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Photocyclization of 2-Chloro-Substituted 1,3-Diarylpropan-1,3-diones to Flavones

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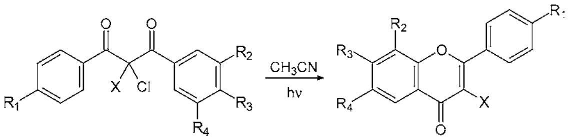
ABSTRACT



The photochemical behavior of 2-halo-substituted 1,3-diarylpropan-1,3-dione strongly depends on the nature of the halogen atom bonded and the presence of electron-donor groups on the phenyl ring. In the case of 2-chloro-1,3-diphenylpropan-1,3-dione and 1-(3,5-dimethoxyphenyl)-3-phenylpropan-1,3-dione, cyclization to flavones was the sole reaction pathway, whereas in the case of 2-chloro-1,3-di(4-methoxyphenyl)-propan-1,3-dione, only products derived from α-cleavage were observed. 2-Fluoro derivatives of 1,3-diarylpropan-1,3-diones were photostable; on the other hand, 2-chloro-2-fluoro derivates resulted in 3-fluoroflavones.

Photochemical behavior of carbonyl groups[1] is connected with excitation of π electrons of the double bond and the formation of the $\pi-\pi^*$ excited state or excitation of n electrons of the oxygen and the formation of the $n-\pi^*$ state. Basic reactions proceeding through these states are α-cleavage or abstraction of the hydrogen atom, and these can take place either intra- or intermolecularly.

The study of 1,3-diketones has received much less attention. It is known that these compounds exist as ketone and enol tautomers, and their ratio in equilibrium depends on the nature of substituents bonded at the α-position, solvent polarity, temperature, and the presence of other proton donors or acceptors in the system. In nonpolar aliphatic hydrocarbons, the enol form is dominant, being stabilized by intramolecular hydrogen bonding. UV spectra of 1,3-dicarbonyl compounds show a strong absorption near 360 nm corresponding to $\pi-\pi^*$ transition. For most 1,3-diketones, fluorescence is relatively weak showing that nonradiative processes are relatively predominant. This is a reason that several phenyl-substituted 1,3-diketones can be used as UV filters in sunscreen protection creams. The widely used entity for this purpose is 4-*tert*-butyl-4′-methoxydibenzoylmethane.[2] The current literature describes phototransformations of 1,3-diketones. For example, *o*-alkylphenyl 1,3-diketones were transformed under irradiation to naphthalenone derivatives.[3] Irradiation of a hexane solution of 1-(*o*-methylphenyl)-2,2-dimethyl-1,3-diketone resulted in benzocyclobutenol.[4] Irradiation of 2,2-dimethyl-1,3-diphenylpropan-1,3-dione in the presence of TEA led to the formation of *anti*-2,2-dimethyl-1,3-diphenylcyclopropan-1,3-diol[5] as the main product. This reaction proceeds via one-electron transfer from the excited state of the diketone to the ground state of amine, followed by rearrangement of the resulting anion radical.

In this communication, we demonstrate a new photocyclization of substituted 2-chloro-1,3-diarylpropan-1,3-diones to flavone derivatives. From a broader perspective, in our opinion this phototransformation raises a question as to whether a photochemical pathway is important for the production of flavones in plants.

2-Chloro-1,3-diphenylpropan-1,3-dione (**1a**) was prepared by a known procedure.[6] From its UV and ^{1}H NMR spectra,

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[1] Gilbert, A.; Baggot, I. In *Essentials of Molecular Photochemistry*; Wagner, P. I., Ed.; Blackwell Scientific Publications: Oxford, 1991; pp 287−353.

[2] Cantrell, A.; McGarvey, D. J. *J. Photochem. Photobiol. B: Biol.* **2001**, *64*, 117−122.

[3] Tobita, S.; Ohba, J.; Nakagawa, K.; Shizuka, H. *J. Photochem. Photobiol. A: Chem.* **1995**, *92*, 61−67.

[4] Saito, M.; Kamei, Y.; Kuribara, K.; Yoshioka, M.; Hasegawa, T. *J. Org. Chem.* **1998**, *63*, 9013−9018.

[5] Hasegawa, E.; Katagi, H.; Nakagawa, D.; Horaguchi, T.; Tanaka, S.; Yamashita, Y. *Tetrahedron Lett.* **1995**, *36*, 6915−6918.

[6] Barluenga, J.; Tomás, M.; López-Ortiz, J. F.; Gotor, V. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2273−2276.

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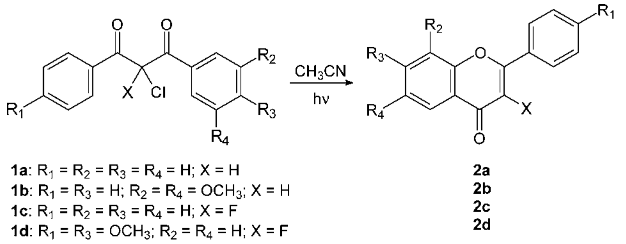
Scheme 1



we inferred that in acetonitrile solution practically only the diketone form is present, and from its fluorescence spectrum, we inferred that emission is very low. In the case of the parent compound, 1,3-diphenylpropan-1,3-dione, 10% of the diketone is in equilibrium with the enol form in the ground state.

A 2 h irradiation of a 0.002 M acetonitrile solution of **1a** with $\lambda = 352$ nm resulted in a 45% conversion to a product. Analysis of the crude reaction mixture by GC and ^{1}H NMR spectra led to the conclusion that flavone (**2a**) was formed as the sole product with quantum efficiency $\phi = 0.022 \pm 0.002$ (Scheme 1, Table 1).

Table 1. Product Distribution after Irradiation of **1a**[a]

entry		1	2	3	4	5
	CH$_3$CN	55	45			
(a)	CH$_3$CN/Ar	50	50			
(b)	CH$_3$CN/O$_2$	46	54			
(c)	CH$_3$CN/naphthalene[b]	51	49			
(d)	CH$_3$CN/piperylene[c]	46	54			
(e)	CH$_3$CN/DTBPC[d]	58	42			
(f)	CH$_3$CN/HClO$_4$[e]	57	7	10	1	25

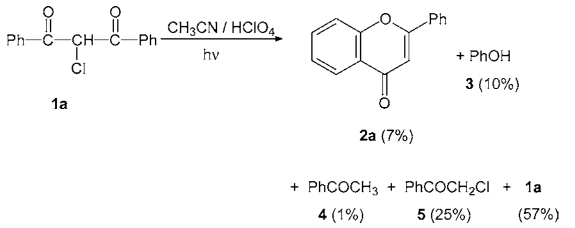
[a] Relative yields in % by GC; irradiation time 2 h; $\lambda = 352$ nm; concentration of **1a** = 0.002 M. [b] Concentration of naphthalene = 0.0005 M. [c] Concentration of piperylene = 0.01 M. [d] Concentration of DTBPC = 0.01 M. [e] Concentration of HClO$_4$ = 0.2 M.

We then performed the reaction under different conditions: (a) in an argon atmosphere, in the presence of (b) oxygen, (c) naphthalene, (d) piperylene, (e) radical inhibitor DTBPC, and (f) in the presence of HClO$_4$. The conversion of **1a** under otherwise identical reaction conditions is summarized in Table 1. In all cases, the results were very similar except when HClO$_4$ was added. In this case, α-cleavage was the dominant process leading to phenol, acetophenone, and α-chloroacetophenone (Scheme 2). This difference can be explained by the fact that in the presence of strong acid a significant proportion of the enol form is also in equilibrium with the diketone.

A dark experiment under identical reaction conditions showed no conversion. After neutralization, evaporation of solvent, and extraction into CH$_2$Cl$_2$, GC and ^{1}H NMR analysis indicated only the presence of starting compound **1a**.

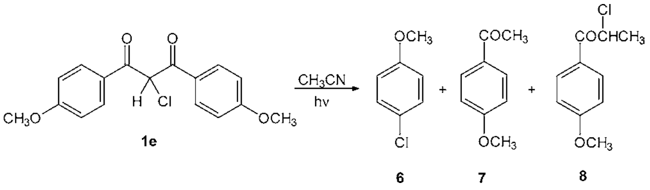
We were also interested in determining if the presence of electron-donor groups bonded to the phenyl ring had any influence on the reaction course during photolysis. For this purpose, we prepared and studied the reaction of 2-chloro-1,3-di(4-methoxyphenyl)propan-1,3-dione[7] (**1e**) and 2-chloro-1-(3,5-dimethoxyphenyl)-3-phenylpropan-1,3-dione (**1b**). Analysis of the crude reaction mixture obtained after irradiating an acetonitrile solution of **1e** for 2 h showed no flavone formation. Only the products derived from α-cleavage were detected (Scheme 3). The structures of the products were determined by GC/MS and by comparison of the GC retention times of the commercial samples. On the other hand, the result of photolysis of **1b** is quite the opposite in which at 75% conversion 6,8-dimethoxyflavone **2b**[8] was formed as a sole product (determined by GC/MS and ^{1}H NMR spectral analysis of crude reaction mixture, $\phi = 0.059 \pm 0.002$).

Scheme 2. Product Distribution in Photolysis of **1a** in CH$_3$CN in the Presence of HClO$_4$[a]



[a] Irradiation time: 2 h; $\lambda = 352$ nm; c(substrate) = 0.002 M; c(HClO$_4$) = 0.2 M.

Scheme 3. Product Distribution in Photolysis of **1e** in CH$_3$CN[a]



[a] Irradiation time: 2 h; $\lambda = 352$ nm; c(substrate) = 0.002 M.

To determine the effect of the halogen atom bonded at the C2 position, we have prepared 2-fluoro-1,3-diphenylpropan-1,3-dione[9] and 2-fluoro-1,3-di(4-methoxyphenyl)-propan-1,3-dione. Irradiation of acetonitrile solutions under the previous conditions showed no conversion in either case. In both cases, the compounds were photostable showing that energy of the C−X bond plays an important role in the phototransformation. The C−F bond is the strongest single bond, and under the conditions used for photolysis ($\lambda = 352$ nm), homolysis cannot occur. From the literature, it is known

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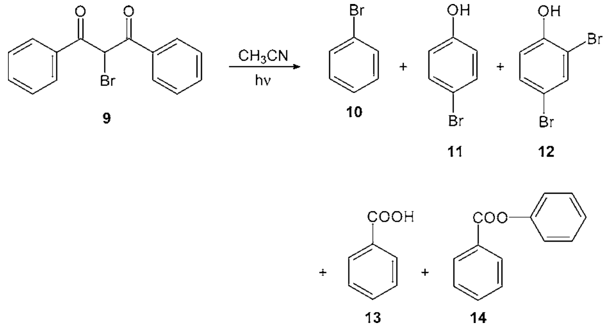
(7) Roshchupkina, G. I.; Gatilov, Y. V.; Rybalova, T. V.; Reznikov, V. A. *Eur. J. Org. Chem.* **2004**, 1765−1773.

(8) Simpson, T. H. *J. Org. Chem.* **1963**, *28*, 2107−2110.

(9) Banks, R. E.; Lawrence, N. J.; Popplewell, A. L. *J. Chem. Soc., Chem. Commun.* **1994**, 343−344.

that light-induced tautomerization of β-dicarbonyl compounds can take place.[10] Introduction of the fluorine atom at the C2 position in the case of 1,3-diarylpropan-1,3-diones completely changed the ground state situation, and practically in all cases only the diketone form is present. By using ^{1}H NMR spectra and UV spectra, we can determine that 2-fluoro compounds cannot photochemically isomerize to the enol form. On the other hand, the photolysis of 2-bromo-1,3-diphenylpropan-1,3-dione[11] (**9**) resulted in a complex reaction mixture containing the products derived from α-cleavage (Scheme 4). No photocyclization to flavone occurred.

Scheme 4. Product Distribution in Photolysis of **9** in CH_3CN



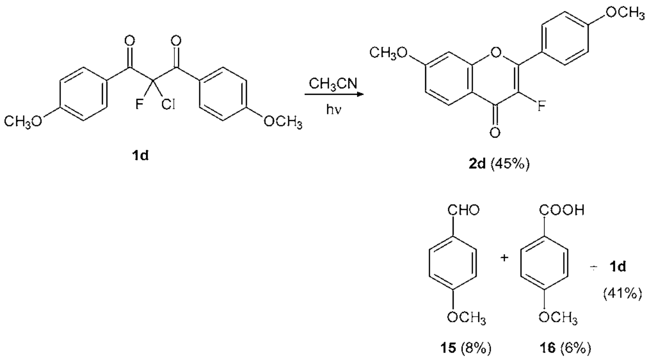
These results led us to prepare and study the photolysis of 2-chloro-2-fluoro derivatives. We were able to prepare 2-chloro-2-fluoro-1,3-diphenylpropan-1,3-dione (**1c**) and 2-chloro-2-fluoro-1,3-di(4-methoxyphenyl)propan-1,3-dione (**1d**), but we were unable to prepare 2-chloro-2-fluoro-1(3,5-dimethoxyphenyl)-3-phenylpropan-1,3-dione.

Over 2 h irradiation of an acetonitrile solution of **1c**, 55% conversion and formation of 3-fluoroflavone (**2c**)[12] as the sole product were observed ($\phi = 0.036 \pm 0.002$). Complete conversion was obtained after 4 h of irradiation. After isolation, the structure of product **2c** was determined by its spectroscopic data and by comparison to the GC retention time of an authentic sample.[12]

Photolysis of **1d** under identical reaction conditions resulted in 59% conversion, and besides 3-fluoro-2-(4-methoxyphenyl)-7-methoxylflavone[13] (**2d**), *p*-methoxybenzaldehyde, and *p*-methoxybenzoic acid, products of α-cleavage were observed (Scheme 5).

In both cases (**1c** and **1d**), we did not detect any 3-chloroflavone derivatives indicating that in 2-chloro-2-fluoro-substituted compounds also no cyclization products derived from C−F bond cleavage were formed. The comparison of the results obtained from **1a** and **1c** or **1e** and **1d** shows that in the case of **1c** the conversion to flavone is a little higher. In the case of **1d**, the fluorine atom bonded at the C2 position completely changes the course of the reaction. The formation of the 3-fluoroflavone derivative becomes the dominant pathway, and α-cleavage occurs only to a minor extent.

Scheme 5. Product Distribution in Photolysis of **1d** in CH_3CN^a



^{a} Irradiation time: 2 h; $\lambda = 352$ nm; *c*(substrate) = 0.002 M.

In conclusion, products in the photolysis of 2-halo-substituted 1,3-diphenylpropan-1,3-diones strongly depend on the type of halogen atom bonded at C2 and also on the position of electron-donor groups in the phenyl rings. 2-Fluoro derivatives are photostable, and 2-bromo derivatives resulted in α-cleavage processes. On the other hand, 2-chloro derivatives resulted in photocyclization to flavone or α-cleavage.

The effect of halogen atoms can be explained by an internal heavy-atom effect. It is known that heavy-atom substituents greatly enhance spin-orbital coupling and therefore also enhance the rates of intersystem crossing.[1] The spin orbital constant is proportional to Z^4, where Z is the atomic number and increases from fluorine to bromine. α-Cleavage for several ketones is essentially a triplet (n,π^*) state process. Only α-cleavage in the case of 2-bromo derivatives is connected with the most rapid intersystem crossing from the singlet to the triplet state.

Quenching experiments using naphthalene and piperylene have shown that photolysis of 2-chloro-1,3-diphenylpropan-1,3-dione to flavone is not quenched by triplet quenchers, so it must proceed through a singlet or a short-lived triplet state. The fact that the photocyclization to flavone is superior in the case of 2-chloro-1-(3,5-dimethoxyphenyl)-3-phenylpropan-1,3-dione ($\phi = 0.059 \pm 0.002$) to that in 2-chloro-1,3-diphenylpropan-1,3-dione ($\phi = 0.022 \pm 0.002$) and that the cyclization exclusively takes place on an activated phenyl ring can be explained by the addition step of an electrophilic oxygen atom in the excited carbonyl group to the benzene ring which is more favored by meta than by ortho/para donor groups.

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(11) Košmrlj, J.; Kočevar, M.; Polanc, S. *Synth. Commun.* **1996**, *20*, 3583−3592.

(12) Hodson, H. F.; Madge, D. J.; Wissowson, D. A. *Synlett* **1998**, *9*, 973−974.

(13) White crystalline compound: mp = 163−165 °C. Spectroscopic data: ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 3.93 (s, 3H), 6.94(d, $J = 2.3$ Hz), 7.00 (dd, $J = 9$; 2.2 Hz), 7.05 (d, $J = 9$Hz), 8.00,(d, $J = 9$ Hz), 8.17 (d, $J = 9$Hz); ^{19}F NMR ($CDCl_3$) δ −163.27 (s); Mass spectrum *m/e* 300(100), 272(10), 257(50); HRMS calcd for $C_{17}H_{13}FO_4$ 300.07979, found 300.08007.

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Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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