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Acid Catalyzed Intramolecular [2+2] Photocycloaddition of 3,5-Dihydroxybenzoic Acid Derivatives

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Abstract: Irradiation of 3-alkenyloxy-5-hydroxybenzoic and the corresponding 3-alkenyloxy-5-methoxybenzoic acid derivatives **1** - **4** in the presence of small quantities of H_2SO_4 produces highly functionalized alkyloxyenones **6** - **8** in good or moderate yields. The products are explained via an acid catalyzed transformation of the primary [2+2] photocycloadducts. © 1998 Published by Elsevier Science Ltd. All rights reserved.

Three types of photochemical cycloaddition reactions of benzene derivatives and alkenes have been reported.[1] Depending on the difference of the redox potentials between the two reaction partners, [2+2], [2+3] and [2+4] cycloadducts can be obtained.[2] Especially in the case of the [2+2] cycloaddition, the primary adducts are photoreactive. They can be easily transformed during the reaction, through a succession of photochemical or thermal steps, and a mixture of rearranged products is observed.[3] For O-alkenylsalicylic acid derivatives, the photochemical and thermal rearrangements following the [2+2] photocycloaddition are accelerated by the presence of acid in the reaction medium and the resulting products can be isolated in good yields.[4]

Similarly, the photoreactivity of phenol and polyphenol derivatives can be remarkably modified in the presence of acid, and most of the investigated compounds were photoreactive only in acidic media.[5] Thus benzocyclobutenes and possibly some rearranged products were isolated from the photolysis of meta-alkenyloxyanisol, the corresponding phenol derivatives and the 1,2,4-trihydroxybenzene derivatives as well. These results contrast with the photoreactivity in neutral media of such compounds substituted with electrondonating groups, which are known to react predominantly via meta cycloaddition.[1,2]

As previously indicated, addition of acid to the reaction mixture gave a clean phototransformation of salicylic esters although the isolated product resulted of a complex reaction path.[4] Introduction of several alkoxy substituents in the meta position of benzoates might modify the stability of primary photoadducts between the alkenyloxy group and the benzene ring. For this reason and in connection with our interest for these adducts for synthetic applications, we decided to investigate the reactivity of dihydroxybenzoic acid derivatives under acidic conditions. In this communication, we report their specific and unusual photochemical reactivity.

When a solution of **1**[6] in acetonitrile was irradiated, in presence of small quantities of sulfuric acid, the 3-alkyloxycyclohex-2-en-1-one **6** could be isolated (Scheme 1, Table). In the absence of acid, a very slow transformation and a complex mixture of products was observed. The reaction was presumably initiated by an

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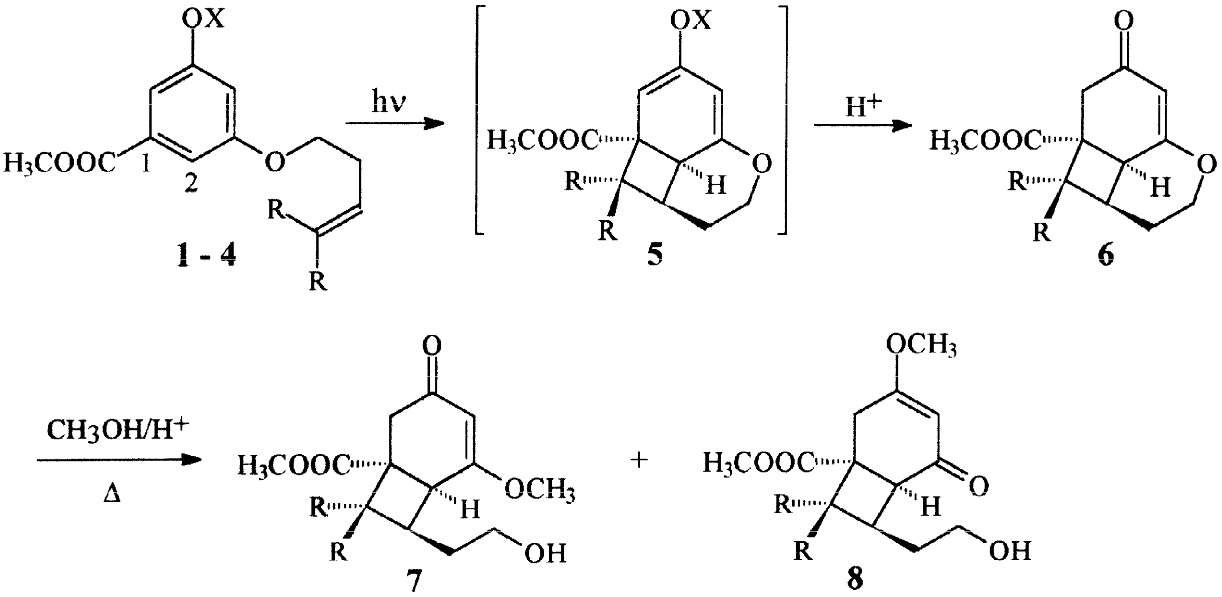
intramolecular [2+2] photocycloaddition between the alkenyl moiety and the α,β-unsaturated positions of the ester function, to give the intermediate **5**. A tautomerism of an enolic function allowed the formation of **6**. The corresponding phenol ether **2** was next examined to test if an hydroxy group was needed for the intramolecular photocycloaddition process to occur. When **2** was irradiated in the same conditions, **6** was isolated with similar and even better yields if the reaction was carried out at λ = 300 nm rather than λ = 254 nm.



Scheme 1: Photochemical reaction of 3,5-dihydroxybenzoic acid derivatives in acidic media.

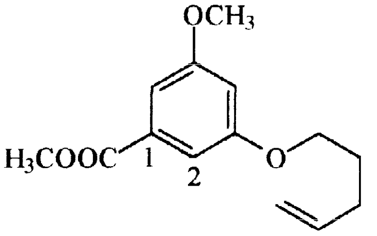
Table: Results of the irradiation of **1** - **4** in acidic reaction media.

Starting Material	X	R	Solvent	λ (nm)	Conversion (%)	Yield (%)[a]		
						6	**7**	**8**
1	H	H	CH_3CN	254	50	47	-	-
2	CH_3	H	CH_3CN	254	52	57	-	-
2	CH_3	H	CH_3CN	300	57	65	-	-
2	CH_3	H	CH_3OH	300	82	-	64	16
3	CH_3	CH_3	CH_3OH	300	100[b]	-	38	10
4	H	CH_3	CH_3OH	300	100	-	48	12

[a] isolated yields based on the conversion. [b] A complex mixture of less polar byproducts (~47 %) was also isolated.

When acetonitrile was replaced by methanol as solvent, the efficiency of the reaction increased and the more stable products 7 and **8** (R = H) rather than **6** were formed in high yields. Substitution of the extremity of the alkenyl side chain did not supress the cycloaddition process even if lower yields of the corresponding products 7 and **8** (R = CH_3) were obtained. The major regioisomer 7 (R = CH_3) could be purified by crystallization from chloroform/ether (F: 113 - 114 °C). Structures and stereochemistry have been determined by NMR spectroscopy. A HMBC pulse sequence was used to distinguish between the regioisomers **7** and **8** ($R=CH_3$). Compounds like **7** and **8** have been used for the synthesis of selective herbicides of commercial interest.[7]

Only a slow and unselective reaction was observed when substrate **9** having a longer alkenyl side chain was irradiated in the same conditions. The acetophenone derivatives **10** and **11** were photostable in the described reaction conditions.



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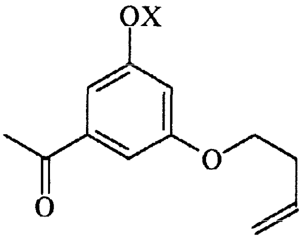
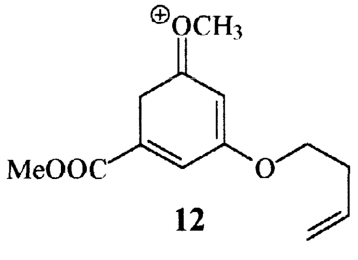


10: X = H
11: X = CH3

Photocycloaddition of 3,5-dihydroxybenzoic acid derivatives **1** - **4** and especially the regioselectivity of the addition contrast with the addition process reported for the reaction of alkenyloxyanisole and alkenyloxyphenol derivatives. Formation of a cyclobutane between the alkenylgroup and the C_1-C_2 bond involves a behaviour of an excited α,β unsaturated ester rather than an excited dialkyloxybenzene. The longer side chain of **9** would generate a less favourable transition state leading to a seven membered ring in the corresponding intermediate **5** and the addition process was not observed.

Whether species like **12** or **13** are precursors of the [2+2] photocycloaddition can not be decided yet. These intermediates could be generated by C-protonation in the acidic reaction medium or by a phototautomerization respectively. No modification of the UV spectra could be detected in the presence of acid. This indicates that if **12** of **13** were intermediates, they should be produced through a reaction of the excited state. The reason why **10** and **11** were unreactive in these conditions is not yet clear.



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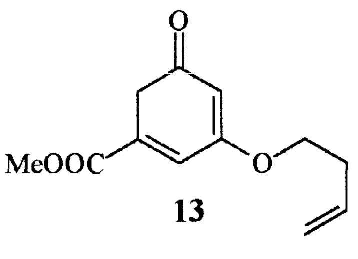

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Experimental Conditions

In a typical experiment, four quartz tubes each containing a solution of 16 ml containing **1** (about 0.5 mmol) and H_2SO_4 (0.1 mmol) were irradiated (Rayonet, T = 30°C). After about 3 h, the reaction was stopped and $NaHCO_3$ was added to the solutions. After evaporation of the solvent, the residue was subjected to flash chromatography with petroleum ether/ethylacetate (v/v : 1/1) for the separation of **1** - **4** and ethylacetate for the separation of 7 and **8**.[8]

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6 The alkylations of the 3,5-dihydroxybenzoic ester derivatives have been carried out as described in [5a].

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8 **6** (R = H) : ^{1}H NMR (250 MHz, CD_3COCD_3) : δ = 5.62 (d, J = 1.5 Hz, 1H), 4.24 (ddd, J = 2.3/4.2/10.7 Hz, 1H), 4.14 (ddd, J = 1.5/10.8/12.5 Hz, 1H), 3.76 (s, 3H), 3.40 (ddt, J = 3.8/9.1/1.1 Hz, 1H), 3.10 (d pen, J = 7.6/9.5 Hz, 1H), 2.57 (ddd, J = 3.9/7.3/11.4 Hz, 1H), 2.48 (d, J = 18.7 Hz, 1H), 2.36 (d, J = 18.7 Hz, 1H) ppm. ^{13}C NMR (62 MHz, CD_3COCD_3) : δ = 194.04, 176.23, 175.92, 108.90, 68.95, 52.84, 46.02, 40.48, 38.72, 37.87, 30.66, 30.00 ppm.

7 (R = CH_3) : ^{1}H NMR (250 MHz, CD_3COCD_3) : δ = 5.47 (s, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.60 (d, J = 10.3 Hz, 1H), 3.46 - 3.55 (m, 3H), 2.66 (d, J = 18 Hz, 1H), 2.60 (dt, J = 10.3/7.7 Hz, 1H), 2.39 (d, J = 18 Hz, 1H), 1.60 (q, J = 7.7 Hz, 2H), 1.05 (s, 3H), 1.00 (s, 3H) ppm. ^{13}C NMR (62 MHz, CD_3COCD_3) : δ = 196.75, 176.59, 175.15, 103.55, 61.17, 55.81, 51.96, 49.99, 43.64, 42.70, 38.34, 37.91, 30.93, 27.98, 19.43 ppm.