Synthesis and Photolytic Coupling Reaction of Tethered Bis-cyclohexa-2,4-dienones as Potential Molecular Measuring Rods

Tae Woo Kwon,* Suk Jin Song, Yong Uk Kwon,† and Sung Kee Chung†

Department of Chemistry, Kyungsung University, Busan 608-736, Korea
†Department of Chemistry, Pohang University of Science Technology, Pohang 790-784, Korea
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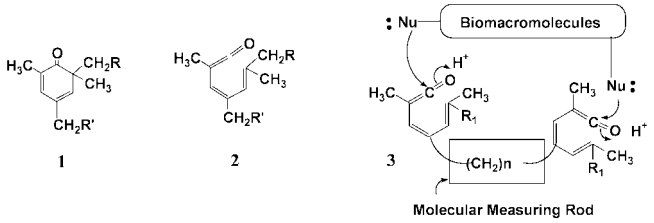
Barton was the first who demonstrated that ortho-type cyclohexa-2,4-dienones **1** could be readily transformed to acrylic acids or acid derivatives under photochemical conditions.[1] According to the subsequent mechanistic studies which were extensively carried out by Quinkert *et al.*, *cis*-ketene, **2** were generated from the phenolic nucleus under UV light.[2] The photochemical ring cleavage of cyclohexa-2,4-dienones represents a potentially new and high yielding method for labelling the terminal amino functionality of amino acids and peptides. The cleavage of the dienones **1** was also found to be effected by visible light as well, a highly desirable feature for ketene generation and subsequent trapping by nucleophiles in the presence of UV light sensitive chromophores of peptides and DNA.[3]



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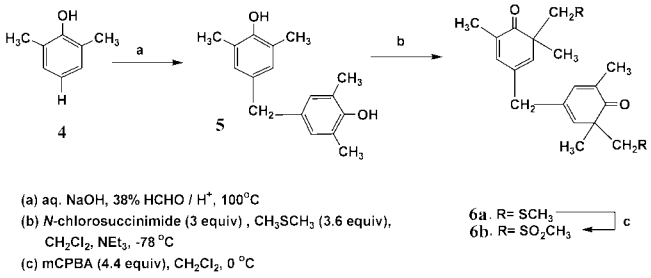
We previously reported the synthesis of several cyclohexa-2,4-dien-1-ones, **1** (R=SCH_3, SO_2CH_3, SPh/R'=CH_3, COOH, $P(O)(OCH_3)_2$, SPh, SO_2Ph) and their photocleavage reactions using a conventional mercury lamp.[4] In the presence of a variety of monoamines or diamines, the reaction gave the amide products containing the diene moieties in good yields. We have been interested in the synthesis and utilities of symmetrical diketene such as **3**, in which two units of the photo active moieties are linked through varying lengths of carbon tether, since this type of compounds might be employed as molecular measuring rods. With these objectives in mind, we have now synthesized tethered bis-cyclohexa-2,4-dien-1-ones, and investigated their photolytic coupling reactions under visible light in the presence of various monoamines.

Scheme 1 shows the preparation of the simplest bis-cyclohexadienone **6a** and **6b**. Treatment of commercially available 2,6-dimethylphenol **4** with 38% HCHO in aqueous NaOH solution gave bisphenol **5** in high yield. Bis-cyclohexadienone **6a** was prepared in 97% yield by reacting **5** with $(CH_3)_2S$[5] and *N*-chlorosuccinimide in the presence of tri-



Scheme 1

ethylamine base in CH_2Cl_2 at 78 °C. The corresponding sulfone (**6b**) was also readily prepared by oxidation with mCPBA in dichloromethane at 0 °C.

We have carried out the photolysis of **6a** in the presence of various amines in diethylether for 5-7 hr below 40 °C using a tungsten light. In all cases, the corresponding bis-amide products **9**-**13** were obtained as pale yellow oils in good to moderate yields, and the results are summarized in Table 1. It is quite apparent that the bis-ketene intermediate **7** could

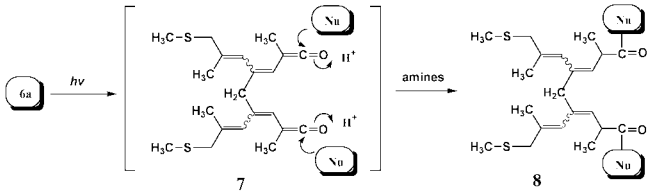
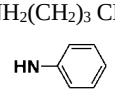
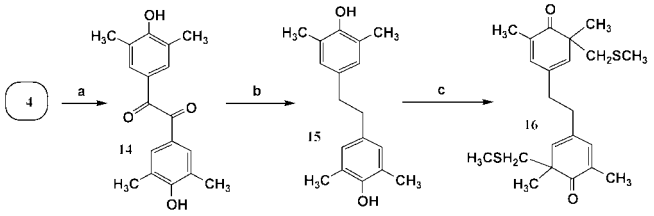


Table 1. Photolysis of bis-cyclohexa-2,4-dienone (**6a**)

Product Number	Amines[a]	Reaction Time	Product	
			Nucleophile	Yield (%)[b]
9	pyrrolidine	7 hr		79
10	piperidine	5 hr		85
11	morpholine	6 hr		82
12	*n*-butyl amine	7 hr	$NH_2(CH_2)_3CH_3$	71
13	aniline	7 hr		63

[a]Amines were purchased from Aldrich and used without further purification. [b]Yields are based on the isolated products after flash column chromatography.



Scheme 2

be efficiently trapped by the amine nucleophiles present in the reaction medium to give E/Z geometric isomers of **9-13**.

The next homologue of compound **3** (n = 2) was prepared as shown in Scheme 2. The Friedel-Craft type reaction of 2,6-dimethylphenol **4** was effected with oxalyl chloride in the presence of $AlCl_3$ to provide **14** in 86% yield. The symmetrical diketone **14** was reduced with Zn/Hg in aq. HCl and ethanol (100 °C, reflux) to give bis phenol **15** in 63% yield. Reaction of **15** with *N*-chlorosuccinimide and dimethylsulfide in the presence of triethylamine in CH_2Cl_2 at -78 °C gave the symmetrical bis-cyclohexadienone **16** in 75 % yield. This methodolgy may provide a reasonable general route to the symmetrical bichromophoric cyclohexadienone compounds (**3**) with a varying length of alkyl chain. We are currently in the process of extending this metholdology to the synthesis of a variety of tethered bis cyclohexadienones (**3**) and their sulfones derivatives in order to examine their potential as molecular measuring rod.

In summary, the simple bis-cyclohexadienones such as compound **6a**, **6b** and **16** could be readily prepared, and the photolytic cleavage and condensation between **6a** and various amines were shown to yield the corresponding bisamide products in moderate yields. Further studies on the preparation of higher homologues and their photolysis reactions are in progress, and results will be communicated in due course.

Experimental Section

Preparation of 5. Commercially available 2,6-dimethylphenol **4** (22.5 g, 184.2 mmol) in 10% aqueous NaOH (45 mL) solution and 38% HCHO (45 mL) were placed in a 250 mL round bottomed flask. The mixture was covered with rubber septum and degassed. Argon was introduced and then the mixture was heated to 100 °C for 3 hr. The crude solid product was filtered and washed with distilled water for 3 times. Recrystallization from hot benzene afforded pure diphenol **5** as a white needle-like solid (20.9 g, 81.5 mmole, 88.4%). mp = 171-172 °C. Lit.[6] mp = 171 °C. ^{1}H NMR (300 MHz, $CDCl_3$) 6.78 (4H, Ph-H, s), 3.69 (2H, CH_2, s), 3.69 (2H, OH, s), 2.19 (12H, four CH_3, s). ^{13}C NMR (75 MHz, $CDCl_3$) 150.30, 133.38, 128.83, 122.85, 40.24, 15.89.

Preparation of 6a. To a solution of *N*-chlorosuccinimide (17 g, 134.7 mmole) in dry CH_2Cl_2 (540 mL) was added dropwise freshly distilled dimethylsulfide (11.7 mL, 161.7 mmol) in an argon atmosphere at 0 °C. After 20 min, the ice bath was removed, and the reaction temperature cooled down to -78 °C. And then diphenol **5** (11.5 g, 44.92 mmol) in dry CH_2Cl_2 (400 mL) was added dropwise so as to maintain the temperature below 70 °C. Stirring was continued for 3 hr at this temperature after which time anhydrous Et_3N (19.1 mL, 137.4 mmol) was added and the mixture was then allowed to attain ambient temperature overnight. The reaction mixture was washed with cold 10% NaOH solution (2 × 200 mL), and cold saturated NH_4Cl solution (2 × 200 mL) and brine (1 × 200 mL), and dried over $MgSO_4$. Evaporation of the solvent afforded crude **6**a (17.0 g) which was further purified by column chromatography (Rf = 0.58, Et_2O : hexane = 1 : 1); A yellow oil (13.6 g, 36.1 mmol, 80.3%). ^{1}H NMR (300 MHz, $CDCl_3$) 6.72 (2H, two vinyl H, s), 5.98 (2H, two vinyl H, s), 3.08 (2H, center CH_2, s), 2.99 (2H, two $\underline{CH_a}$-SCH_3, d, J = 13.92 Hz) 2.67 (2H, two $\underline{CH_b}$-SCH_3, d, J = 13.92 Hz), 1.99 (6H, two S-$\underline{CH_3}$, s), 1.84 (6H, two $\underline{CH_3}$-C=, s), 1.18 (6H, two $\underline{CH_3}$-C-CH_2, s), ^{13}C NMR (75 MHz, $CDCl_3$) 204.36 (C=O), 140.97, 140.34, 133.52, 129.93, 51.09, 44.70, 40.96, 25.65, 17.49, 15.52. IR (neat) 2966-2950, 1689, 1575, 1422, 1375 cm^{-1}.

Preparation of 6b. To a stirring solution of **6a** (1.0 g, 2.65 mmol) in dichloromethane (80 mL) at 0 °C was added mCPBA (3.60 g, purity 57%, 11.93 mmole) dissolved in CH_2Cl_2 (30 mL) at ambient temperature. After 4 hr, the reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (3 × 60 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (Rf = 0.63, 100% ethylacetate) to give **6b** (1.1 g, 2.39 mmol, 90%) as a pale yellow solid. mp = 75-76 °C. ^{1}H NMR (300 MHz, $CDCl_3$) 6.78 (1H, CH=C, s), 6.72 (1H, CH= C, s), 6.16 (2H, CH=C, two s), 3.95 (2H, CH_2SO_2, d, J = 13.90 Hz), 3.14 (2H, CH_2SO_2, d, J = 13.90 Hz), 3.06 (2H, center CH_2, s), 2.67 (6H, two CH_3, two s), 1.80 (6H, two CH_3, s), 1.12 (6H, two CH_3, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) 201.62 (C=O), 201.54 (C=O), 141.17, 141.18, 137.99, 137.81, 133.07, 133.00, 129.88, 129.72, 62.94, 62.95, 47.52, 47.44, 42.72, 42.54, 40.65, 40.20, 26.73, 26.64, 15.33, 15.20. HRMS; m/z calcd for $C_{21}H_{28}O_6S_2$; $[M+H]^+$, 441.5638. Found 441.5635.

Representative photolysis reaction (preparation of 10). A typical experimental procedure for the photolysis of **6a** is as follows: A tungsten lamp (220 W) was employed to irradiate **6a** (215 mg, 0.57 mmol) in 3 mL of absolute diethyl ether in the presence of piperidine (107 mg, 1.25 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 30 mL of CH_2Cl_2. The organic layer was washed with 10% HCl (2 × 10 mL), water (1 × 10 mL) and dried over $MgSO_4$. Volatiles were evaporated *in vacuo*. The residue was subjected to flash chromatography (Rf = 0.15, Et_2O : Hexane = 1 : 1) over silica gel to give **10** (265 mg, 0.48 mmol, 85%) as E/Z mixture. **10**; ^{1}H NMR (300 MHz, $CDCl_3$) 5.32 (2H, two CH-$\underline{CH}$=C, d, J = 9.28 Hz), 5.58 (2H, two $\underline{CH}$=C-C=, s), 3.51-3.32 (8H, four $\underline{CH_2}$-N, m), 3.43 (2H, two $\underline{CH}$-CH_3, m), 3.02 (4H, $\underline{CH_2}$-SCH_3, s), 2.72 (2H, center CH_2, s), 1.61-

1.30 (12H, six CH_2 in the ring, m), 1.95 (6H, two S-CH3, s), 1.72 (6H, two CH_3-C=), and 1.06 (6H, two CH_3-CH, two d) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) 172.71 and 173.85 (two C=O) ppm. HRMS; m/z calcd for $C_{31}H_{50}N_2O_2S_2$; $[M+H]^+$, 547.3410. Found 547.3408. **9**; ^{1}H NMR (300 MHz, $CDCl_3$) 5.59 (2H, two CH=C-C, S), 5.36 (2H, two CH-CH=C, d), 3.35-3.53 (8H, four CH_2-N, m), 3.46 (2H, two CH-CH_3, m), 3.09(4H, two CH_2-SCH_3), 2.74 (2H, center CH_2, s), 1.96 (6H, two CH_3-S, s), 1.88 (8H, four CH_2 in two rings, m) 1.75 (6H, two CH_3-C=, s), 1.08 (6H, two CH_3-CH, d). IR (neat); 2850.2, 1635.7 (C=O) cm^{-1}. MS(EI) 518 (Calcd for $C_{29}H_{46}N_2O_2S_2$), Found 518. **11**; ^{1}H NMR (300 MHz, $CDCl_3$) 5.60 (2H, two CH=C-C, s), 5.35 (2H, two CH-CH=C, d), 3.27-3.82 (16H, two morpholine, m), 3.43 (2H, two CH-CH_3, m), 3.05 (4H, two CH_2-SCH_3, s), 2.76 (2H, center CH_2, s), 1.97 (6H, two CH_3-S, s), 1.73 (6H, two CH_3-C=, s), 1.09 (6H, two, CH_3-CH, d). IR(neat); 3010.5, 2897.6, 1658.5 (C=O) cm^{-1}. MS (EI) 550 (Calcd for $C_{29}H_{46}N_2O_4S_2$), Found 550. **12**; ^{1}H NMR (300 MHz, $CDCl_3$) 5.54 (2H, two CH=C-C=, s), 5.28 (2H, two CH-CH=C, d), 3.35 (2H, two CH-CH_3, m), 3.21 (4H, two CH_2-NH, m), 3.01 (4H, two CH_2-SCH_3, s), 2.72 (2H, center CH_2, s), 1.93 (6H, two SCH_3, s), 1.70 (6H, two CH_3-C=, s), 0.71-1.05 (6H, two CH_3-CH, d/ 6H, four CH_2 chain/6H, two terminal CH_3). IR (neat); 3312.8 (NH), 1642.9 (C=O), 1640.2 cm^{-1} MS (EI) 522 (Calcd for $C_{29}H_{50}N_2O_2S_2$), Found 522. **13**; ^{1}H NMR (300 MHz, $CDCl_3$) 8.52 (1H, NH, brs), 6.89-7.72 (10H, two phenyl $CDCl_3$) 8.52 (1H, NH, brs), 6.89-7.72 (10H, two phenyl ring, m), 5.65 (2H, two CH=C-C=, s), 5.39 (2H, two CH-CH=C, d), 3.48 (2H, two CH-CH_3, m), 3.08 (4H, two CH_2-SCH_3, s), 2.80 (2H, center CH_2, s), 2.01 (6H, two CH_3-CH, d), 1.79 (6H, two CH_3-C=, s) and 1.10 (6H, two CH_3-CH, d). IR (neat); 3239.3, 1661.2 (C=O), 1640.2 cm^{-1} MS (EI) 562 (Calcd for $C_{33}H_{42}N_2O_2S_2$), Found 562.

Preparation of 14. To a solution of commercially available **4** (2.15 g, 17.5 mmol) and oxalyl chloride in carbon disulfide (40 mL) at 0 °C was added aluminium chloride (5.20 g, 38.6 mmol) portionwise over 30 min. Vigorous stirring was continued for 4 hr at ambient temperature after which time the mixture was poured into ice (100 g) concentrated HCl (20 mL) mixture. The white solid was isolated by filtration and washed three times with H_2O (100 mL) and purified by column chromatography (Rf = 0.51, Et_2O : Hexane, 1 : 1) to give 4.48 g (15.08 mmol, 86%) of **14**. ^{1}H NMR (300 MHz, $CDCl_3$) 7.56 (4H, Ar-H, s), 3.19 (2H, two OH, br s) and 2.27 (12H, four CH_3, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) 194.85 (C=O), 160.22, 131.21, 125.94, 125.20 and 16.28.

Preparation of 15. Zinc powder (9.05 g, 136.6 mmol) was added slowly to a mixture of $HgCl_2$ (0.90 g) and 16 mL of H_2O in the presence of 0.45 mL of concentrated HCl. The mixture was stirred for 5 min and aqueous portion was decanted. Diketone (1.36 g, 4.57 mmol), con. HCl (11.2 mL) in 5.38 mL of H_2O and 95% ethanol (5.38 mL) was added and the mixture was refluxed for 24 hr. After cooling the reaction mixture, solid portion was filtered. Ethanol was evaporated and the crude product was diluted with 50 mL of Et_2O, washed with H_2O (3×15 mL) and dried over $MgSO_4$. Removal the solvent with a rotary evaporator afforded 0.78 g (2.87 mmoL, 63%) of solid. The solid was purified by flash chromatography (Rf = 0.46, Et_2O : hexane, 1 : 1) to give **15** as a colourless solid. mp = 168-169 °C. ^{1}H NMR (300 MHz, $CDCl_3$) 6.81 (4H, Ar-H, s), 4.49 (2H, two OH, br s), 2.70 (4H, two CH_2, s), 2.24 (12H, four CH_3, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) 150.23, 133.82, 128.45, 122.78, 37.68, 15.89 ppm. IR (KBr) 3521-3021, 1615, 1512, 1493 and 1327 cm^{-1}.

Preparation of 16. To a solution of *N*-chlorosuccinimide (937 mg, 7.43 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C under argon atmosphere, was added dropwise freshly distilled dimethylsulfide (0.65 mL, 8.92 mmole). After 20 min, the reaction temperature cooled down to 78 °C, and then diphenol **15** (670 mg, 2.51 mmol) in dry CH_2Cl_2 (25 mL) was added dropwise, maintaining the temperature below 70 °C. Stirring was continued for 3 hr at this temperature, anhydrous Et_3N (1 mL, 7.19 mmol) was added and the mixture was allowed to the ambient temperature overnight. The reaction mixture was washed with cold 10% NaOH solution (2×15 mL), and cold saturated NH_4Cl solution (2×15 mL) and brine (1×15 mL), and dried over $MgSO_4$. Evaporation of the solvent afforded crude **16** which was further purified by column chromatography (Rf = 0.57, Et_2O : Hexane = 1 : 1) as a yellow oil (730 mg, 1.87 mmol, 74.6%); ^{1}H NMR (300 MHz, $CDCl_3$) 6.70 (2H, two HC=, s), 5.87 (two HC=, s), 2.87 (2H, two CH_aS, J =12.46 Hz, d), 2.62 (2H, two CH_bS, J = 12.46 Hz, d), 2.35 (4H, two allylic CH_2, s), 1/95 (6H, two SCH_3, s), 1.82 (6H, two CH_3-C=, s), 1.11 (6H, two CH_3-chiral C, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) 204.38 (C=O), 141.57, 138.59, 132.98, 131.74, 50.77, 44.55, 34.43, 25.43, 17.53, 15.43 ppm. HRMS; m/z calcd for $C_{22}H_{30}O_2S_2$; $[M+H]^+$, 391.1820. Found 391.1819.

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