

Photolytic Cleavage and Condensation Reactions of Cyclohexa-2,4-dienones with Diamines

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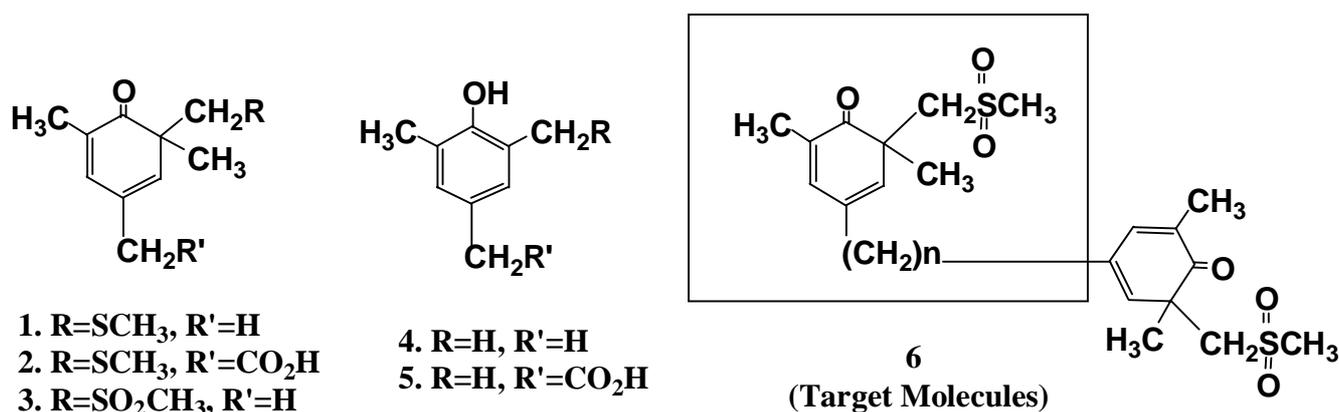
Abstract: Cyclohexa-2,4-diene-1-one sulfone derivative undergoes ring cleavage to afford bis-amides containing a diene moiety on irradiation with visible light in the presence of various diamines.

Keywords: cyclohexa-2,4-diene-1-one, diamines, ketene, photolytic cleavage.

Introduction

We previously reported that the photochemical ring cleavage of cyclohexa-2,4-dienones represents a new and high yielding method for labeling the terminal amino functionality of amino acids and peptides [1]. Since the pioneering work of Barton and Quinkert [2], it has been established that the cleavage of cyclohexa-2,4-dien-1-ones by photolysis using UV light generates ketenes [3]. For the cleavage of the dienones of type **1**, it was found that UV light can be replaced by visible light, a highly desirable feature for ketene generation in the presence of light sensitive chromophores in peptides or in DNA [4].

We have also shown that the photolysis of **1** in EtOH in the presence of amines resulted in the formation of amides [5]. However, one drawback of the parent dienones **1** and **2** is their sensitivity to acid and, resultant conversion to the aromatic compounds **4** and **5** [6] (Scheme 1). Oxidation of sulfone **3** obviated the stability problem. We have been interested in the synthesis of symmetrical bis-cyclohexadienones of the type **6**, in which two units of chromophores are linked *via* varying lengths of carbon tether. These type of compounds may be envisaged as a molecular measuring rod for nucleophilic functionalities on a polypeptide or DNA fragment. The photolytic coupling reactions of **3** were studied with dibasic functionality such as diamines, in order to test whether ketenes derived from **3** could react with diamines to produce symmetrical bis-amides without any problems such as polymerization. Herein we wish to report the results of the photochemical coupling reactions (Scheme 2).



Scheme 1.

Results and Discussion

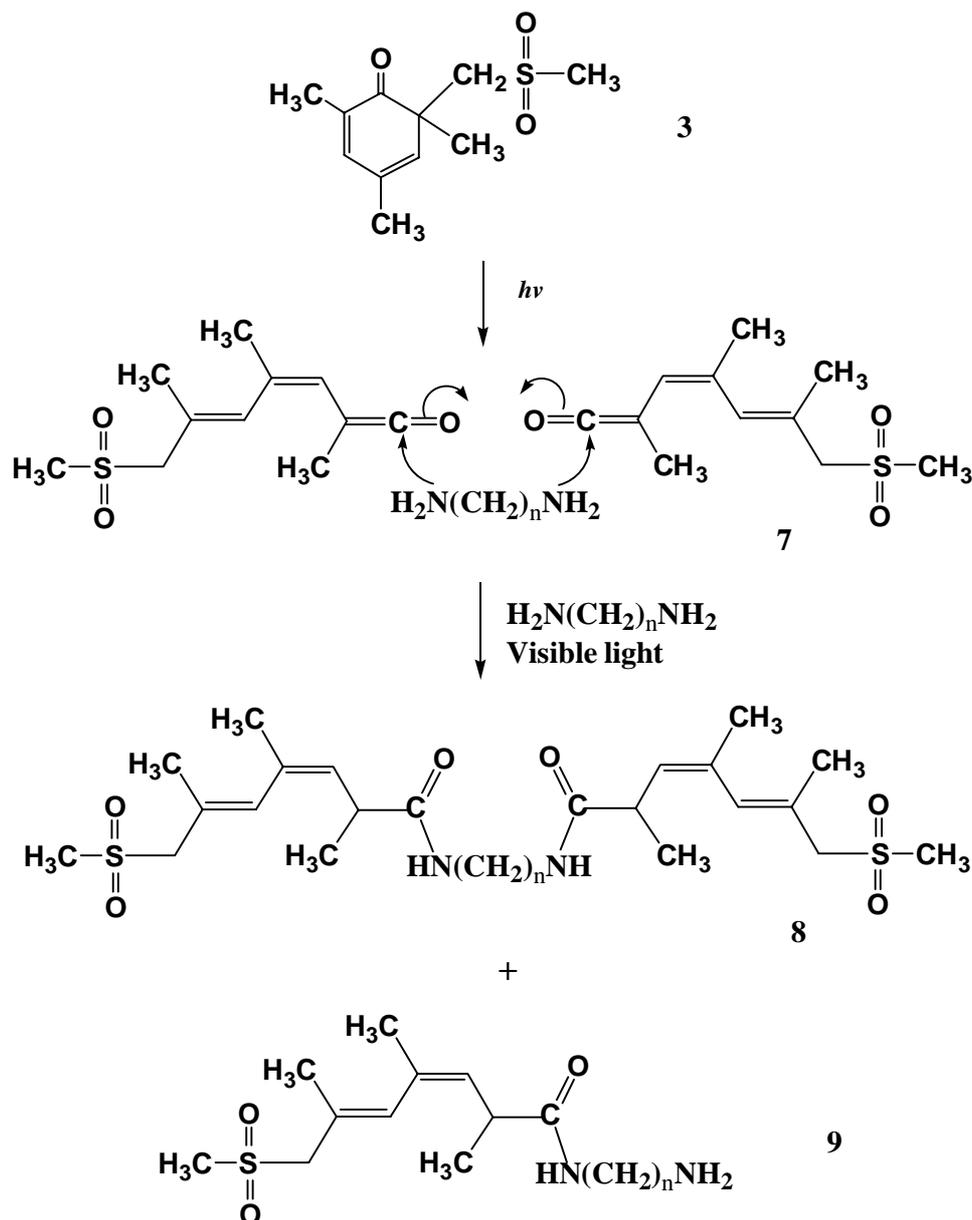
The sulfone **3** was prepared by treating mesitol with Me₂S-*N*-chlorosuccinimide followed by oxidation using *m*-chloroperbenzoic acid [5, 7 and 8]. Photolysis of **3** with a tungsten lamp in the presence of diamines afforded the corresponding bis (amide) products **8** from the reaction of two molecules of the ketene from **3** in ethanol or ethanol-DMSO below 38°C and the results are summarized in Table 1.

The reactions were over within 5-8 hr and the major products (**8**) were obtained in 43-70%. Longer reaction time did not increase the yields. The ring cleavage led to both *cis* and *trans* isomers which were difficult to separate by flash column chromatography. A trace amount of terminal amine products (**9**; n=2, 3, 4, 8 and 10) from monoacylation were also detected by TLC and compared with authentic samples (n=3) [7]. For the preparation of **8d** and **8e**, we carried out the reaction in EtOH/DMSO, which provided enough solubility for the diamines.

Table 1. Photolysis of cyclohexa-2,4-dienone (**3**, 2.3 equiv.) in the presence of diamine (1equiv.).

Product No.	Diamines ^a	Reaction Time	Product (8)			
			Solvent	Rf ^b	n	Yield ^c
8a	1,2-Diaminoethane	5 hr	EtOH	0.26 ^c	2	69%
8b	1,3-Diaminopropane	8 hr	EtOH	0.13 ^d	3	43%
8c	1,4-Diaminobutane	5 hr	EtOH	0.12 ^d	4	61%
8d	1,8-Diaminooctane	5 hr	EtOH/DMSO 1:1	0.15 ^d	6	70%
8e	1,10-Diaminodecane	7 hr	EtOH/DMSO 1:1	0.17 ^d	8	47%

^aDiamines were purchased from Aldrich and used without further purification. ^bTLC plates were made with E. Merck AB Darmstadt Silica gel 60 F254. ^c90% Et₂O/10% MeOH. ^d95% Et₂O / 5% MeOH. ^eYields of isolated product based on **3** after flash column chromatography.



Scheme 2.

Conclusion

In summary, photolytic cleavage and condensation reactions between sulfone **3** and various diamines were found to yield the corresponding bis-amide products in moderate yields. These results augur well for the potential utility of the symmetric bichromophoric cyclohexadienones (**6**) as molecular measuring rods. Additional studies on the preparation and uses of **6** are in progress and results will be communicated in due course.

Acknowledgments: Dedicated to the memory of Sir Derek H. R. Barton (deceased March 16th, 1998). This research was supported by the Non Directed Research Fund, Korea Research Foundation (1998) and the Kyungseong University Research Grants in 2000.

Experimental

General

A typical experimental procedure for the photolysis of **3** is as follows: A tungsten lamp (220 W) was employed to irradiate **3** (345 mg, 1.51 mmole) in 5 mL of absolute ethyl alcohol in the presence of 1,2-diaminoethane (39 mg, 0.66 mmole) under argon atmosphere. The solution was irradiated at a distance of 2 cm and the temperature kept below 38°C with a water cooling bath. The reactions were monitored by TLC. Irradiation was continued for 5 hr. The volatiles were removed *in vacuo* and the crude product was diluted with 20 mL of CH₂Cl₂. The organic layer was washed with 10% HCl (2×10mL) and dried over MgSO₄, filtered and evaporated *in vacuo*. The residue was subjected to flash chromatography (MeOH : Et₂O = 5 : 95) over silica gel to give **8a** (540 mg, 1.04 mmol, 69%) as an oil.

Spectral Data

7-Methanesulfonyl-2,4,6-trimethylhepta-3,5-dienoic acid [2-(7-methanesulfonyl-2,4,6-trimethylhepta-3,5-dienoylamino)-ethyl]-amide, 8a

¹H NMR (300 MHz, CDCl₃) 6.75 (2H, two NH, broad t), 6.00 (2H, two =CH, s), 5.32-5.28 (2H, two =CH, d, J=9.54 Hz), 3.76 (4H, two CH₂SO₂, s), 3.24 (4H, two NCH₂, m), 3.03 (2H, two CHCO, m), 2.97 (6H, two SO₂CH₃, s), 1.79 (6H, two CH₃C=, s), 1.75 (6H, two CH₃C=, s), 1.13 (6H, two CH₃-CH, d); IR (neat); 3392.3 (amide), 2980.2, 1644.0, 1540.3, 1448.4, 1380.1, 1297.6, 1131.6 cm⁻¹ HRMS; *m/z* Calcd for C₂₄H₄₀N₂O₆S₂; [M+H]⁺=517.3582 /Found 517.3578.

7-Methanesulfonyl-2,4,6-trimethylhepta-3,5-dienoic acid [3-(7-methanesulfonyl-2,4,6-trimethylhepta-3,5-dienoylamino)-propyl]-amide, 8b

¹H NMR (300 MHz, CDCl₃) 6.63 (2H, two NH, broad t), 6.05 (2H, two =CH, s), 5.37-5.34 (2H, two =CH, d, J=9.60 Hz), 3.78 (4H, two CH₂SO₂, s), 3.16 (4H, two NCH₂, m), 3.03 (2H, two CHCO, m), 2.94 (6H, two SO₂CH₃, s), 1.84 (6H, two CH₃C=, s), 1.78 (6H, two CH₃C=, s), 1.54 (4H, -CH₂-, m), 1.17 (6H, two CH₃-CH, dd); IR (neat); 3390.4, 2975.1, 2933.6, 1646.9, 1540.1, 1448.4, 1378.8, 1297.0, 1131.6 cm⁻¹ HRMS; *m/z* Calcd for C₂₅H₄₂N₂O₆S₂; [M+H]⁺=531.3743 /Found 531.3735.

7-Methanesulfonyl-2,4,6-trimethylhepta-3,5-dienoic acid [4-(7-methanesulfonyl-2,4,6-trimethylhepta-3,5-dienoylamino)-butyl]-amide, 8c

¹H NMR (300 MHz, CDCl₃) 6.43 (2H, two NH, broad t), 5.99 (2H, two =CH, s), 5.37-5.33 (2H, two =CH, d, J=9.78 Hz), 3.77 (4H, two CH₂SO₂, s), 3.15 (4H, two NCH₂, m), 3.14 (2H, two CHCO, m), 2.99 (6H, two SO₂CH₃, s), 1.82 (6H, two CH₃C=, s), 1.75 (6H, two CH₃C=, s), 1.43 (4H, two -CH₂-, m), 1.16 (6H, two CH₃-CH, d); IR (neat); 3375.4, 2977.0, 2933.9, 1648.9, 1542.6, 1448.2, 1378.4, 1299.6, 1128.3, 1097.5 cm⁻¹ HRMS; *m/z* Calcd for C₂₆H₄₄N₂O₆S₂; [M+H]⁺=545.3897 /Found 545.3871.

7-Methanesulfonyl-2,4,6-trimethylhepta-3,5-dienoic acid [8-(7-methanesulfonyl-2,4,6-trimethylhepta-3,5-dienoylamino)-octyl]-amide, **8d**

¹H NMR (300 MHz, CDCl₃) 6.23 (2H, two NH, broad t), 5.96 (2H, two =CH, s), 5.35-5.32 (2H, two =CH, d, J=9.68 Hz), 3.74 (4H, two CH₂SO₂, s), 3.10 (4H, two NCH₂, m), 3.10 (2H, two CHCO, m), 2.96 (6H, two SO₂CH₃, s), 1.79 (6H, two CH₃C=, s), 1.73 (6H, two CH₃C=, s), 1.38 (12H, -(CH₂)₆-, m), 1.16, 1.13 (6H, two CH₃-CH, d, J=6.80 Hz); IR (neat); 3393.2, 2933.3, 2874.1, 1654.0, 1540.1, 1437.5, 1378.6, 1298.5, 1139.4 cm⁻¹ HRMS; *m/z* Calcd for C₂₈H₄₈N₂O₆S₂; [M+H]⁺=573.4096/ Found 573.4075.

7-Methanesulfonyl-2,4,6-trimethylhepta-3,5-dienoic acid [10-(7-methanesulfonyl-2,4,6-trimethylhepta-3,5-dienoylamino)-decyl]-amide, **8e**

¹H NMR (300 MHz, CDCl₃) 6.16 (2H, two NH, broad t), 5.99 (2H, two =CH, s), 5.38-5.35 (2H, two =CH, d, J=9.82 Hz), 3.74 (4H, two CH₂SO₂, s), 3.13 (4H, two NCH₂, m), 3.05 (2H, two CHCO, m), 2.98 (6H, two SO₂CH₃, s), 1.83 (6H, two CH₃C=, s), 1.76 (6H, two CH₃C=, s), 1.45 (4H, two -CH₂-, m), 1.24 (12H, -(CH₂)₆-, m), 1.19-1.16 (6H, two CH₃-CH, d, J=6.81 Hz); IR (neat); 3295, 3368.4, 2930.2, 2856.0, 1649.7, 1540.8, 1448.3, 1375.3, 1301.0, 1132.6, 1083.2 cm⁻¹ HRMS; *m/z* Calcd for C₃₂H₅₆N₂O₆S₂; [M+H]⁺=629.4837 /Found 629.4912.

(3,5-Dimethyl-3-methylsulfonylmethyl-4-oxo-cyclohexa-1,5-dienyl)-acetic acid, **2**

R_f=0.18 (50% hexane/50% Ethyl acetate). ¹H NMR (300 MHz, D₂O/CDC₃OD) 6.95 (1H, s), 6.01 (1H, s), 3.04 (2H, s, CH₂C=O), 2.84 (1H, d), 2.61 (1H, d), 1.91 (3H, s, CH₃-S), 1.75 (3H, s, CH₃-C=), 1.08 (3H, s, CH₃) ppm; IR(neat); 3650-2700, 1628, 1560, 1379, 1250 cm⁻¹ HRMS; *m/z* Calcd for C₁₂H₁₆O₃S; [M+H]⁺=241.0609 /Found 241.0621.

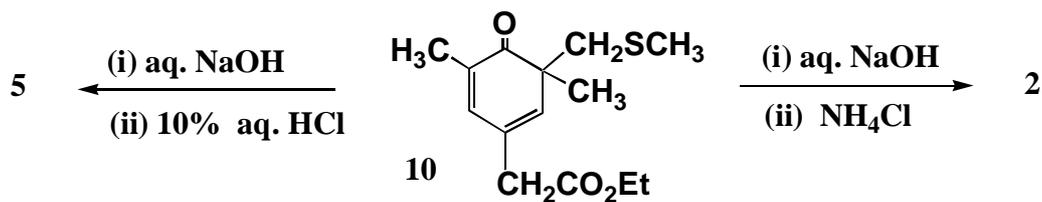
(4-Hydroxy-3,5-dimethylphenyl)-acetic acid, **5**

¹H NMR (300 MHz, CDCl₃) 6.85 (2H, s, Ar-H), 3.49 (2H, s, Ar-CH₂-), 2.21 (6H, s, two CH₃); ¹³CNMR (300 MHz, CDCl₃) ; 178.10, 151.64, 129.61, 124.90, 123.42, 39.98, 15.59 ppm; IR(neat); 3440, 2997, 2970, 1680, 1290, 1189, 923 cm⁻¹. mp = 145-147°C.

References and Notes

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- For example, saponification of dienone **10** with aqueous NaOH afforded the carboxylate salt quan-

titatively. However, neutralization attempts with 10% aqueous HCl gave the phenol **5**, although compound **2** could be obtained by careful neutralization with NH_4Cl ;



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Sample Availability: Not available.