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The Influence of Substituents on the Photochemical Generation and Stability of 2-Morpholinocyclopropanols

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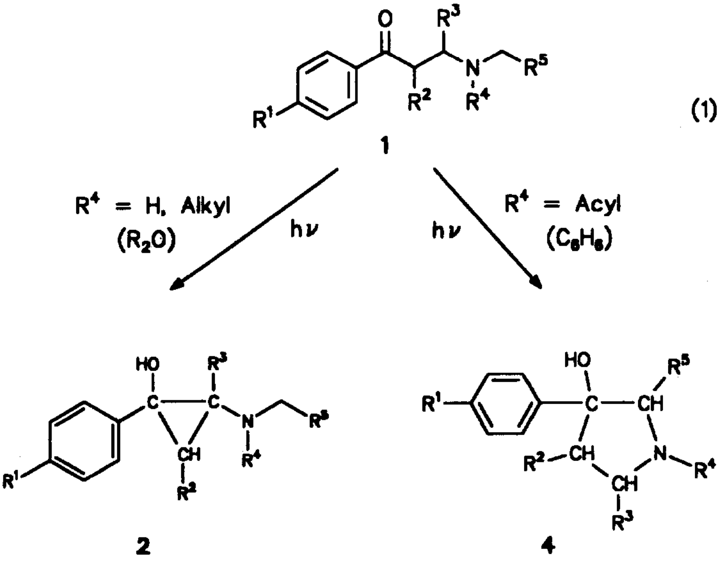
Abstract: By irradiation in oxygen-free ether α- or β-substituted β-morpholinopropiophenones **1a-c** form the corresponding cyclopropanols **2** with 1-aryl and 2-morpholino group in a relative *cis*-configuration in high yields. The photocyclization of pure **1a-c** enantiomers proceeds enantioselectively under these conditions. In methanol and presence of oxygen electronically excited **1c-h** are converted to enaminones **3c-h** via oxidation of intermediate cyclopropanols **2c-h**. In the presence of electron-acceptor molecules this reaction apparently follows a SET mechanism.

The intramolecular cyclization of n,π*-excited β-aminopropiophenones **1** is well documented. In addition to the solvent particularly substituents at the N-atom determine the regioselectivity of the reaction. In the case of R^4=alkyl ether or tetrahydrofuran as solvents favour the conformation of the intermediate state leading to 2-aminocyclopropanols **2**.[1,2] On the other hand N-acyl groups R^4 = R-X=O stabilize a conformation giving pyrrolidinols **4** (eq. 1).[2,3]



The influence of substituents R^{1-3} on the course of the photocyclization received only little attention.[1] Particularly the photochemical behavior of pure enantiomers **1** was not studied. For an investigation of these problems we chose as a model reaction the photocyclization of β-morpholinopropiophenones **1a-h** to 2-morpholinocyclopropanols **2** in diethyl ether and methanol, respectively.

Irradiation of oxygen-free etheric solutions of the α- or β-substituted **1a-c** gave the corresponding **2** in high yields (Table 1.). Under the same conditions **1d-h** also generated cyclopropanols proved by HPLC. An isolation of the less stable **2d-h** was unsuccessful in our hands. By irradiation of **1c-h** in methanol in the presence of air the enaminones **3c-h** were formed (Table 1.). On the other hand under the same conditions the α-substituted **1a,b** were not oxidized to **3**.

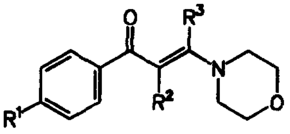


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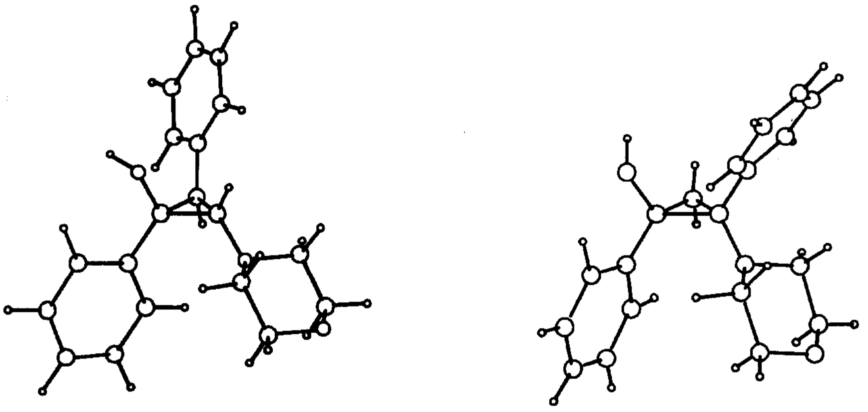
Table 1. Results of the irradiation (λ_{irr}>300nm) of β-morpholinopropiophenones **1**

1	R^1	R^2	R^3	**2**-yield [%] (Et_2O/Ar)	**3**-yield [%] (MeOH/O_2)
a	H	Ph	H	98[a]	0
b	H	$PhCH_2$	H	75	0
c	H	H	Ph	87[a]	52[c]
d	H	H	H	[b]	46[c]
e	F	H	H	[b]	38
f	Cl	H	H	[b]	42
g	MeO	H	H	[b]	22[d]
h	CN	H	H	[b]	60

[a] For **2a,c** see ref. (1.). [b] Formation proved by HPLC.
[c] For **3a,c,d** see ref. (4.). [d] G.P. Hager, J.S. Hauker, *J. Am. Pharm. Assoc.* **44**, 138 (1935).

Obviously, in the first reaction step **1** always generate the cyclopropanols **2**, which differ in stability against oxygen. The comparison of the yields of the reactions of **1a-d** shows a considerable influence of the substituents R^2 and R^3 on the formation and stability of the cyclopropanols **2**.

The relative configurations of racemic **2a** and **2c** were proved by X-ray structural analysis.[5] As to be seen from Fig. 1 in **2a** and **2c** the substituents 1-phenyl and 2-morpholino are situated in a relative *cis*-configuration. At the other side of the cyclopropane ring 1-OH and 3-Ph (**2a**) or 2-Ph (**2c**), respectively, also are placed in a relative *cis*-position. These results correspond with the ^1H NMR spectra of **2a** and **2c**. In $CDCl_3$ the vicinal coupling constant $J_{2H/3H}$ of **2a** is 5.7 Hz [cp. ref. (6.)].



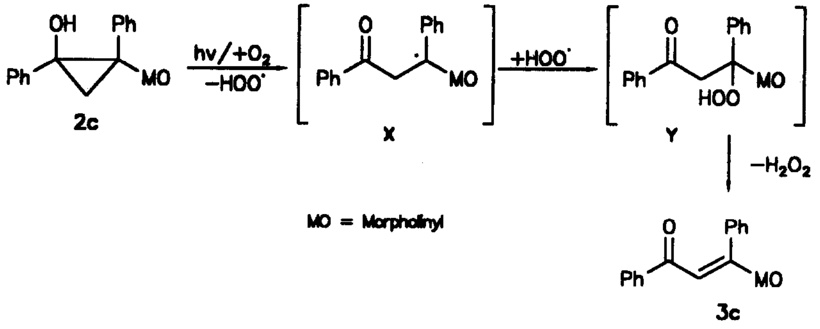
2a **2c**

Fig. 1. Relative configurations of **2a** and **2c**

The racemic Mannich bases **1a-c** can be separated by HPLC giving the pure enantiomers.[7] We found that the photocyclizations of these enantiomers run enantioselectively. Instead of four stereoisomeric products we obtained in each case only one isomer of the corresponding 2-morpholinocyclopropanol.

It is well known that the cyclopropane ring can be opened by photochemical or thermal methods.[8,9] Irradiation (254nm) of **2c** in air-saturated methanol generates the enaminone **3c** in a relatively slow reaction (15% yield). Under these conditions the 3-substituted **2a** and **2b** do not form **3** as products of oxidative ring opening.

The formation of the enaminones **3** may be explained by an oxidative splitting of the C(1)/C(2)-bonding in the cyclopropanols **2**. The radical **X** generated with triplet oxygen recombines to the hydroperoxide Y (eq. 2). Y then eliminates H_2O_2 to give the enaminone **3**. In **2a** and **2b** an oxidative cleavage of the C(1)/(3)-bonding is preferred[10] not producing 3-type compounds.



(2)

We found that the reaction **2c** → **3c** is considerably promoted in presence of photoexcited electron acceptors like triphenylpyrylium tetrafluoroborate in CH_2Cl_2 (36% yield) or 9,10-dicyanoanthracene in acetonitrile (41% yield). The fluorescence quenching rate of the triphenylpyrylium salt by **2c** amounts to 1.5×10^{10} $l \cdot mol^{-1} \cdot s^{-1}$ which points to diffusion control. The DCA anion radical was detected by EPR during the photolysis of **2c** and 9,10-dicyanoanthracene in acetonitrile. Therefore we propose a photoinduced single electron transfer (SET)[11,12] for reaction **2c** → **3c** with an interaction of the generated cyclopropanol cation radical and the superoxide anion radical to give **3c**. Under these conditions **2a** forms the α-morpholinochalcone as product of a regioselective, oxidative C(1)/C(3)-ring opening.

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