

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

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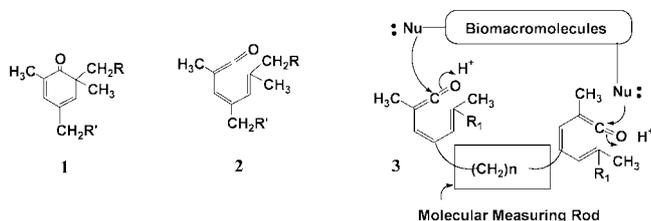
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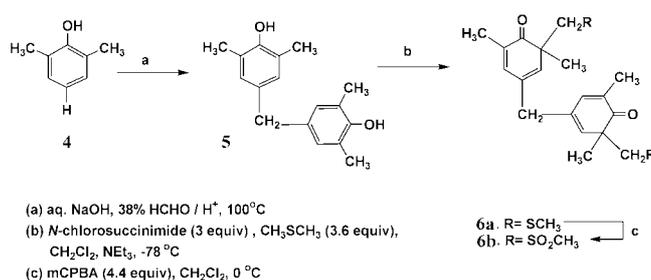
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Barton was the first who demonstrated that ortho-type cyclohexa-2,4-dienones **1** could be readily transformed to acrylic acids or acid derivatives under photochemical conditions.¹ According to the subsequent mechanistic studies which were extensively 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

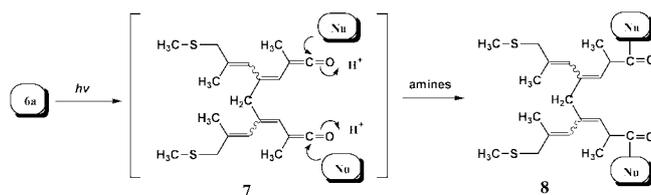


Scheme 1



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



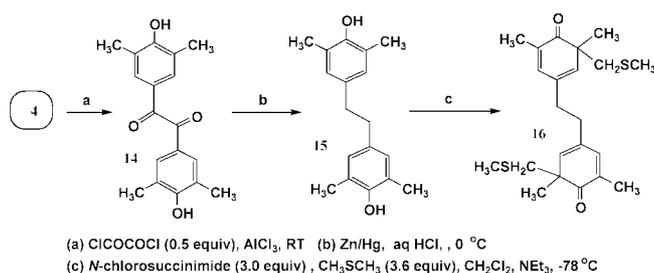
We previously reported the synthesis of several cyclohexa-2,4-dien-1-ones, **1** ($\text{R}=\text{SCH}_3$, SO_2CH_3 , $\text{SPh}/\text{R}'=\text{CH}_3$, COOH , $\text{P}(\text{O})(\text{OCH}_3)_2$, SPh , SO_2Ph) and their photocleavage reactions using a conventional mercury lamp.⁴ In the presence of 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 $(\text{CH}_3)_2\text{S}^5$ and *N*-chlorosuccinimide in the presence of tri-

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	<i>n</i> -butyl amine	7 hr	$\text{NH}(\text{CH}_2)_3\text{CH}_3$	71
13	aniline	7 hr		63

^aAmines were purchased from Aldrich and used without further purification. ^bYields 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 AlCl₃ 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 CH₂Cl₂ at -78 °C gave the symmetrical bis-cyclohexadienone **16** in 75 % yield. This methodology 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 methodology 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. ¹H NMR (300 MHz, CDCl₃) 6.78 (4H, Ph-H, s), 3.69 (2H, CH₂, s), 3.69 (2H, OH, s), 2.19 (12H, four CH₃, s). ¹³C NMR (75 MHz, CDCl₃) 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 CH₂Cl₂ (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 CH₂Cl₂ (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 Et₃N (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 NH₄Cl solution (2 × 200 mL) and brine (1 × 200 mL), and dried over MgSO₄. Evaporation of the solvent afforded crude **6a** (17.0 g) which was further purified by column chromatography (R_f = 0.58, Et₂O : hexane = 1 : 1); A yellow oil (13.6 g, 36.1 mmol, 80.3%). ¹H NMR (300 MHz, CDCl₃) 6.72 (2H, two vinyl H, s), 5.98 (2H, two vinyl H, s), 3.08 (2H, center CH₂, s), 2.99 (2H, two CH_a-SCH₃, d, $J = 13.92$ Hz) 2.67 (2H, two CH_b-SCH₃, d, $J = 13.92$ Hz), 1.99 (6H, two S-CH₃, s), 1.84 (6H, two CH₃-C=, s), 1.18 (6H, two CH₃-C-CH₂, s), ¹³C NMR (75 MHz, CDCl₃) 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 mmol) dissolved in CH₂Cl₂ (30 mL) at ambient temperature. After 4 hr, the reaction mixture was washed with saturated aqueous NaHCO₃ solution (3 × 60 mL), dried over MgSO₄, and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (R_f = 0.63, 100% ethylacetate) to give **6b** (1.1 g, 2.39 mmol, 90%) as a pale yellow solid. mp = 75-76 °C. ¹H NMR (300 MHz, CDCl₃) 6.78 (1H, CH=C, s), 6.72 (1H, CH=C, s), 6.16 (2H, CH=C, two s), 3.95 (2H, CH₂SO₂, d, $J = 13.90$ Hz), 3.14 (2H, CH₂SO₂, d, $J = 13.90$ Hz), 3.06 (2H, center CH₂, s), 2.67 (6H, two CH₃, two s), 1.80 (6H, two CH₃, s), 1.12 (6H, two CH₃, s) ppm. ¹³C NMR (75 MHz, CDCl₃) 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 C₂₁H₂₈O₆S₂; [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 CH₂Cl₂. The organic layer was washed with 10% HCl (2 × 10 mL), water (1 × 10 mL) and dried over MgSO₄. Volatiles were evaporated *in vacuo*. The residue was subjected to flash chromatography (R_f = 0.15, Et₂O : Hexane = 1 : 1) over silica gel to give **10** (265 mg, 0.48 mmol, 85%) as E/Z mixture. **10**; ¹H NMR (300 MHz, CDCl₃) 5.32 (2H, two CH-CH=C, d, $J = 9.28$ Hz), 5.58 (2H, two CH=C-C=, s), 3.51-3.32 (8H, four CH₂-N, m), 3.43 (2H, two CH-CH₃, m), 3.02 (4H, CH₂-SCH₃, s), 2.72 (2H, center CH₂, s), 1.61-

1.30 (12H, six CH₂ in the ring, m), 1.95 (6H, two S-CH₃, s), 1.72 (6H, two CH₃-C=), and 1.06 (6H, two CH₃-CH, two d) ppm. ¹³C NMR (75 MHz, CDCl₃) 172.71 and 173.85 (two C=O) ppm. HRMS; m/z calcd for C₃₁H₅₀N₂O₂S₂; [M+H]⁺, 547.3410. Found 547.3408. **9**; ¹H NMR (300 MHz, CDCl₃) 5.59 (2H, two CH=C-C, s), 5.36 (2H, two CH-CH=C, d), 3.35-3.53 (8H, four CH₂-N, m), 3.46 (2H, two CH-CH₃, m), 3.09 (4H, two CH₂-SCH₃), 2.74 (2H, center CH₂, s), 1.96 (6H, two CH₃-S, s), 1.88 (8H, four CH₂ in two rings, m) 1.75 (6H, two CH₃-C=, s), 1.08 (6H, two CH₃-CH, d). IR (neat); 2850.2, 1635.7 (C=O) cm⁻¹. MS(EI) 518 (Calcd for C₂₉H₄₆N₂O₂S₂), Found 518. **11**; ¹H NMR (300 MHz, CDCl₃) 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-CH₃, m), 3.05 (4H, two CH₂-SCH₃, s), 2.76 (2H, center CH₂, s), 1.97 (6H, two CH₃-S, s), 1.73 (6H, two CH₃-C=, s), 1.09 (6H, two, CH₃-CH, d). IR(neat); 3010.5, 2897.6, 1658.5 (C=O) cm⁻¹. MS (EI) 550 (Calcd for C₂₉H₄₆N₂O₄S₂), Found 550. **12**; ¹H NMR (300 MHz, CDCl₃) 5.54 (2H, two CH=C-C=, s), 5.28 (2H, two CH-CH=C, d), 3.35 (2H, two CH-CH₃, m), 3.21 (4H, two CH₂-NH, m), 3.01 (4H, two CH₂-SCH₃, s), 2.72 (2H, center CH₂, s), 1.93 (6H, two SCH₃, s), 1.70 (6H, two CH₃-C=, s), 0.71-1.05 (6H, two CH₃-CH, d/ 6H, four CH₂ chain/6H, two terminal CH₃). IR (neat); 3312.8 (NH), 1642.9 (C=O), 1640.2 cm⁻¹ MS (EI) 522 (Calcd for C₂₉H₅₀N₂O₂S₂), Found 522. **13**; ¹H NMR (300 MHz, CDCl₃) 8.52 (1H, NH, brs), 6.89-7.72 (10H, two phenyl CDCl₃) 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-CH₃, m), 3.08 (4H, two CH₂-SCH₃, s), 2.80 (2H, center CH₂, s), 2.01 (6H, two CH₃-CH, d), 1.79 (6H, two CH₃-C=, s) and 1.10 (6H, two CH₃-CH, d). IR (neat); 3239.3, 1661.2 (C=O), 1640.2 cm⁻¹ MS (EI) 562 (Calcd for C₃₃H₄₂N₂O₂S₂), 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 H₂O (100 mL) and purified by column chromatography (Rf = 0.51, Et₂O : Hexane, 1 : 1) to give 4.48 g (15.08 mmol, 86%) of **14**. ¹H NMR (300 MHz, CDCl₃) 7.56 (4H, Ar-H, s), 3.19 (2H, two OH, br s) and 2.27 (12H, four CH₃, s) ppm. ¹³C NMR (75 MHz, CDCl₃) 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 HgCl₂ (0.90 g) and 16 mL of H₂O 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 H₂O 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

Et₂O, washed with H₂O (3 × 15 mL) and dried over MgSO₄. 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, Et₂O : hexane, 1 : 1) to give **15** as a colourless solid. mp = 168-169 °C. ¹H NMR (300 MHz, CDCl₃) 6.81 (4H, Ar-H, s), 4.49 (2H, two OH, br s), 2.70 (4H, two CH₂, s), 2.24 (12H, four CH₃, s) ppm. ¹³C NMR (75 MHz, CDCl₃) 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 CH₂Cl₂ (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 CH₂Cl₂ (25 mL) was added dropwise, maintaining the temperature below 70 °C. Stirring was continued for 3 hr at this temperature, anhydrous Et₃N (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 NH₄Cl solution (2 × 15 mL) and brine (1 × 15 mL), and dried over MgSO₄. Evaporation of the solvent afforded crude **16** which was further purified by column chromatography (Rf = 0.57, Et₂O : Hexane = 1 : 1) as a yellow oil (730 mg, 1.87 mmol, 74.6%); ¹H NMR (300 MHz, CDCl₃) 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 CH₂, s), 1/95 (6H, two SCH₃, s), 1.82 (6H, two CH₃-C=, s), 1.11 (6H, two CH₃-chiral C, s) ppm. ¹³C NMR (75 MHz, CDCl₃) 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 C₂₂H₃₀O₂S₂; [M+H]⁺, 391.1820. Found 391.1819.

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