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# PHOTOCLEAVAGE COUPLING REACTIONS BETWEEN CYCLOHEXA-2,4-DIENONE SULFONE DERIVATIVES AND AMINES BY VISIBLE LIGHT IRRADIATION

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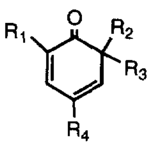
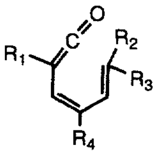
**Abstract**: A stable sulfone derivative of 2,4,6-trimethylcyclohexa-2,4-diene-1-one (**7**) undergoes facile ring cleavage under visible light to produce a ketene intermediate, which could be efficiently captured by amines to give amides even in the presence of competing nucleophiles such as water and ethanol.

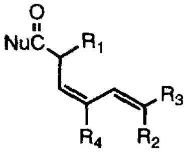
We previously reported the synthesis of several water soluble cyclohexa-2,4-dienones of type **1** and their cleavage to form *cis*-ketenes by photolysis using a conventional mercury lamp. A coupling reaction between the *cis*-ketens (**2**) and various amino-acids and dipeptides (glycine, glycyl-glycine, glycyl-L-leucine) showed the noticeably higher affinity of the amino function for the *cis*-ketene than that of the solvent water.[1] The mechanistic aspects of the dienone cleavage reaction have already been well studied.[2] Thus, nucleophilic trapping of **2** to give **3** could be carried out in an aqueous environment without a serious concern of water trapping the ketene species. In view of the sensitivity of certain chromophores in peptides (or in DNA) to UV light irradiation, it was also an important prerequisite to show that visible light could be used instead for the cleavage of the dienones of type **1**.[3]



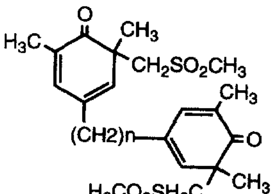
**1**



**2** cis-ketene



**3**



**4**

In our most recent investigations[4], we showed that a series of $\alpha,\omega$-diamines would furnish either mono- or bis-derivatives by sequential trapping of the *cis*-ketene **2**. In the previous studies we used *cis*-ketenes where $R_2$=$CH_2$-$SCH_3$ for the synthetic convenience. However, such dienones (**1**) were rather sensitive to acid and, without precautions, readily returned to the aromatic state.[5] In fact, even upon chromatography over silica gel, compound **6** was converted to **5** in high yield. It was reasoned that the stability problem of (**6**) might be overcome by oxidation to the corresponding sulfones (**1**, $R_2$=$CH_2SO_2CH_3$).

Toward this goal, we have now examined the reactivity of the cyclohexa-2,4-dienone sulfone

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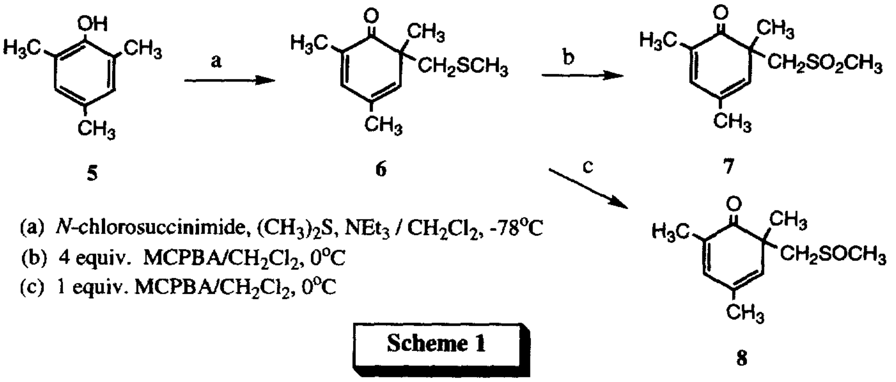
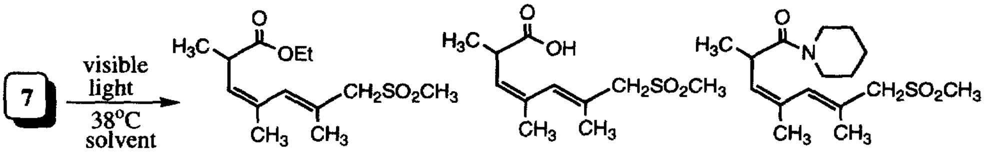
derivative (7). Reaction of mesitol **5** with $Me_2S$ / *N*-chlorosuccinimide yielded **6**,[6] which upon oxidant with *m*-chloroperbenzoic acid provided either, the sulfone 7 or the sulfoxide **8** dependining on the amount of the oxidation used (Scheme 1). The dienone 7 is a viscous oil and stable in the absence of light. It could be obtained in high purity by silica gel column chromatography (Rf=0.37;100% $Et_2O$) with no sign of decomposition.



(a) *N*-chlorosuccinimide, $(CH_3)_2S$, $NEt_3$ / $CH_2Cl_2$, -78°C
(b) 4 equiv. MCPBA/$CH_2Cl_2$, 0°C
(c) 1 equiv. MCPBA/$CH_2Cl_2$, 0°C

**Scheme 1**

**Table 1. Photolytic Reaction of 7 in the Presence of EtOH, $H_2O$, THF and Piperidine**

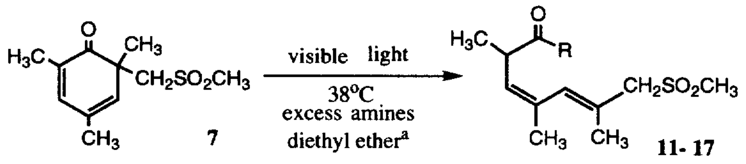


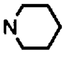
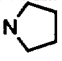
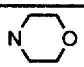
**9** ; Rf= 0.68(100% $Et_2O$) **10**; Rf= 0.27(100% $Et_2O$) **11**; Rf= 0.21(100% $Et_2O$)

| Entry | Solvent mL (mmol) | | | | Piperidine (Equiv.) | Reaction Time (hr) | Major Product Yield (%) |
|---|---|---|---|---|---|---|---|
| | EtOH | $H_2O$ | THF | $Et_2O$ | | | |
| 1 | 2 (34.1) | 0 | 0 | 0 | 0 | 7 | **9** (45%) |
| 2 | 1 (17.0) | 1 (55.5) | 0 | 0 | 0 | 7 | **9**:**10** (34% : 35%) |
| 3 | 0 | 1 (55.5) | 1 (12.3) | 0 | 0 | 7 | **10** (72%) |
| 4 | 2 (34.1) | 0 | 0 | 0 | 1.2[a] (0.4) | 7 | **11** (75%) |
| 5 | 1 (17.0) | 1 (55.5) | 0 | 0 | 1.2[a] (0.4) | 7 | **11** (66%) |
| 6 | 0 | 0 | 2 (24.6) | 0 | 1.2[a] (0.3) | 7 | **11** (68%) |
| 7 | 0 | 1 (55.5) | 1 (12.3) | 0 | 1.2[a] (0.4) | 7 | **11** (46%) |
| 8 | 0 | 0 | 0 | 2 (19.1) | 1.2[a] (0.3) | 2 | **11** (97%) |

[a] Based on one equivalent of 7.

**Table 2. Photolytic Reactions of Dienone 7 in an Excess of Various Amines at 38-40°C**



| Entry | Amines$^b$ | Reaction Time (hr) | Products | | | |
|---|---|---|---|---|---|---|
| | | | Rf$^c$ | No. | R | Yield$^h$ (%) |
| 1 | Piperidine | 2 | 0.21$^d$ | **11** |  | 97 |
| 2 | Pyrrolidine | 2 | 0.22$^e$ | **12** |  | 67 |
| 3 | Morpholine | 2 | 0.25$^e$ | **13** |  | 65 |
| 4 | $H_2NCH_2CH_2OH$ | 2.5 | 0.14$^f$ | **14** | $NHCH_2CH_2OH$ | 56 |
| 5 | $NH_2CH_2CH_2NH_2$ | 5 | 0.11$^g$ | **15** | $NHCH_2CH_2NH_2$ | 67 |
| 6 | $NH_2CH_2CH_2CH_2NH_2$ | 5 | 0.10$^g$ | **16** | $NHCH_2CH_2CH_2NH_2$ | 88 |
| 7 | $H_2NCH_2CH(OCH_3)_2$ | 5 | 0.14$^d$ | **17** | $HNCH_2CH(OCH_3)_2$ | 78 |

[a]Diethyl ether was purified by standard methods. [b]Amines were purchased from Aldrich and used without further purification. [c]TLC plates were made of E. Merck AG Darmstadt Silica gel 60 F254. [d] 100% $Et_2O$ [e]1% MeOH/99% $Et_2O$, [f]5% MeOH/95% $Et_2O$, [g]30% MeOH/70% ethylacetate. [h]Yield of isolated product.

Next, we examined the photolysis reaction of 7 in the various solvent such as EtOH, $H_2O$, THF and $Et_2O$. The results are summarized in Table 1. When absolute ethanol was used, ester **9** and unreacted starting material was isolated as 45:55. When 7 (18.5 mg, 81.1 mmol) was photolyzed in EtOH and $H_2O$ mixture (1:1), 10 mg (36.5 mmol, 45%) of **9** and 6.8 mg (27.6 mmol, 34%) of **10** were isolated. Addition of THF instead of EtOH to $H_2O$ gave more carboxylic acid derivative, **10** (72%) and only a trace of the starting material (Entry 3). We did not carry out the photolysis in pure $H_2O$ because of a solubility problem. Addition of 1.2 equiv. of piperidine to the solution of 7 in EtOH, THF, $H_2O$ or $Et_2O$ gave exclusively the amide product, **11**. The ketene intermediate is apparently captured by the amine much faster than water of ethanol. The yield could be maximized when the reaction was carried out in the $Et_2O$ solution (Entry 8). The photolysis reaction of sulfone 7 in $Et_2O$ was then examined in detail in the presence of various amines. The results summarized in Table 2 indicate that the sulfone-containing cyclohexadienone 7 readily generates the ketene intermediate, which can efficiently capture the amine functionality, as the sulfide-containing analog **6** did. Currently we are preparing symmetric difunctional molecules (**4**) in which two units of the photo active cyclohexa-2,4-dienone derivatives are linked with a varying length of carbon tethers and exploring the ring cleavage reaction with various amines as a potential geometric probe for biologically important molecules.

*Synthesis of cyclohexa-2,4-dien-1-one (7).* To a solution of **6** (0.98 g, 5.10 mmol) in $CH_2Cl_2$ at 0℃ was added *m*-chloroperbenzoic acid dissolved in $CH_2Cl_2$. The solution was stirred for 4hr and washed with aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$) and evaporated *in vacuo* to afford a crude product, which was purified by flash chromatography to give 7 (0.91 g, 3.98 mmol, 79%) as a viscous oil. $^1$H NMR($CDCl_3$); $\delta$ 6.78(1H, s), 6.11(1H, s), 3.98(1H, d, J=13.68Hz), 3.23(1H, d, J=14.31Hz), 2.81(3H, S, $CH_3$), 1.97(3H, s, $CH_3$), 1.95(3H, s, $CH_3$), 1.21(3H, s, $CH_3$) ppm. HRMS: *m/z* Calcd for $C_{11}H_{16}O_3S$; $[M+H]^+$=229.0898/Found 229.0897.

*A typical experimental procedure for the photolysis of 7.* Light from a tungsten lamp (220W) was employed to irradiate the dienone solution 7 (90 mg, 0.39 mmole; 1 equivalent) in 3 mL of freshly distilled diethyl ether in the presence of aminoacetaldehyde dimethyl acetal (49 mg, 0.47 mmole; 1.2 equivalent). The solution was irradiated at a distance of 2 cm and the temperature was kept below 38℃ by external water cooling. Progress of the reactions was monitored by TLC. After 5hr, the volatiles were removed *in vacuo* and the crude product was diluted with 20 mL of $CH_2Cl_2$ and washed with water (2 X 10 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated. The residue was subjected to flash chromatography ($MeOH:Et_2O$=1:99) on silica gel to give **17** as an oil. $^1$H NMR($CDCl_3$); $\delta$ 6.26(1H, NH, broad s), 6.06(1H, s), 5.34(1H, d, J=9.81 Hz), 4.37(1H, t, J=5.46Hz), 3.74(2H, $\underline{CH_2}S$, s), 3.34(3H, $O\underline{CH_3}$, s), 3.33(3H, $O\underline{CH_3}$, s), 3.32-3.33(3H, m), 3.01(3H, $SO_2\underline{CH_3}$, s), 1.76(3H, s), 1.15(3H, $\underline{CH_3}CH$, d, J=6.90 Hz) ppm. HRMS: *m/z* Calcd for $C_{15}H_{27}NO_5S$;$[M+H]^+$=334.1688/Found 334.1702.

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