higher yield (70%). Sulfoximine **3c** with an ethyl group at the alkynyl moiety led to **9c** in 79% yield, whereas **3h**, bearing a phenyl substituent, yielded only 45% of RCEYM product **9h**. Probably due to the steric hinderance induced by the bulky silyl substituent, sulfoximine **3i** with a TES group did not react at all. Interestingly, homocoupled products were not detected in any case. Experiments with methyl- or dimethyl-substituted alkenes **3d–g** remained unsuccessful indicating the required presence of an unsubstituted alkenyl moiety.



Scheme 3 RCEYM and Diels–Alder–aromatization reactions leading to tricyclic sulfoximines

Reactions of RCEYM product **9a** with *N*-methyl maleiimide and *N*-phenyl maleiimide in toluene under reflux for three hours gave Diels–Alder products **11a** and **11b** in 87% and 96% yield, respectively.[11] Under the same conditions, attempts to use maleic acid anhydride, maleiic acid methyl ester, and diethylacetylenedicarboxylate as dienophiles in combination with **9a** remained unsuccessful. When *p*-benzoquinone was applied, aromatized product **12a** stemming from a domino Diels–Alder–aromatization reaction sequence was obtained in 99% yield. Analogously, RCEYM products **9b**,**c**,**h** gave the aromatized products **12b**,**c**,**h** in yields ranging from 73–85%.

With the goal to expand the reaction scope and to open synthetic access to new heterocyclic sulfoximines with larger rings, doubly unsaturated substrates **13–18** with various tether lengths were prepared (Figure 1). Unfortunately, however, none of them reacted well under the RCEYM conditions described in Scheme 3, and low con-

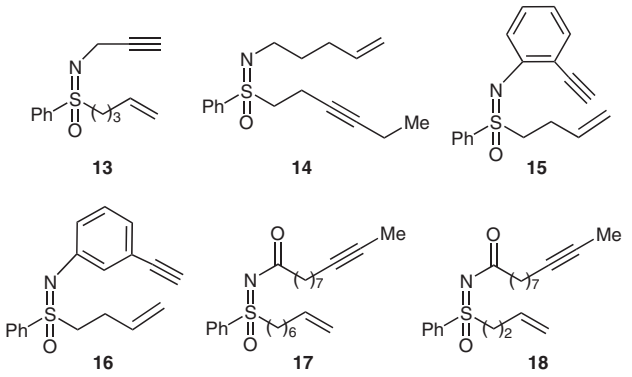


Figure 1 Doubly unsaturated sulfoximines, which were unreactive in the RCEYM reaction

versions led at best to trace amounts (<10%) of cyclized products.

In summary, we investigated the RCEYM reaction of *N*-alkynyl-*S*-alkenyl sulfoximines. The product yields were highly dependent on the substrate structure. Seven-membered heterocyclic sulfoximines were obtained in up to 79% yield. The resulting RCEYM products could be converted to more complex heterocycles by Diels–Alder reactions. With *p*-benzoquinone as dienophile a domino Diels–Alder–oxidation sequence led to products with aromatized cores in up to 99% yield. Heterocylic sulfoximines with larger ring or aromatic tethers remained inaccessible.

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(9) **Sonogashira Coupling**
A mixture of **3a** (0.286 mmol, 1.0 equiv), PhI (0.858 mmol, 3.0 equiv), [$Pd(PPh_3)_2Cl_2$] (0.029 mmol, 10 mol%), CuI (0.057 mmol, 20 mol%), and Ph_3P (0.029 mmol, 10 mol%) was dissolved in dry Et_3N–DMF (5.71 mL/2.86 mL, 2:1) and stirred under Ar at 70 °C for 4 h. After workup (CH_2Cl_2, brine) and column chromatography [silica gel, pentane–EtOAc (3:1)] **3h** was obtained as orange oil (0.181 mmol, 63%).

(10) **Silylation**
A soln of **3a** (0.715 mmol, 1.0 equiv) in dry THF (10 mL) was cooled to –78 °C. *n*-BuLi in hexane (0.787 mmol, 1.1 equiv) was added dropwise via syringe. After 30 min at this temperature, TESCl (1.431 mmol, 2.0 equiv) was added slowly. After stirring for 1 h at –78 °C, the reaction was quenched with brine. After workup (Et_2O, brine) and column chromatography [silica gel, pentane–EtOAc (6:1)] **3i** was obtained as colorless oil (0.526 mmol, 74%).

(11) The RCEYM reactions were performed under argon using standard Schlenk techniques. *N*(H)- and *N*-alkynyl sulfoximines (**7a–c** and **3a–i**) were synthesized according to literature procedures[8,12] and used as racemates.
Ring-Closing Enyne Metathesis Reactions – Typical Procedure for the Synthesis of 9c
A dried Schlenk flask was charged with doubly unsaturated sulfoximine **3c** and dry toluene (0.01 M). After heating to 120 °C under argon, the catalyst (Grubbs II, 10 mol%) was added under vigorous stirring in one batch. The dark brown reaction mixture was refluxed for 15 min. After cooling to r.t., the mixture was concentrated in vacuo. The residue was subjected to column chromatography [silica gel, pentane–EtOAc (3:1)], which afforded **9c** as a light brownish oil in 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07–8.04 (m, 2 $H_{arom.}$), 7.62–7.57 (m, 1 $H_{arom.}$), 7.55–7.49 (m, 2 $H_{arom.}$), 5.91–5.84 (m, 1 H), 5.06 (br s, 1 H), 4.92 (br s, 1 H), 4.43 (d, 1 H, *J* = 16.5 Hz), 3.97 (d, 1 H, *J* = 16.5 Hz), 3.56 (ddd, 1 H, *J* = 13.5, 9.6, 1.9 Hz), 3.09 (ddd, 1 H, *J* = 13.3, 9.6, 1.9 Hz), 2.80–2.69 (m, 1 H), 2.64–2.54 (m, 1 H), 2.27 (q, 2 H, *J* = 7.4 Hz), 1.08 (t, 3 H, *J* = 7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.3, 146.5, 138.8, 133.0, 128.9, 128.0, 123.4, 110.0, 55.6, 42.8, 27.2, 22.1, 13.2. IR ($CHCl_3$): 2965, 2846, 1447, 1231, 1135, 887, 754, 688 cm^{-1}. MS (EI): *m/z* (%) = 261.1 (16) $[M]^+$, 246.1 (4) $[M - CH_3]^+$. HRMS (EI): *m/z* calcd for $C_{15}H_{19}NOS$: 261.1187; found: 261.1186.

Diels–Alder Reactions – Typical Procecure for the Synthesis of 12c

To a soln of **9c** in toluene (0.032 M) was added *p*-benzoquinone (5 equiv). The reaction mixture was refluxed at 120 °C for 3 h. After cooling to r.t., the yellowish solution was concentrated in vacuo and subjected to column chromatography [silica gel, pentane–EtOAc (2:1)]. Tricyclic product **12c** was obtained as a yellow solid in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (m, 3 $H_{arom.}$), 7.62–7.57 (m, 1 $H_{arom.}$), 7.53–7.47 (m, 3 $H_{arom.}$), 6.90 (d, 1 H, *J* = 10.4 Hz), 6.86 (d, 1 H, *J* = 10.2 Hz), 4.96 (d, 1 H, *J* = 15.1 Hz), 4.59 (d, 1 H, *J* = 14.8 Hz), 4.54 (ddd, 1 H, *J* = 14.8, 7.7, 1.1 Hz), 3.81–3.71 (m, 2 H), 3.05–2.93 (m, 3 H), 1.33 (t, 3 H, *J* = 7.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.5, 184.8, 150.1, 147.7, 141.9, 140.5, 139.0, 136.8, 133.2, 131.5, 129.0, 128.4, 127.6, 126.9, 55.4, 40.3, 28.0, 23.0, 15.7. IR (KBr): 3441, 2967, 1657, 1578, 1308, 1117, 844, 783 cm^{-1}. MS (CI): *m/z* (%) = 365.8 (100) $[M + H]^+$, 240.4 (86) $[M - C_6H_5SO]^+$. HRMS (EI): *m/z* calcd for $C_{21}H_{19}NO_3SC_6H_5SO$: 240.1019; found: 240.1010.

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