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Synthesis of Thiophenyl Substituted Cyclohexa-2,4-dien-1-one and its Photocleavage Coupling Reaction with Amines

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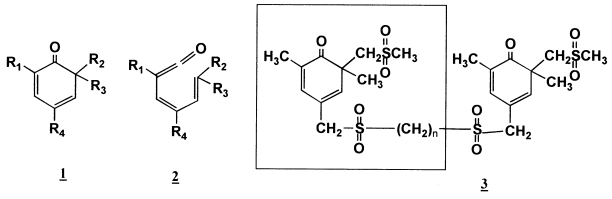
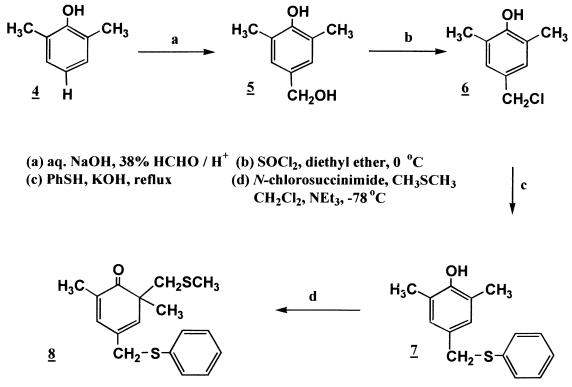
Abstract—Thiophenyl substituted cyclohexa-2,4-dien-1-ones were synthesized and photolyzed in the presence of various amines to afford the amides containing diene moeties via the ketene intermediate under visible light irradiation at 38 °C. © 2000 Elsevier Science Ltd. All rights reserved.

Since the pioneering work by Barton et al. on the photochemistry of cyclohexadienones of the *ortho*-type, **1**, it has been known that the phenolic nucleus are readily cleaved to produce *cis*-ketene, **2**, under UV light.[1] We have been interested in the synthesis and utilities of symmetrical *bis*-cyclohexadienones such as **3**, in which two units of the photo active molecules are linked through varying lengths of carbon tether. These type of compounds, in principle, can be employed as molecular measuring rods, e.g., measurement of the distance between nucleophilic functional groups present on a protein or DNA fragment. We previously reported the synthesis of several cyclohexa-2,4-dien-1-ones, **1** ($R_1=CH_3$, $R_2=CH_2SCH_3$, $CH_2SO_2CH_3$ and CH_2SPh, $R_3=CH_3$, $R_4=CH_3$, CH_2COOH and $CH_2P(O)(OCH_3)_2$) and their photocleavage reactions using a conventional mercury lamp.[2] In the presence of a variety of amines the reaction gave the amide products containing the diene moieties in good yields. In order to have a ready access to the symmetrical bichromophoric cyclohexadienone compounds, it was thought desirable to have a functional group at the C-4 position, which is robust to the photolysis and amenable to further synthetic manipulations. With this objective in mind, we synthesized new cyclohexa-2,4-dien-1-ones with the CH_2SPh functional group at the C-4 position, and investigated its photolytic cleavage reaction.



Scheme 1 summarizes the preparation of disulfide **8**. Commercially available 2,6-dimethylphenol, **4** was reacted with 38% aqueous HCHO in NaOH solution to provide **5** in 64% yield. The product **5** was treated with thionyl chloride (0 °C, diethylether) to give **6** in quantitative yield (mp = 99–100 °C, lit[3] 100.5 °C). Reaction of **6** with thiophenol in the presence of KOH gave the substitution product **7** in 86.2% yield.[4] The target compound



Scheme 1.

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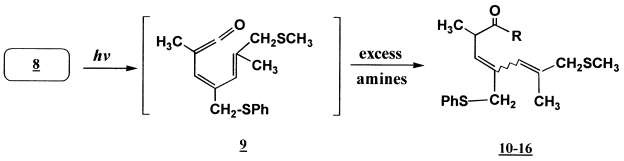
PII: S0960-894X(00)00291-2

Table 1. Photolytic reactions of dienone **8**.



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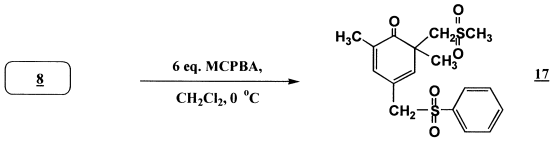
Product No.	Amines[a]	Reaction time	Products		
			R_f[b]	R	Yield[c] (%)
10	Pyrrolidine	9	0.19[d]		66
11	Piperidine	4	0.41[d]		51
12	Morpholine	9	0.22[d]		72
13	$NH_2CH_2CH_2CH_2CH_3$	10	0.16[e]	$-NHCH_2CH_2CH_2CH_3$	69
14	$NH_2\ CH_2CH_2CH_2OH$	9	0.29[d]	$-NHCH_2CH_2CH_2OH$	46
15	$NH_2CH_2CH(OCH_3)_2$	10	0.28[d]	$-NHCH_2CH(OCH_3)_2$	70
16	$NH_2C(CH_3)_2CH_2OH$	10	0.31[d]	$-NHC(CH_3)_2CH_2OH$	39

[a]The amines were purchased from Aldrich and used without further purification.
[b]TLC plates were prepared with E. Merck AB Darmstadt Silica gel 60 F254.
[c]Isolation yield after flash column chromatography.
[d]85% Et_2O/15% Hexane.
[e]50% Et_2O/50% Hexane.

8 was prepared in 89.7% yield[5] by treatment of *N*-chlorosuccinimide and dimethylsulfide in the presence of triethylamine in CH_2Cl_2 at $-78\,^{\circ}C$.[6]

Upon photolysis in the presence of a variety of amines, cyclohexa-2,4-dienone generates ketene intermediates, which is captured by amines to furnish the corresponding amide products. The mechanistic aspects of the dienone cleavage reaction have already been well studied.[7] Thus we have examined the photolysis reaction of **8** in the presence of various amines in ethanol for 4–10 hr below $40\,^{\circ}C$. In all cases, the respective amide products were obtained as colorless oils in good to moderate yields.[8] The nucleophilic amine traps the *cis*-ketene intermediate **9** to give two isomers of **10**–**16**, and the results are summarized in Table 1. Oxidation of **8** with *m*-chloroperbenzoic acid (MCPBA) gave the sulfone product **17** as a white solid which was quite stable under acidic condition without light and could be purified by silica gel chromatography without any noticeable decomposition. The sulfone **17** was very polar but slightly soluble in absolute ethyl alcohol.[9]



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In conclusion the synthetic procedure presented here can offer a reasonable route to the symmetrical bichromophoric cyclohexadienone compounds via the replacement of the phenyl-thio group. Preparation of such bichromophoric compounds and photolysis are currently in progress, and the results will be communicated in due course.

Acknowledgements

We would like to dedicate this article to the memory of Sir Derek H. R. Barton (Deceased March 16th, 1998). This work was supported by the Non Directed Research Fund, Korea Research Foundation (1998).

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4. **Compound 7**; A white crystalline solid, mp = 50–52 °C. ^1H NMR (300 MHz, $CDCl_3$) 7.4.1 (5H, m), 6.91 (2H, s), 4.60 (1H, br. s), 4.01 (2H, s) and 2.19 (6H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) 151.3, 136.8, 129.3, 129.0, 128.7, 128.4, 126.0, 123.0, 38.3 and 15.8 ppm. GC/MS 244(M^+), 227, 215, 135, 115, 109, 91 and 77.
5. **Compound 8**; A pale yellow oil (89.7%). ^1H NMR shows ca. 96% purity. R_f = 0.4 (100% $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) 7.40.23 (5H, SPh, m), 6.9 (1H, =CH, s), 5.80 (1H, =CH, s), 3.64 (2H, CH_2SPh, s), 2.84 (1H, CHS, d, J = 12.6 Hz), 2.59 (1H, CHS, d, J = 12.6 Hz), 1.97 (3H, SCH_3, s), 1.91 (3H, =CCH_3, s), and 1.00 (3H, CCH_3, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) 204.0, 140.2, 140.1, 134.3, 131.6, 128.3, 127.0, 50.8, 44.2, 39.5, 25.2, 17.7, and 15.5 ppm. GC/MS 304(M^+), 289, 243, 211, 135, 109, 91, and 61.
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8. **A representative photolysis experiment (Table 1, Product 11)**. The solution of the dienone, **8** (0.5 g, 1.64 mmol) in 5 mL of freshly distilled ethyl alcohol in the presence of piperidine (0.167 g, 1.97 mmole, 1.2 equiv) in a cooling bath was irradiated at a distance of 2 cm with a tungsten lamp (220 W) while maintaining the bath temperature below 40 °C. The cleavage reaction was monitored by TLC. The starting material completely disappeared after 4 h and the volatiles were removed in vacuo. The crude product was diluted with CH_2Cl_2 (15 mL) and extracted with distilled water (2×10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated. After purification by flash column chromatography over silica gel (17:3/Et_2O:hexane), a clear oil, **1·1** was obtained (0.33 g, 0.84 mmol, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) 7.52.20 (5H, m), 5.81 (1H, s), 5.56 (1H, d, J=9.9 Hz), 3.62 (2H, $\underline{CH_2}SO_2$, s), 3.51 (4H, $N\underline{CH_2}$, m), 3.30 (1H, $\underline{CH}CO$, m), 3.14 (2H, $\underline{CH_2}SPh$, s), 3.08 (3H, $SO_2\underline{CH_3}$, s), 2.05 (3H, s), 1.61.32 (6H, m, ring $\underline{CH_2}$), 1.05 (3H, d, J=6.8 Hz); IR(neat);3550 ($\underline{CO}NH$), 3215($\underline{SPh}$; $\underline{C}$-H), 2910, 1635($\underline{CO}NH$), 1420, 1310/1105($\underline{SO_2}$) cm^{-1}. HRMS; m/z calcd for $C_{22}H_{31}NOS_2$; $[M+H]^+$, 390.2685. Found 390.2697.

9. **Compound 17**; A white crystalline solid, mp=169–171 °C, 93.7%, Rf=0.46 (100% ethyl acetate), ^{1}H NMR (300 MHz, $CDCl_3$) 7.8.7 (2H, SPh, m), 7.7.4 (3H, SPh, m), 6.69 (1H, =CH, s), 6.06 (1H, =CH, s), 3.91 (2H, $\underline{CH_2}SO_2Ph$, s), 3.90 (1H, d, J=13.98 Hz, $\underline{CH}SO_2CH_3$), 3.11 (1H, d, J=13.98Hz, $\underline{CH}SO_2CH_3$), 2.76 (3H, $SO_2\underline{CH_3}$, s), 1.82 (3H, CH_3-C=, s), and 0.99 (3H, $\underline{CH_3}C$, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) 200.3(C=O), 143.9, 139.6, 137.8, 134.0, 133.4, 129.6, 129.27, 128.67, 122.04, 62.37, 61.6, 53.5, 48.1, 42.9, 26.2 and 15.6 ppm. Anal. calcd for $C_{17}H_{20}O_5S_2$:C, 55.41; H, 5.46; S, 17.40. Found: C, 55.56; H, 5.82; S, 17.85.