Photochemical Synthesis of 3,4-Dihydro-2*H*-1,3-oxazin-4-ones

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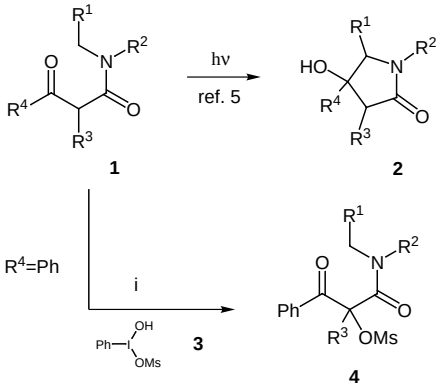
Abstract: The first example of a C–O bond formation in the course of the Norrish–Yang reaction is described. Starting with readily accessible α-mesyloxy-β-keto amides **4**, a δ-hydrogen transfer to the excited carbonyl group occurs and the diradicals thus formed undergo a very rapid elimination of methane sulfonic acid providing enolate diradicals. These ambidental enolate diradicals undergo a regioselective cyclization to 3,4-dihydro-2*H*-1,3-oxazin-4-ones **5**. In two cases a cleavage reaction is observed, giving cyclic imines. The mechanism is investigated by means of DFT- and *ab initio* methods.

Key words: Norrish–Yang reaction, diradicals, oxazinones, photocyclization, heterocycles

The Norrish–Yang reaction is one of the best investigated and widely used photochemical reactions.[1] Over the last years many interesting synthetic applications have been published and have impressively proven its preparative value. Besides the synthesis of cyclobutanes, which was developed more than 40 years ago by Yang and Yang,[2] the reaction was successfully applied on the preparation of highly functionalized heterocycles, in particular.[3] The field of application extends from azetidines up to macrocyclic compounds. Possibly, the most important advantage of the reaction is the ability to attack non- or less activated C–H bonds highly regioselectively. But this fact implies at the same time a limitation because the size of ring formed in the course of a Norrish–Yang reaction of a given reactant may barely be influenced. Consequently, a process that would change the number of atoms between the radical centers of intermediate diradical and thus alter the ring size of the product should widen the scope of the Norrish–Yang reaction considerably.

Very recently we published a novel route to cyclopropanes starting with alkyl aryl ketones bearing a leaving group in the α-position with respect to the carbonyl group.[4] The basic idea of our method was an adaptation of the well-known behavior of α-hydroxy radicals, i.e., to eliminate acids very rapidly if a leaving group is bonded to the carbon atom adjacent to the radical center. Herein, we wish to report on the second application of this approach, the photochemical behavior of α-sulfonyloxy-β-keto amides.

The photochemical cyclization of β-keto amides **1**, which are easily accessible by aminolysis of β-keto esters or by coupling of β-ketocarboxylic acids with amines, provided γ-lactams **2** and was investigated previously.[5] Upon treatment with 1-hydroxy-1-phenyl-λ^3-iodanyl mesylate **3**, the amides **1** were converted into the corresponding α-mesyloxy-β-keto amides **4** with good yields[6] (Scheme 1, Table 1). Only in the case of the iminodiacetic acid derivative, the morpholinedione **6** was obtained instead of the desired mesylate.



Scheme 1 Reagents and conditions: i) **3**, CH_2Cl_2, for react. time and temp. see Table 1

The irradiation of α-sulfonyloxy-β-keto amides **4** was performed according to the conditions optimized for the synthesis of cyclopropanes (CH_2Cl_2, 2 equivalents *N*-methylimidazole, $\lambda_{IRR} \geq 300$ nm).[4] In the initial photochemical step, a hydrogen abstraction from the δ-position by the n-π* excited carbonyl group occurs, giving the 1,5-diradicals **A** followed by a rapid elimination of methanesulfonic acid. We could not detect any product of a direct cyclization of diradicals **A** in analogy to the formation of **2** (see Scheme 1). Obviously, the acid elimination proceeds very fast. The newly formed diradicals **B** are characterized by three features. Firstly, the spin density of one of the radical centers in **A** is shifted to the neighboring atom. Secondly, the diradicals **B** are ambidental in that both a 1,6-diradical **B^1** and a 1,4-diradical **B^2** must be considered. Nevertheless, diradicals **B** are conjugated (provided that none of the dihedral angles between the radical centers amounts exactly 90°, which is not very likely). Bearing in mind that the spin density of enolate radicals is markedly higher at the carbon atom and based on our previous experience,[4] we expected that diradicals **B** react as 1,4-C-C-diradicals **B^2**. Surprisingly, we obtained solely the 3,4-dihydro-2*H*-1,3-oxazin-4-ones **5** which originate from the 1,6-O-C diradicals **B^1** (Scheme 2, Table 2).

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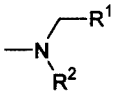
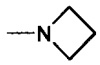
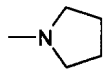
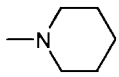
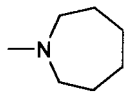
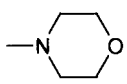
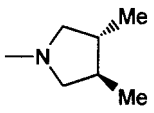
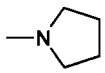
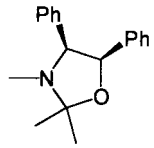
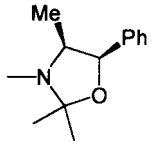
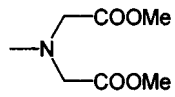
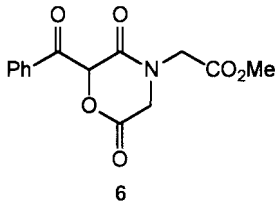
Table 1 Reaction of β-Keto Amides **1** with 1-Hydroxy-1-phenyl-λ³-iodanyl Mesylate **3**

Product		R^3	React. Time (h)	Temp (°C)	Yield (%)
4a	-NMe_2	H	1	40	97
4b		H	24	20	91
4c		H	1.5	40	90
4d		H	4 d	20	88
4e		H	4 d	20	75
4f		H	16	20	90
4g		H	1	40	75
4h	-$N(i\text{-}Pr)_2$	H	24	20	95
4i		Me	1	40	61
4j		H	1	20	50
4k		H	16	20	55
6		H	24	20	46[a]

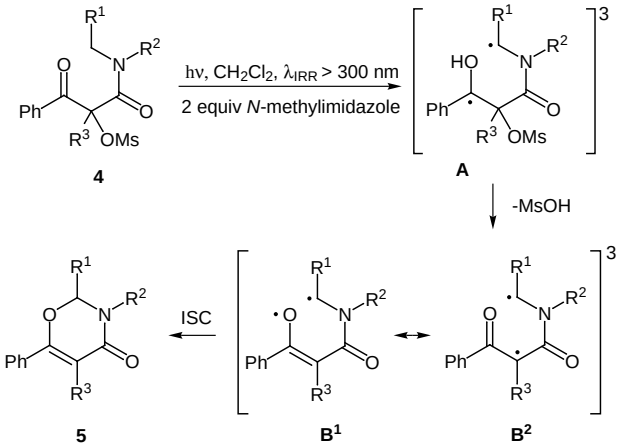
[a] Compound **6** was obtained (Figure 1).



6

Figure 1

It should be noted that despite there is not yet an experimental proof for the diradicals **B**, we consider their existence as very likely based on quantum chemical calculations. Thus, we found a very low activation barrier for the reaction **A** → **B** (approx. 1 kcal/mol).



Scheme 2

The structure of products **5** could be proven unambiguously by X-ray structure analysis of **5c**.[15] 3,4-Dihydro-2*H*-1,3-oxazin-4-ones **5**, which may be considered as cyclic derivatives of β-keto acids, are versatile synthetic building blocks,[7] and have also been found in natural products.[8] Up to now only few methods are known to obtain these compounds and most of them are characterized either by low yields[8b,9] or by low flexibility with respect to the substituents (e.g., using diketene as reactant[7]).

In case the radical center formed in the heterocycle is more stabilized, the reaction goes another way. Thus, upon irradiation of the *N*-acylated oxazolidines **4j**, **k**, the intermediate diradicals **C** undergo a cleavage giving oxazolines **7**.[10] Due to the UV spectroscopic properties of the oxazinones **5**, we can rule out that a subsequent photochemical cleavage of these compounds is responsible for the reaction outcome of oxazolidines **4j**, **k**. Obviously, the thermodynamical driving force of the cleavage of the diradicals **C** prevents cyclization. Benzoylketene is assumed to be the second cleavage product but could not be isolated, presumably due to its high reactivity. Although this course of reaction should be limited to such reactants bearing radical stabilizing groups at the carbon atom adjacent to the nitrogen atom, it should be an interesting synthetic route to cyclic imines, which are barely accessible by any other methods. Interestingly, **7a** shows a remarkable tendency to react with oxygen. An attempt to grow crystals of **7a** provided the stable hydroperoxide **8** (Scheme 3).

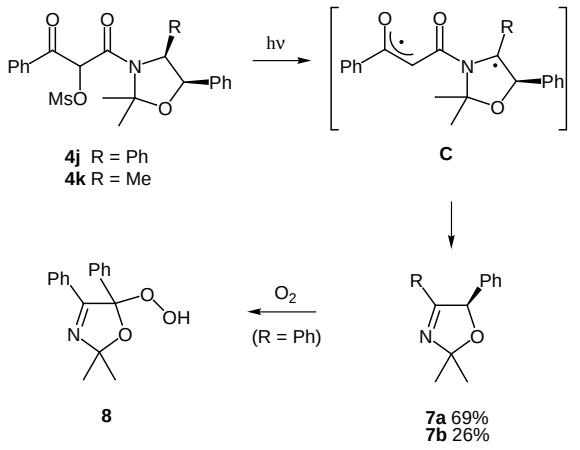
Although the main emphasis of this issue is synthetic applications, we wish to discuss the mechanism of photochemical oxazinone synthesis briefly. The aim was to determine why the cyclization of diradicals **B** (Scheme 2) is characterized by an opposite regioselectivity compared with our previously investigated systems.[4] In order to enable quantum chemical investigations at a high level of theory, we simplified the structure of the intermediate of

Table 2 3,4-Dihydro-2*H*-1,3-oxazin-4-ones **5**

Product	Yield (%)	Mp (°C)	IR (KBr) ν (cm^{-1})	^1H NMR (300 MHz, $CDCl_3$/TMS) δ, *J* (Hz)	MS *m/z* (%)
5a	44	117	1657, 1486, 1449, 1380, 1082, 1022, 886, 823, 781, 771, 693	7.70–7.66 (m, 2H), 7.47–7.41 (m, 3H), 5.94 (s, 1H, CH), 5.22 (s, 2H, CH_2-N), 3.04 (s, 3H, CH_3-N)	189 (M^+, 42)
5b	58	–	1657, 1449, 1417, 1377, 1238, 1176, 1096, 771	7.66–7.62 (m, 2H), 7.44–7.39 (m, 3H), 5.95 (dd, 1H, *J* = 3.6, 5.5, CH-N), 5.88 (s, 1H, CH), 4.34 (dt, 1H, *J* = 5.7, 9.0), 4.08 (dt, 1H, *J* = 6.0, 8.1), 2.89–2.68 (m, 2H)	201 (M^+, 10)
5c	42	106	3072, 1657, 1447, 1379, 1349, 773, 695	7.69–7.66 (m, 2H), 7.48–7.28 (m, 3H), 5.93 (s, 1H, CH=), 5.51 (dd, 1H, CH-N), 3.80–3.75 (m, 1H), 3.53–3.47 (m, 1H), 2.45–2.32 (m, 2H), 2.08–1.93 (m, 2H)	215 (M^+, 52)
5d	57	74	3395, 2950, 2872, 1675, 1664, 1661, 1449, 1414, 1377, 774, 693	7.71–7.65 (m, 2H), 7.45–7.38 (m, 3H), 5.87 (s, 1H, CH), 5.17 (dd, 1H, *J* = 4.3, 9.2, CH-N), 4.31–4.24 (m, 1H), 2.78–2.68 (m, 1H), 2.32–2.25 (m, 1H), 1.97–1.80 (m, 3H), 1.63–1.44 (m, 2H)	229 (M^+, 41)
5e	64	82	2923, 1647, 1461, 1453, 1424, 1371, 1309, 772, 693	7.69–7.65 (m, 2H), 7.44–7.34 (m, 3H), 5.94 (s, 1H, CH), 5.41 (dd, 1H, *J* = 2.8, 5.1, CH-N), 4.19 (dd, 1H, *J* = 5.7, 14.7), 3.21 (dd, 1H, *J* = 9.4, 14.7), 2.47–2.38 (m, 1H), 2.16–1.94 (m, 2H), 1.78–1.47 (m, 5H)	243 (M^+, 13)
5f	42	61	1662, 1449, 1421, 1394, 1370, 1279, 1123, 989, 773, 691	7.71–7.39 (m, 5H), 5.90 (s, 1H, CH), 5.25 (dd, 1H, *J* = 4.5, 9.0, CH-N), 4.28 (dd, 1H, *J* = 4.5, 11.3), 4.13–3.99 (m, 2H), 3.72–3.59 (m, 2H), 3.10–3.00 (m, 1H)	231 (M^+, 11)
5g[a]	73	68	1667, 1452, 1436, 1392, 1363, 770, 691	7.70–7.41 (m, 5H), 5.91 (s, 1H, CH), 5.10 (d, 1H, *J* = 7.2, CH-N), 3.86 (dd, 1H, *J* = 7.9, 11.3, N-CH_AH_B), 3.16 (dd, 1H, *J* = 10.0, 11.3, N-CH_AH_B), 2.15–2.07 (m, 1H, C*H*-CH-N), 1.98–1.90 (m, 1H, CH-CH_2), 1.27 (d, 3H, *J* = 6.4, CH_3), 1.15 (d, 3H, *J* = 6.4, CH_3)	243 (M^+, 15)
5h	43	47	2929, 1656, 1450, 1422, 1379, 1359, 769, 692	7.67–7.62 (m, 2H), 7.42–7.36 (m, 3H), 5.79 (s, 1H, CH), 3.70 (br s, 1H, CH), 1.75 (s, 6H, 2 × CH_3), 1.51/1.49 (s/s, 6H, 2 × CH_3	245 (M^+, 8)
5i	44	68	1641, 1629, 1450, 1376, 1076, 1064, 758, 703	7.50–7.49 (m, 2H), 7.43–7.39 (m, 3H), 5.47 (dd, 1H, *J* = 4.1, 5.7, CH-N), 3.86–3.78 (m, 1H), 3.53–3.45 (m, 1H), 2.42–2.33 (m, 1H), 2.29–2.18 (m, 1H), 2.10–1.83 (m, 2H), 1.98 (s, 3H, CH_3-C)	229 (M^+, 28)

[a] Mixture of diastereomers.

interest. Thus, we chose the diradical **D**, derived from *N*-formylacetyl methylamine, as a model system. It is easy to recognize that the diradical **D** consists of two nearly planar subunits defined, at the one hand, by atoms 1–3 (enolate radical moiety) and, on the other hand, by atoms 4–7 (amide radical moiety). Bearing in mind the well-known high rotation barrier of amide bonds, we only considered the *s-cis*- and *s-trans*-conformers with respect to the enolate radical moiety. After a conformational analysis of both types (B3PW91/6–31G*[11]), we determined accurate



Scheme 3

energies of the appropriate minimum geometries at a very high level of theory (CBS-QB3[12]). Amongst the four obtained diradical conformers **D**^{1}–**D**^{4}, the conformer **D**^{3} was identified as the global minimum, followed by **D**^{4}. The formation of oxazinones **5** cannot be realized from *s*-*trans*-conformers **D**^{3} and **D**^{4} and therefore the question arose whether a rotation around the bond 1–2-3–4 in the enolate radical moiety is actually possible within the lifetime of the triplet diradicals (approx. 100 ns[13]). We found that the activation barrier for such a rotation amounts to approx. 13 kcal/mol and thus only conformers **D**^{1} and **D**^{2} can be considered. In fact, the regioselectivity could be understood by the lower energy of the diradical conformer **D**^{1} compared with **D**^{2} (Figure 2).

Nevertheless, we should not withhold another possible explanation. As mentioned above, the diradicals **B**–**D** must be considered as coupled diradicals, which means that a conjugation exists between the two radical-bearing moieties. The consequence of this fact is exactly that what was called "increased ionic character" of the singlet state in the legendary rules by Salem and Rowland.[14] These rules allow a qualitative estimation of the spin orbit coupling (SOC), which is the most important mechanism for the intersystem crossing. From this point of view, we cannot rule out that the lifetimes of the diradicals **B** and **C** are extremely short and that the observed regioselectivity simply reflects the reactant conformation (memory effect). We will investigate this aspect thoroughly in future.

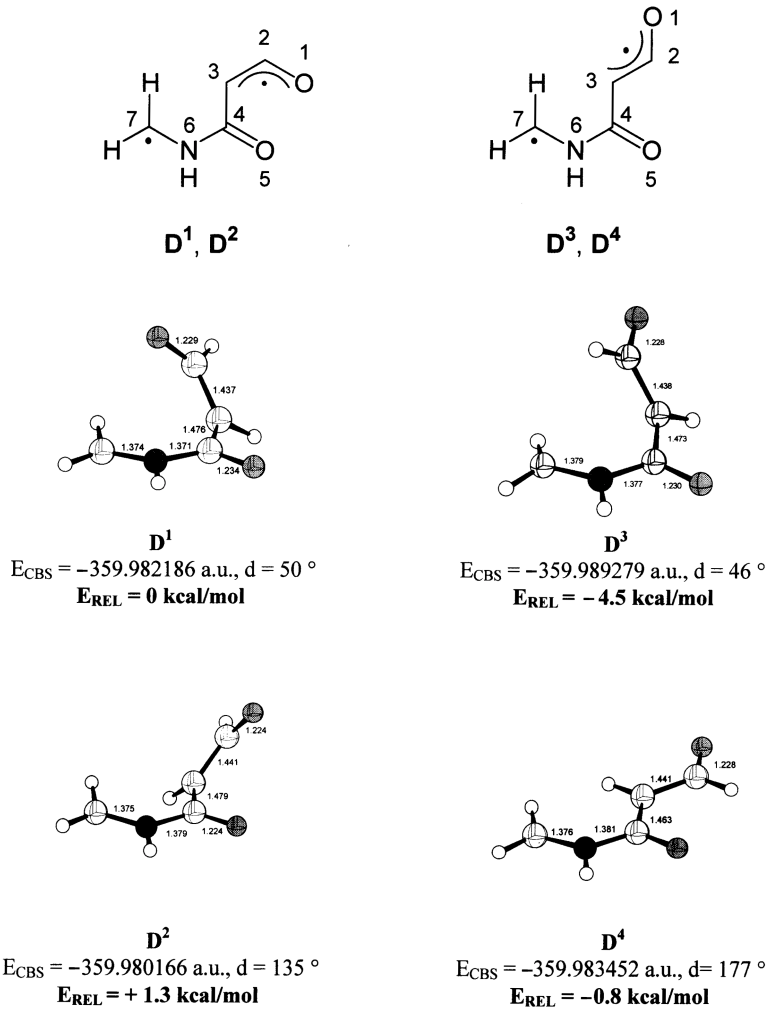


Figure 2 CBS-Q(B3)-Energies (0 K), dihedral angles 2–3-4–6 and relative energies of the diradical conformers D^1–D^4

In summary, we have developed a novel efficient method for the preparation of 3,4-dihydro-2*H*-1,3-oxazin-4-ones and cyclic imines. The method is especially remarkable in that it allows the regioselective oxidation of less activated C-H bonds. It should be noted, that the ring-closure described herein is the first example of a C–O bond formation in the course of the Norrish–Yang reaction.

TLC was performed on alumina sheets with silica gel 60 F_{254} (Merck), detected by UV light. Silica gel 40–63 μm (Merck) and mobile phase of CH_2Cl_2–MeOH mixtures were used for flash chromatography. The uncorrected mps were determined on a Boetius micro melting point apparatus (Wagema). IR spectra were taken with a Perkin–Elmer-881 (solids as KBr pellets, oils on NaCl plates). NMR spectra were recorded with a Bruker DPX300 (^{1}H 300 MHz, ^{13}C 75.5 MHz), using TMS as internal standard. EI-mass spectra were taken with a Hewlett Packard 5995 A, 70 eV at 293–593 K.

α-Sulfonyloxy-β-keto Amides 4; General Procedure

Amide **1** (1.00 mmol) dissolved in anhyd CH_2Cl_2 (30 mL) was treated with 1-hydroxy-1-phenyl-λ^3-iodanyl mesylate **3** (1.00 mmol, for reaction time and temperature see Table 1). Reaction completion was detected by TLC (CH_2Cl_2–MeOH, 100:1 to 100:2). Products **4** were isolated by crystallization or flash chromatography.

Photocyclization of α-Sulfonyloxy-β-keto Amides 4 to 3,4-Dihydro-2*H*-1,3-oxazin-4-ones 5; General Procedure

Irradiations of amides **4** were performed in CH_2Cl_2 (300 mL) at concentrations of 3 mg/mL in the presence of *N*-methylimidazole (2 equiv), using a high-pressure mercury arc lamp (150 W). Light of wavelength below 300 nm was absorbed using a Pyrex™ glass jacket between the lamp and the reaction vessel. The reaction was monitored by TLC and aborted when the reactant had completely disappeared. The solution was washed with H_2O, dried and evaporated in vacuo. The products **4** were isolated by flash chromatography.

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