

Photochemical Cleavage of Cyclohexa-2,4-dienones under Irradiation with Visible Light.

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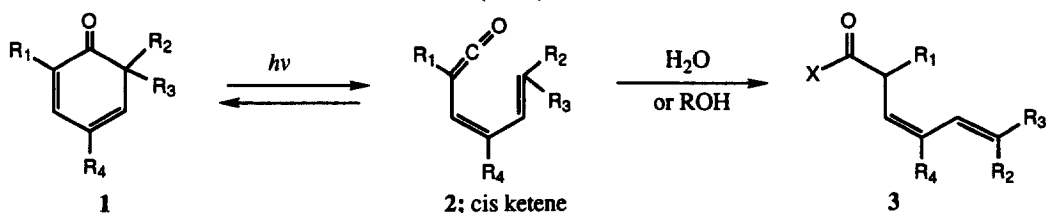
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Abstract: 2,4,6-Trimethylcyclohexa-2,4-dien-1-one derivatives undergo ring cleavage to furnish amides on irradiation with visible light in the presence of various amines. Seven different amides containing a substituted diene moiety were synthesized in 87-95% yield.

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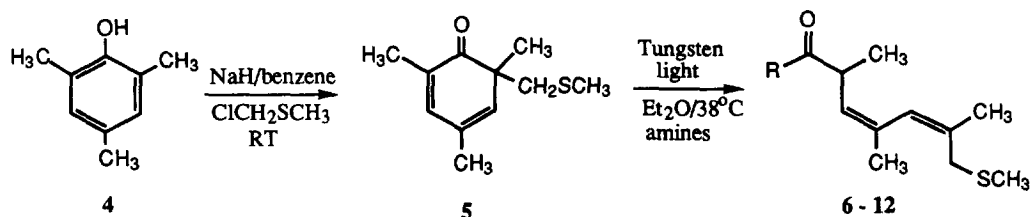
Some years ago,¹ it was reported that upon irradiation with ultra-violet light *ortho*-type cyclohexa-2,4-dienones **1** underwent smooth conversion into acids or acid derivatives *via* trapping of the reversibly formed *cis*-ketenes **2**.² This type of reaction was extensively studied by Quinkert and his colleagues and all the mechanistic details were established.³ Recently,⁴ we reported the synthesis of several water soluble cyclohexa-2,4-dienones of type **1**. By photolysis using a conventional mercury lamp (175 W), the opening of the ring to form *cis*-ketenes could be demonstrated. Addition of various amino acids and dipeptides showed the preference of the *cis*-ketene for the amino-function rather than for the solvent (water).



Scheme 1

In principle, this photochemical generation of ketenes could be used for the exploration of the basic amino-functions on the exterior of an enzyme. However, the use of mercury lamps for ketene formation has some disadvantages since irradiation would be injurious to tryptophan and similar functions. Clearly, the use of visible light would be preferable. In the course of a project for a new labeling procedure of biologically important compounds, we have found that visible light is an excellent energy source for the photochemical cleavage of 2,4,6-trimethylcyclohexa-2,4-dien-1-one derivatives. Our first thought was to make compounds of type **1** with a thione function instead of the conventional ketone group. Although cross-conjugated thiodienones are known,⁵ the linear thiodienones now being proposed are unknown. However, before placing emphasis on the synthesis of this new class of compounds, we decided to see if the light produced by a conventional tungsten lamp would be adequate for the cleavage of the linear dienones of type **1**.

Table 1. Photolytic Reaction of 5 and Various Amines in Diethyl ether at 38-40°C.



Amide	Amine (R group)	Time (hr)	Yield (%) ^a	Rf ^b	High Resolution Mass Spectrum ^c	
					Calculation ; [M+H] ⁺	Found
6	Pyrrolidine	6	87	0.19	C ₁₅ H ₂₅ NOS ; 268.17351	268.1734
7	Piperidine	5	93	0.25	C ₁₆ H ₂₇ NOS ; 282.1885	282.1885
8	Morpholine	5.5	90	0.13	C ₁₅ H ₂₅ NO ₂ S ; 284.16843	284.1696
9	Cyclohexylamine	3	95	0.38	C ₁₇ H ₂₉ NOS ; 296.20481	296.2057
10	<i>n</i> -Butyl amine	4	92	0.37	C ₁₅ H ₂₇ NOS ; 270.18916	270.1896
11	Aminoacetaldehyde diethylacetal	3	95	0.63	C ₁₅ H ₂₇ NO ₃ S ; 302.17900	302.1801
12	Ethanolamine	6	92	0.07	C ₁₃ H ₂₃ NO ₂ S ; 258.15278	258.1512

^aYield of isolated product; all products were characterized by their ¹H, ¹³C NMR, GC/MS, IR spectrums.

^b1:1=Et₂O:Hexane; TLC plates were made of E. Merck AG Darmstadt Silica gel 60 F₂₅₄. ^cHigh resolution mass spectra were recorded on a VG analytical 70S high resolution, double focusing sector (EB) mass spectrometer. High resolution FAB spectra were obtained with a 10 keV Xe beam at 2 mA (primary beam).

The dienone 5⁶ is easily prepared from the reaction of 4 with NaH/chloromethyl methyl sulfide in benzene and was readily and quantitatively converted into a series of amides (6-12) on irradiation in ether at 38°C under reflux. The results are summarized in Table 1. All reactions were completed in less than 6 hrs and yielded, in most cases, the desired product in *ca.* 90% yield. This is not more than twice as long as the time for UV irradiation. As before, the ring cleavage led to both *cis* and *trans* isomers. These are difficult to separate by flash column chromatography, but the twin peaks were detected with a GC/MS spectrometer for 6, 7, 8, 11 and 12. Only one single adduct was detected in the case of the cyclohexyl amide derivative 9.

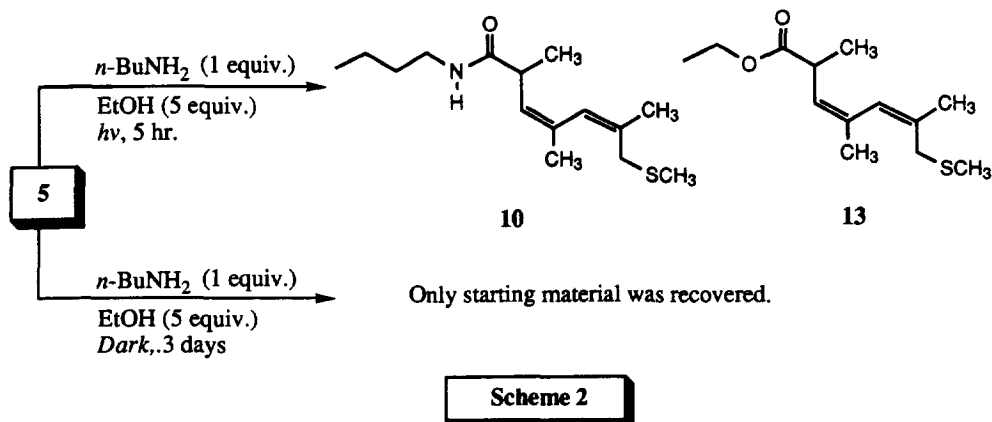
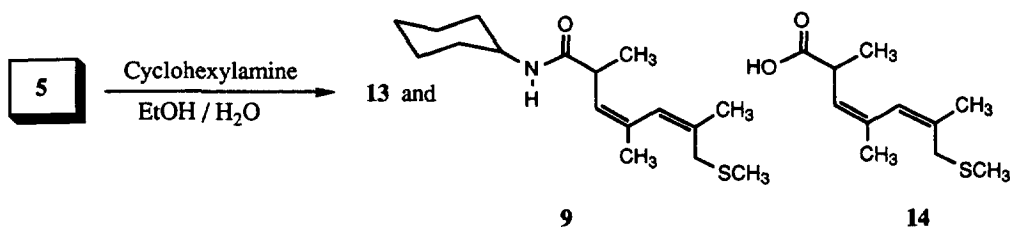


Table 2. Photolytic Reaction of 5 and cyclohexylamine in the presence of EtOH and H₂O



Entry	EtOH (equiv.)	H ₂ O (equiv.)	Cyclohexyl amine (equiv.)	Light condition	Time	Product (% yield)
1	5	5	0	Dark	3 days	5 (100%) ^c
2	5	5	5	Dark	3 days	5 (100%) ^c
3	10	10	5	UV(254 nm) ^a	2 days	9 (5%) ^d + 5 (95%) ^d
4	10	10	0	UV(300 nm) ^b	1.5 hr	13 (80%) ^d + 14 (20%) ^d
5	10	10	5	UV(300 nm) ^b	1.5 hr	9 (85%) ^e

^aSpectroLine Model ENF-260C, 115 Volt, 60 Hz, 0.16 A, Short-wave, UV (254 nm).

^bRayonet photochemical reactor using 8 300 nm lamps. ^cOnly starting material was detected by ¹H NMR.

^dRatio was determined by proton integration of ¹H NMR. ^eIsolated yield.

We have also examined the photolysis reaction of 5 with *n*-butylamine in the presence of absolute ethanol. Even though excess ethanol (5 equiv.) was used, 10 and 13 were obtained after 5 hrs of irradiation as a 9.5:1 ratio after purification by flash column chromatography. As shown in Table 1, the reaction of 5 with ethanolamine which has two functional groups (NH₂ and OH) gave exclusively the amide product 12. This result is in agreement with Scheme 2. The ketene intermediate captures the amine much faster than the alcohol functional group to give amide 10. We have confirmed that these reactions are dramatically enhanced by light by comparing

the same experiments in the absence of light. Thus **5**, *n*-butylamine and alcohol mixtures were stirred for 3 days after wrapping the flasks with aluminium foil. Neither **10** nor **13** were detected and only starting material was recovered.

As shown in Table 2, **5** was reacted with EtOH/H₂O or EtOH/H₂O/cyclohexylamine mixtures in the absence of light. As expected, neither **9**, **13** nor **14** were detected on TLC even after 3 days (entries 1 and 2). We also used a UV lamp (for TLC) for the photolysis reaction. In this case, after 2 days, 5% conversion of amide **9** occurred without forming **13** and **14** (entry 3). We then investigated the photolysis reaction of **5** using a Rayonet Apparatus (Southern New England Ultraviolet Co.). As a blank experiment, **5** in EtOH/H₂O mixture was irradiated at 25-30°C. Within 1.5 hrs, the reaction gave **13** and its carboxylic acid derivative **14** in a 4:1 ratio (entry 4). However, in the presence of cyclohexylamine, **9** was exclusively isolated (entry 5).

In summary, we have shown that irradiation with visible light is a good procedure for the photolytic cleavage of 2,4,6-trimethylcyclohexa-2,4-dien-1-one type compounds with primary, secondary and functionalized amines to give the corresponding amides. Primary amines generally react faster with the ketene intermediate than secondary amines in this photolysis ring cleavage reaction. Currently, we are exploring the application of these cyclohexadienone reagents for the functionalization of biologically important molecules. These results will be reported in due course.

General experimental procedure for tungsten irradiated photolysis of 2,4,6-trimethylcyclohexa-2,4-dien-1-ones (**6-12**) is as follows: Light from a tungsten lamp (220W) was employed to irradiate the dienone solution **5** in 3 ml of freshly distilled diethyl ether in the presence of amines. The solution was then irradiated at a distance of 3 cm and the temperature kept below 40°C by external water cooling. The reactions were monitored by TLC and were all completed within 3-6 hrs. The solutions were diluted with 20 ml of diethyl ether and washed with 10% HCl (2X) and water (2X). The organic phases were dried over MgSO₄, filtered and the volatiles removed *in vacuo*. The residue was subjected to flash chromatography (diethyl ether/hexane=1:1) over silica gel.

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