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Synthesis of Benzo[*c*]xanthones from 2-Benzylidene-1-tetralones by the Ultraviolet Radiation-Mediated Tandem Reaction

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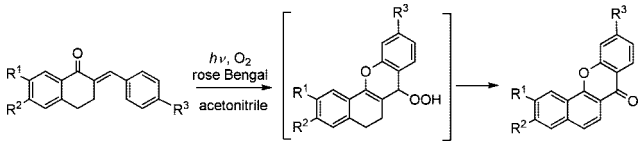
Received April 24, 2008

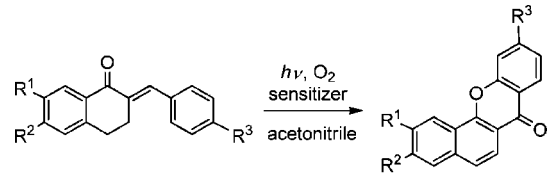


A facile one-pot method to prepare benzo[*c*]xanthones from readily accessible benzylidene-1-tetralones by the ultraviolet radiation-mediated tandem reaction is reported. The overall transformation presumably involves cis−trans isomerization, oxa-6π electrocyclization, singlet oxygen ene reaction, dehydration, and aromatization.

Xanthones have engendered a great deal of interest due to their wide range of biological and pharmacological activities, e.g., antibacterial, anti-inflammatory, antioxidant, antiulcer, and antitumor.[1] Mangostins, a kind of xanthones isolated from the pericarps of mangosteen, can induce caspase-3-dependent apoptosis in human leukemia HL60 cells or cell-cycle arrest and apoptosis in human colon cancer DLD-1 cells. They would be candidates for preventive and therapeutic application for cancer treatment.[2]

Two main methods have been applied for the synthesis of xanthones. One is through the intermediates of benzophenones. 2,2′-Dioxygenated benzophenones, which can be prepared by acylation or Fries arrangement, are cyclized through the dehydrative or oxidative process to form xanthones.[3] Another is through the intermediates of diary ethers. 2-Carboxy biphenyl ethers, which are obtained by the Ullmann method or Smiles rearrangement, are cyclized in one step with lithium diisopropylamide or with acetyl chloride to yield xanthones.[4] Recently, Zhao and Larock reported a facile one-pot coupling method to synthesize xanthones and thioxanthones from arynes and substituted benzoates with good yields.[5] The key intermediate of this method is a diaryl (thio)ether. Other less used methods of synthesis of xanthones include thermal condensation of phenols and β-keto-esters (to prepare dihydrobenzo[*a*]xanthones),[6] Diels−Alder reaction of chromone-3-carboxaldehydes with *o*-benzoquinodimethane (to prepare benzo[*b*]xanthones),[7] benzannulation of 1,2-adducts derived from 3-(*o*-anisoyl)-4-substituted cyclobutenediones,[8] and cycloaddition of 2-styrylchromones with appropriate dienophiles.[9] In particular, photooxidative cyclization of 2-styrylchromones,[10] 2-benzyl-3-benzoylchromones,[11] and 2-styryl-4*H*-chromen-4-ones[12] can also afford benzoxanthones. But most reported methods are multistep, with harsh reaction conditions, or are not atom-economic. Here, we reported a new one-pot method to prepare benzo[*c*]xanthones from readily accessible benzylidene-1-tetralones by the ultraviolet radiation-mediated tandem reaction. The overall transformation presumably involves cis−trans isomerization, oxa-6π electrocyclization, singlet oxygen ene reaction, dehydration, and aromatization. Moreover, in contrast to the methods described above, the oxygen atom of the carbonyl group of xanthone comes from the oxygen dissolved in the solvent.

SCHEME 1. Synthesis of Benzo[*c*]xanthones from Benzylidene-1-tetralones



Irradiating the solution of 2-benzylidene-1-tetralone (**1e**) in acetonitrile with ultraviolet light (a 500 W middle-pressure Hg

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10.1021/jo8008929 CCC: $40.75
Published on Web 06/14/2008

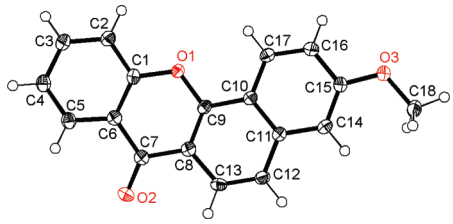


FIGURE 1. Crystal structure of compound **2i**. The 50% thermal ellipsoid is shown for the non-hydrogen atoms.

TABLE 1. Optimization of the Photooxidative Cyclization of 2-Benzyliene-7-bromo-1-tetralone (1b)

entry	filter	sensitizer	yield (%)[a]
1	no		8
2	glass filter		7
3	toluene/hexane		6
4	1,4-dimethylbenzene/EtOH		10
5	1,3,5-trimethylbenzene/EtOH		19
6	1,3,5-trimethylbenzene/EtOH	fullerene C_{60}[b]	26
7	1,3,5-trimethylbenzene/EtOH	methylene blue[b]	trace
8	1,3,5-trimethylbenzene/EtOH	rhodamine B[b]	11
9	1,3,5-trimethylbenzene/EtOH	rose bengal[b]	35
10	1,3,5-trimethylbenzene/EtOH	9,10-dicyanoan-thracene[b]	27

[a] All the reactions were carried out for 24 h except entry 2 (42 h). [b] With 0.027 equiv of singlet oxygen sensitizer.

lamp) for several days, we obtained a new compound from the reaction mixture (Scheme 1). Compared with the original tetralone structure, this product displays no methylene hydrogen signals in its ^{1}H NMR spectrum. The high-resolution mass spectrum indicates that its chemical formula is $C_{17}H_{10}O_2$. The final structure of the product has been deduced to be 7*H*-benzo[*c*]xanthen-7-one (**2e**), whose NMR spectra coincide with the reported data.[5a] The crystal structure of **2i** (Figure 1), which was synthesized by our method from 2-benzylidene-6-methoxy-1-tetralone, has confirmed the core structure of 7*H*-benzo[c]-xanthen-7-one.[13]

The conditions of this ultraviolet radiation-mediated reaction have been optimized carefully. We first studied the effect of different solvents and found that acetonitrile could give the best yield. This reaction did not occur in other solvents such as acetone, THF, dioxane, ethyl acetate, CCl_4, and DMF. Due to the complicated side reactions found in most ultraviolet radiation-mediated reactions, it is necessary to control the irradiation wavelength. We have used a 360 nm glass filter, but the yield was as low as without it (Table 1). Many solution filters have also been investigated. Irradiating 2-benzylidene-1-tetralones through the solution filters of chlorobenzene/ethanol, aniline/water, acetone/hexane, acetophone/ethanol, and pyridine/hexane did not afford the xanthones. The solution filter of 1,4-dimethylbenzene/EtOH and toluene/hexane did not affect reaction. Only the solution filter of 1,3,5-trimethylbenzene/EtOH improved the yield of the reaction. Finally, the role of oxygen was investigated. When the reaction solution was degassed with an argon stream for 30 min prior to irradiation, the cis isomer of benzylidene-1-tetralone was isolated, but it slowly converted into starting material on standing. Therefore, the additional oxygen atom of the final product should come from the oxygen

(13) Crystal data for **2i**: $C_{18}H_{12}O_3$, $M = 276.28$, orthorhombic, space group $Pna2_1$, $a = 10.5803(14)$ Å, $b = 23.761(3)$ Å, $c = 4.9298(7)$ Å, $V = 1239.3(3)$ Å^3, $Z = 4$, μ(Mo Kα) $= 0.101$ mm^{-1}, $T = 113(2)$ K, final residuals (191 parameters) $R_1 = 0.0439$ for 1570 reflections with $I > 2\sigma(I)$, and $R_1 = 0.0467$, $wR2 = 0.1114$, GoF $= 1.076$ for all 1644 data.

TABLE 2. Ultraviolet Radiation-Mediated Oxidative Cyclization of Benzylidene-1-tetralones to Benzo[*c*]xanthones[a]

entry	tetralone	R^1	R^2	R^3	time (hr)	xanthone (yield %)
1	**1a**	Br	H	Bu^t	12	**2a** (48)
2	**1b**	Br	H	H	24	**2b** (35)
3	**1c**	Br	H	CH_3	42	**2c** (34)
4	**1d**	Br	H	Br	42	**2d** (40)
5	**1e**	H	H	H	64	**2e** (45)
6	**1f**	H	H	Br	72	**2f** (36)
7	**1g**	H	H	Bu^t	48	**2g** (31)
8	**1h**	H	OCH_3	CH_3	43	**2h** (50)
9	**1i**	H	OCH_3	H	22	**2i** (39)
10	**1j**	Br	Ph	H	100	/[a]
11	**1k**	H	NO_2	H	100	/[a]
12	**1l**	H	OCH_3	H	100	/[a]
13	**1m**	H	H	Cl	100	/[a]

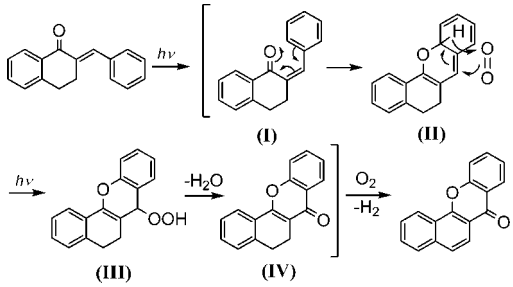
[a] No oxidative cyclization product was isolated.

dissolved in the solution. We have also carried out the reaction with a continuous stream of oxygen, but the yield could not be increased. However, the yield of this ultraviolet radiation-mediated reaction could be improved upon addition of a singlet oxygen sensitizer. A number of typical singlet oxygen sensitizers have been screened, and rose bengal is the best one for this reaction. These results also indicate that it is the singlet oxygen that participates in the oxidative cyclization.

The scope and limitation of the photoinduced oxidative cyclization were examined under optimized conditions (Table 2). The results show that the substituents on the phenyl group of tetralone have no apparent effect on the reaction. The irradiation of 2-benzyliene-1-tetralones containing less electron-poor aromatic rings (**1a**−**d**), neutral aromatic rings (**1e**−**g**), or electron-rich aromatic rings (**1h**−**j**) affords the expected xanthones with moderate yields. But the tetralone skeleton is essential here. Under the same condition, we only isolated the [2 + 2] cyclization dimer starting from 2-benzylidenecyclohexanone. On the other hand, the nature of the substituents present at para or meta positions of the benzylidene unit greatly influences the reaction. Neither a strong electron-withdrawing group (NO_2) nor a strong electron-donating group (OCH_3) atthe para position of the benzylidene (**1k**, **1*l***) is tolerated. For the 2-benzyliene-1-tetralones with these groups, the cleaved benzoic acids were occasionally isolated. The substituent located at the meta position of benzylidene is also disadvantageous, and the transformation of **1m** did not occur. However, it is not easy to find a clear rule for the substitutent effect, which may be due to the nature of the photochemical reactions.

The mechanism shown in Scheme 2 is proposed for this process. The benzylidene-1-tetralone undergoes cis−trans isomerization first. We noticed that this oxidative cyclization could not take place upon irradiating the crystalline powder of benzylidene-1-tetralone. It may be interpreted that the cis−trans isomerization is not easy in the solid state. By TLC, GC-MS, and NMR (see the Supporting Information), we have also observed the cis-isomer of benzylidene-1-tetralone (**I**) as an

SCHEME 2. Proposed Mechanism for Benzo[*c*]xanthones Formation



intermediate in the reaction, which emerged upon ultraviolet irradiation and disappeared at the end. The *cis*-benzylidene-1-tetralone is easily cyclized to generate the (^{2}H)-pyran ring through a thermoneutral oxa-6π electrocyclization, which cyclizes with low activation energies.[14] Then the intermediate 6,11a-dihydro-5*H*-benzo[*c*]xanthene (**II**), which could not be isolated in the absence of oxygen due to highly reversible electrocyclization,[14b] is oxidized to afford an allylic hydroperoxide in a typical singlet oxygen ene reaction.[15] This process is strongly supported by the fact that the reaction yield was improved significantly upon adding the singlet oxygen sensitizers (Table 1).

The next step is the dehydration[16] of the hydroperoxide (**III**) to afford 5*H*-benzo[*c*]xanthen-7(6*H*)-one (**IV**). In all cases shown in Table 2, compound **IV** was easily aromatized to yield the final product benzo[*c*]xanthone.[17] However, for the 2-(naphthalen-2-ylmethylene)-1-tetralones (**1n**,**o**), there is no further dehydrogenation (Scheme 3). Only the 5*H*-dibenzo[*c*,*h*]xanthen-7(6*H*)-ones (**2n**,**o**) have been isolated with low yields (16% and 19%, respectively). This outcome also supports the mechanism of the overall transformation.

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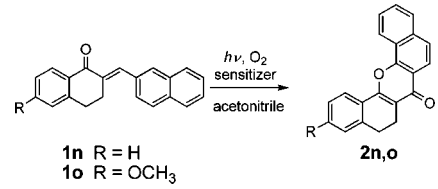
SCHEME 3. Formation of 5*H*-Dibenzo[*c*,*h*]xanthen-7(6*H*)-ones



In conclusion, we report herein a facile one-pot approach to synthesize biologically interesting benzo[*c*]xanthones from readily accessible 2-benzylidene-1-tetralones by an ultraviolet radiation-mediated tandem reaction.

Experimental Section

Experimental Procedure of Photooxidation Cyclization. A quartz tube was charged with a solution of benzylidene-1-tetralone (0.2 mmol) and rose Bengal (0.027 equiv) in acetonitrile (10 mL). The solution was saturated with oxygen for 30 min and then irradiated through a filter solution (1,3,5-trimethylbenzene/EtOH 1:1) with a high-pressure mercury lamp (500 W) for the time indicated in Table 2. The reaction mixture was then concentrated under vacuum and the residue was purified by silica gel column chromatography with petroleum ether/EtOAc as eluent.

2-Bromo-10-*tert*-butyl-7*H*-benzo[*c*]xanthen-7-one (2a). Mp 214−216 °C; yield 48%. IR (KBr) ν 2956, 1649, 1632, 1618, 1446, 847 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 7.52 (dd, J = 8.4, 1.8 Hz, 1H), 7.68−7.71 (m, 2H), 7.79 (m, 2H), 8.30 (t, J = 8.1 Hz, 2H), 8.84 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 31.1, 35.6, 114.5, 118.3, 120.1, 121.0, 122.2, 122.6, 123.5, 125.4, 126.2, 129.7, 132.6, 134.8, 152.6, 155.8, 159.4, 176.4. MS (EI) *m*/*z* (%) 382 (73), 380 (73), 367 (96), 365 (100). HRMS (EI) *m*/*z* calcd for $C_{21}H_{17}O_2{}^{81}Br$ 382.0391, found 382.0395; calcd for $C_{21}H_{17}O_2{}^{79}Br$ 380.0412, found 382.0408.

Acknowledgment. We are grateful to the National Natural Science Foundation of China and the Chinese Academy of Sciences for financial support. Dr. Q.-Y. Zheng thanks Prof. Y. Shi and Prof. M.-X. Wang for discussion of this work.

Supporting Information Available: Full experimental details for the syntheses reported together with spectroscopic and X-ray crystallographic information file. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8008929