

Synthesis of Cyclic Peroxides via Enyne-RCM/Diels-Alder Reaction Sequence

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The sequence of an enyne ring-closing metathesis (enyne-RCM)^{1,2} followed by a Diels-Alder reaction has been applied widely in organic synthesis for the expeditious generation of molecular complexity. Although several dienophiles have been employed to date in Diels-Alder reactions of the cyclic conjugated dienes generated from enyne-RCM, singlet oxygen has not been one of them. The conjugated dienes **5**, which are readily obtained by enyne-RCM, could be reacted with singlet oxygen³ to generate the corresponding cyclic peroxides **6**, as shown in Scheme 1. The cyclic peroxide unit is a component of many biologically important structures; furthermore, it can be transformed into several other valuable skeletons. For example, reductive cleavage of the O—O bond could generate allylic diols.⁴ Base- or transition metal-catalyzed O—O bond cleavage, followed by dehydration, is a well-known reaction strategy to synthesize furans.^{4b,5} We have recently reported the synthesis of 1,2-oxaza and 1,2-diaza heterocycles, having a diverse range of scaffolds, by ring-closing metathesis.^{6,7} Herein, we report our recent results on the synthesis of cyclic peroxides by Diels-Alder reactions between singlet oxygen and enyne-RCM adducts.

The substituted enyne substrates **3** were prepared from the secondary alcohols **2** and *N*-Boc-protected alkynyl hydroxylamines **1** under the Mitsunobu conditions (Scheme 1). The enynes **3** were treated with Grubbs' catalyst **4a** according to our previously reported procedure^{6b} to give the enyne-RCM adducts **5** in moderate to good yields (Table 1). For substrates **3e** and **3g**, more reactive second generation Grubbs' catalyst **4b** was used for the metathesis reactions (Table 1, entries 5 and 7).

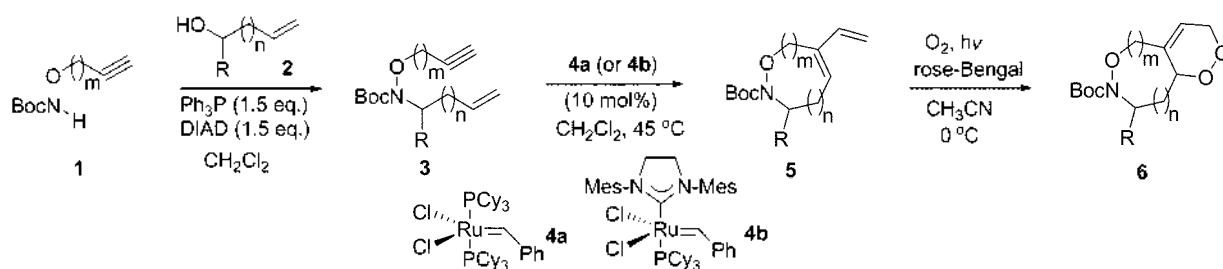
The substituted conjugated dienes **5** and previously synthesized ones^{6b} were utilized in the cycloaddition reaction with singlet oxygen. Acetonitrile solutions of the dienes and a catalytic amount of rose Bengal sensitizer were irradiated using a 400-W tungsten lamp while a steady flow of oxygen

was passed through the solution. The reaction flask was cooled in an ice-bath during this procedure. Table 2 summarizes the results of these cycloaddition reactions. The formation of **6a** from the corresponding enyne-RCM adduct was complete after 7 h; this product was isolated in 73% yield (Table 2, entry 1). The analogous peroxide **6b** was obtained in 82% yield (Table 2, entry 2). The homologues with adjacent 7- and 8-membered 1,2-oxaza rings were also

Table 1. Synthesis of Conjugated Dienes by Enyne-RCM

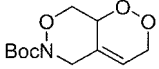
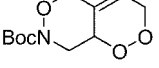
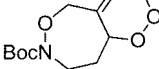
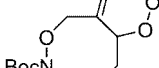
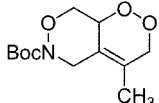
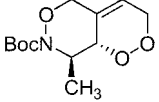
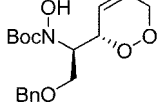
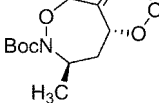
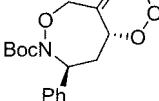
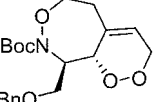
Entry	3	Conditions ^a	5 (% yields) ^b
1		28 h 0.02 M	5a (75)
2		15 h 0.02 M	5b (82)
3		29 h 0.02 M	5c (72)
4		21 h 0.02 M	5d (77)
5 ^c		15 h 0.02 M	5e (80)
6		4 h 0.03 M	5f (83)
7 ^c		16 h 0.02 M	5g (79) E/Z = 50 : 29

^aReaction time and concentrations. ^bIsolated yields. ^cUsed 10 mol% of **4b**, toluene, reflux.



Scheme 1

Table 2. Diels-Alder Reactions of Conjugated Dienes with Singlet Oxygen^a

Entry	Time ^b	Product	Yield (%)
1	7 h		73
2	7 h		82
3	6 h		75
4	6 h		80
5	8 h		69
6	11 h		66 (<i>trans</i> only) ^d
7	12 h		70 (<i>trans</i> / <i>cis</i> = 80 : 20) ^d
8	7 h		78 (<i>trans</i> / <i>cis</i> = 51 : 49) ^d
9	11 h		71 (<i>trans</i> / <i>cis</i> = 58 : 42) ^d
10	16 h		54 (89) ^c (<i>trans</i> only) ^d

^aReaction conditions: O₂, cat. rose Bengal, 400-W tungsten lamp, CH₃CN, 0 °C. ^bReaction time. ^cThe yield in parenthesis is based on the recovered starting material. ^dThe relative stereochemistries were determined by nOe experiments.

prepared in good yields (Table 2, entries 3 and 4).

Next, we examined dienes featuring greater degrees of substitution on either their 1,2-oxaza or 1,2-dioxine ring. Trisubstituted peroxide **6e** was synthesized in 69% yield (Table 2, entry 5). Additional substituents on the 1,2-oxaza rings results in the generation of two diastereoisomeric products. In general, substituents on the carbon atom adjacent to the ring-forming sites produced the higher diastereoisomeric ratios. The peroxides **6f** and **6j** were obtained as single diastereoisomers and **6g** was obtained as the major product in a 4 : 1 ratio (Table 2, entries 6, 10, and 7, respectively). On the other hand, compounds having substituents positioned one extra carbon atom away from the

ring-forming sites exhibited poor diastereoselectivity – they yielded nearly equal amounts of their two diastereoisomers – but the yields of their products are comparable to those of the other reactions (Table 2, entries 8 and 9).

In conclusion, we have shown that the reaction sequence of an enyne-RCM followed by a [4+2] cycloaddition with singlet oxygen is synthetically valuable method for the synthesis of cyclic peroxides. By this reaction sequence, we have synthesized several cyclic peroxides fused with a cyclic hydroxylamine ring.

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- Representative procedure for the singlet oxygen Diels-Alder reaction:** An acetonitrile solution (5 mL) of the RCM adduct (100 mg, 0.444 mmol) and a catalytic amount of rose Bengal sensitizer (2 mg) was irradiated using a 400-W tungsten lamp while a steady flow of oxygen was passed through the solution. The reaction flask was cooled in an ice-bath during this procedure. After 6 h, the solvent was removed under reduced pressure and the residue mixture was column chromatographed on silica gel (elution with 5% ethyl acetate in hexanes) to give 86 mg (75%) of **6c**. Spectral data for **6c**: colorless oil; *R_f* = 0.2 (silica gel, hexane/EtOAc = 2 : 1); ¹H NMR (500 MHz, CDCl₃) δ = 5.79 (s, 1H), 4.68-4.61 (m, 3H), 4.56-4.48 (m, 2H), 3.99 (d, *J* = 13.4 Hz, 1H), 3.34-3.28 (m, 1H), 2.26-2.24 (m, 1H), 2.14-2.11 (m, 1H), 1.49 (s, 9H); ¹³C NMR (62.9 MHz, CDCl₃) δ = 155.7, 137.2, 120.7, 81.9, 79.0, 75.1, 69.8, 46.3, 32.6, 28.7; IR (film, cm⁻¹) 2976, 2930, 1706, 1404, 1368, 1251, 1168, 1117; HRMS: *m/z* calcd. for C₁₂H₁₉NO₃ (*M*+H)⁺: 258.1341; found: 258.1343.