A New Photochemical Route to Cyclopropanes**

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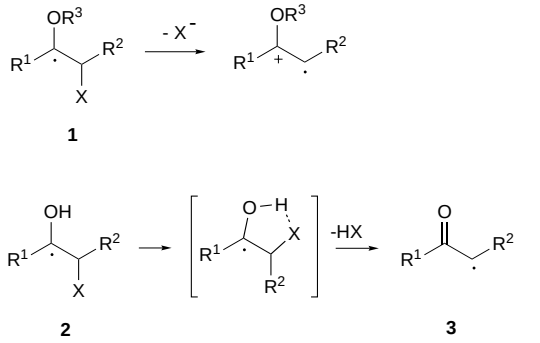
Cyclopropanes have always fascinated organic chemists. Due to their considerable ring strain they are very versatile synthetic building blocks and many interesting applications are published every year. Furthermore, the cyclopropane ring is found in many natural products[1] and has been used to restrict the conformational flexibility of molecules (for example, peptides[2]). There are many valuable methods for the preparation of cyclopropanes,[3] but nevertheless, there is still a great need for new methods. Herein, we wish to report on a new photochemical route to cyclopropanes.

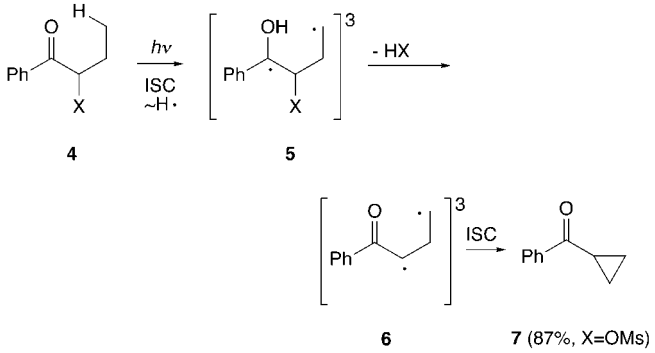
The Norrish–Yang reaction, one of the best investigated photochemical reactions,[4] was used to synthesize many homo- and heterocyclic molecules. Among these cyclizations the formation of cyclopropanes is conspicuous in that it was very rarely observed. Obviously, the considerable ring strain of the five-membered transition state accounts for this. In almost all cases of cyclopropane synthesis using the Norrish–Yang reaction an initial photoelectron transfer process (PET) has been proven or seems very likely.[5]

As expected, the intramolecular hydrogen abstraction in the course of the Norrish–Yang reaction takes place preferentially at the γ-position to form 1,4-diradicals, unless this position is blocked. (For exceptions, see ref. [6].) Based on this fact we developed a method that makes use of a well-known property of monoradicals, namely that they are excellent neighbors for the displacement of leaving groups.[7] Particularly when the radical center is stabilized by an oxygen atom elimination occurs very fast. Two cases must be distinguished that differ crucially from each other in their reaction mechanisms. While α-alkoxy radicals **1** are cleaved heterolytically to give free ions, α-hydroxy radicals **2** undergo a concerted elimination of the acid HX (Scheme 1).[8] We were particularly interested in the latter case because α-hydroxy radicals are intermediates in the Norrish–Yang reaction. It is noteworthy that the spin density in the formed enolate radical **3** is shifted to the adjacent atom. The question is whether the elimination of the acid HX is fast enough to proceed within the very short lifetime (approximately 10 ns) of the triplet diradicals produced in the Norrish–Yang reaction.

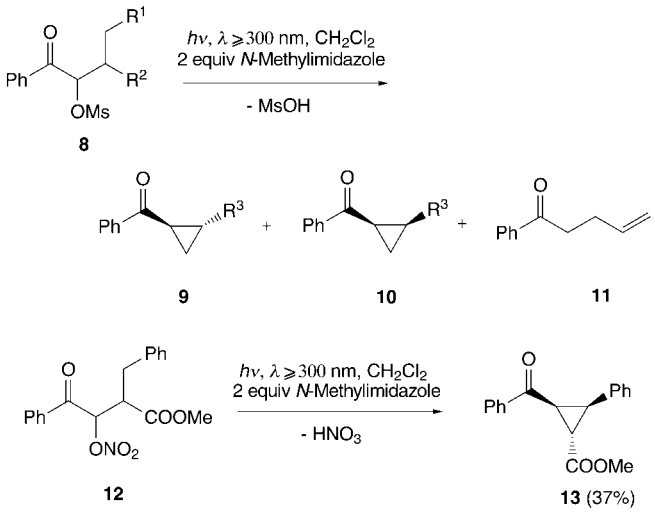


Scheme 1. Cleavage mechanisms for α-alkoxy radicals **1** and α-hydroxy radicals **2**.

We first optimized the reaction conditions with the model reactant 2-X-butyrophenone **4** where X^- represents a leaving group (Scheme 2). We found that the most suitable solvent is dichloromethane because in some other solvents, such as diethyl ether, the Norrish Type II cleavage of the triplet 1,4-diradicals **5** predominates. The leaving group X^- must be the counterion of a strong acid. Amongst carboxylates only trifluoroacetate can be used. Sulfonates are preferable, partly due to their straightforward introduction, although in one case (**12**, see Scheme 3) we used the nitrooxy group. Naturally, the elimination **5** → **6** produces a strong sulfonic acid and we found that this acid is a serious problem in our reaction. While benzoylcyclopropane **7** by itself is stable under the irradiation conditions ($\lambda_{irr} \geq 300$ nm), the cyclopropane ring is rapidly opened if the irradiation is performed in the presence of the



Scheme 2. Photochemical behavior of 2-substituted butyrophenones **4**. ISC = intersystem crossing, Ms = mesyl = methanesulfonyl.



Scheme 3. Photochemical behavior of di- and trisubstituted butyrophenones **8**.

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acid. Therefore, the addition of an acid scavenger, which must be compatible with the photochemistry, is necessary. Amongst several tested scavengers *N*-methylimidazole proved to be most suitable. After these optimizations we obtained benzoylcyclopropane **7** with a remarkable yield of 87% (Scheme 2).

We introduced various substituents to investigate their influence on the chemo- and stereoselectivity of the cyclopropane formation. The reaction outcome substantially depends on the position of the substituents. Whereas 2-mesyloxyvalerophenone **8a** gave a mixture of the desired cyclopropane **9a** (63%) and the unsaturated ketone **11a** (16%, a product of the well-known ring opening of *cis*-1-benzoyl-2-alkylcyclopropanes;[9] Scheme 3, Table 1), the branched isovalero-phenone **8b** provided exclusively the *trans*-1-benzoyl-2-methylcyclopropane **9b**.

Table 1. Photochemical synthesis of cyclopropanes **9** and **10**.

Reactant	R^1	R^2	R^3	Yields [%]		
				9	**10**	**11**
8a	Me	H	Me	63	0	16
8b	H	Me	Me	90	0	0
8c	Ph	H	Ph	47	31	–
8d	H	Ph	Ph	26	18	–
8e	H	COOMe	COOMe	59	0	–
8f[a]	OBn	H	OBn	46	0	–

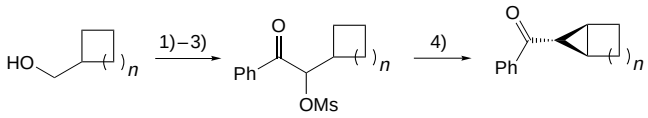
[a] Bn = benzyl.

The photochemical behavior of β- and γ-phenyl-substituted butyrophenones **8c**, **d** was surprising at first. No matter at which position the phenyl group was placed we always obtained a 60:40 mixture of *cis*- and *trans*-1-benzoyl-2-phenylcyclopropane isomers **9c**, **10c**, despite the fact that the yields differed significantly. The same product ratio was obtained by irradiation of each of the pure isomers **9c** and **10c** respectively. Obviously, aryl-substituted benzoylcyclopropanes undergo photochemical *cis*–*trans* isomerization, probably through an intramolecular charge transfer.[10]

The stereochemical course of the cyclization of alkyl- and aryl-substituted reactants should mainly be controlled by steric interactions. In contrast to this, **8e**, which bears an ester group in β-position, gave only the *trans*-configured ketoester **9e** in good yield. A photochemical behavior similar to that of the ester **8e** is shown by the ether **8f**. Upon irradiation, only the *trans*-cyclopropane **9f** is formed. The stereoselective ring closure of **8e**, **f** clearly indicates the importance of dipole–dipole interactions for the stereocontrol.

The photochemical behavior of the 2,3,4-trisubstituted butyrophenone **12** (Scheme 3) illustrates the efficiency of our method. Despite the moderate yield, we obtained only one diastereomer of the trisubstituted cyclopropane **13** while the known thermal synthesis provided either a 1:1 mixture of two diastereomers[11a] or a mixture of **13** and an isomeric furan derivative.[11b] It is noteworthy that the expected *cis*–*trans* isomerization was not observed.

Our method is not only suited for the preparation of monocyclic cyclopropanes. Thus, we also developed a straightforward route to highly strained bicyclic molecules. Starting with commercially available hydroxymethylcycloalkanes **14a–c** we prepared the benzoyl[*n*.1.0]alkanes **15a–c** in few steps and with good to excellent yields (Scheme 4). Furthermore, the cyclization proceeds in a fully diastereoselective manner to the *exo* compounds, as proven by NOE NMR experiments and in the case **15b** also by a crystal structure analysis.



14a *n*=1
14b *n*=2
14c *n*=3

15a 61%
15b 80%
15c 86%

Scheme 4. Preparation of [*n*,1,0]bicycloalkanes **15**. 1) pyridinium chlorochromate; 2) $PhC(OSiMe_3)(CN)Li$; 3) Ms_2O/pyridine, 4) CH_2Cl_2, $h\nu$ ($\lambda \geq$ 300 nm), *N*-methylimidazole (2 equiv).

After exploring the synthetic scope of this very efficient method, whose most important results are described herein, for the diastereoselective preparation of highly substituted cyclopropanes, we hope to soon report on applications for the synthesis of more complex target molecules.

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