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New Access to Spiranic β-Lactams

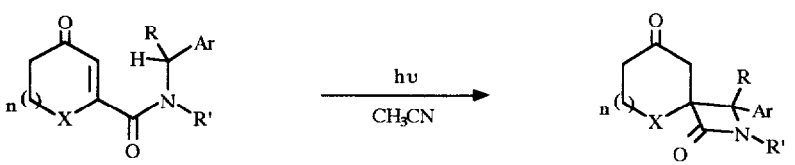
Sylvie Le Blanc, Jean-Pierre Pete and Olivier Piva*

Laboratoire des Réarrangements Thermiques et Photochimiques associé au C.N.R.S.
Université de Reims - Champagne-Ardenne - U.F.R. Sciences - F 51062 Reims - France

Key words: Spiranic β-lactams; N-benzyl α,β-unsaturated oxoamides; UV irradiation; hydrogen abstraction; radical cyclisation.

Abstract: *N-benzyl α,β-unsaturated γ-oxoamides undergo under irradiation intramolecular hydrogen abstraction and consecutive cyclisation leading to spiranic β-lactams; Extension of the reaction to one spiranic oxapenam is also reported.*

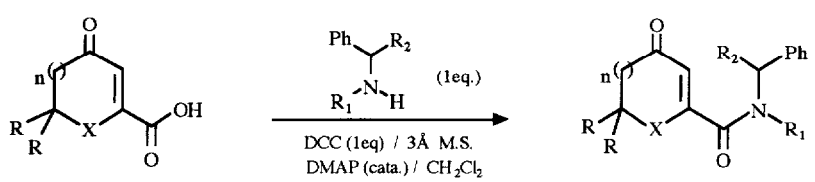
Synthesis of β-lactams represents a very important tool in the field of pharmaceutical compounds especially as antibiotics. Access to these compounds has been extensively studied under various conditions [1], thermal cycloaddition between imines and ketenes[2], between alkenes and isocyanates[3], carbonylation of aziridines[4] or radical cyclisations[5] for example. Photochemically, various methods of synthesis of β-lactams have been explored. Among them, γ-hydrogen abstraction[6], photoreduction[7] of α-oxoamides, isomerization of acrylic amides[8] and Wolff rearrangement[9] led efficiently to azetidinones. Otherwise few example of synthesis of spiranic β-lactams are known[10] in contrast with the well documented access to homologous spiranic γ- or δ-lactams[11]. We report here the direct conversion of unsaturated N-benzyl α,β-unsaturated cyclic oxoamides **1** or **3** to spiranic β-lactams **2** or **4** by intramolecular hydrogen abstraction under photochemical activation.



1 X = CH_2
3 X = O

2
4

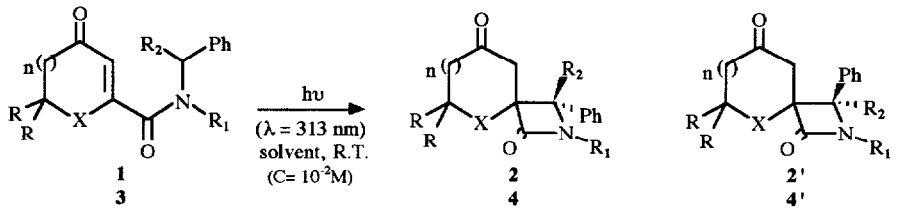
Starting oxoamides **1** were synthesized from the corresponding known unsaturated oxoacids[12] or from the commercially available oxoacid for **3** and primary or secondary benzylamines[13]. Among the different methods tested, DCC activation[14] in the presence of molecular sieves gave higher chemical yields (60-95%) than methods using oxalyl chloride and DMF[15] or



methodologies with previous formation of the acyl carbonate [16].

Irradiation of the oxoamides **1** or **3** at 313 nm in acetonitrile led in few hours to the formation of spiranic products. Results are collected in Table 1.

Table 1 : Irradiation of N-benzyl α,β -unsaturated oxoamides **1** and **3** .



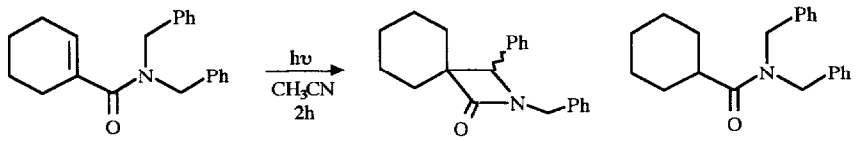
1 **3** **2** **4** **2'** **4'**

Substrate 1/3	X	n	R	R_1	R_2	solvent	Time (mn)	c.y. (%) [a]	2/2' [b] 4/4'
1a	CH_2	0	H	Me	H	CH_3CN	420	trace	-
1b	CH_2	1	H	Bz	H	CH_3CN	75	70	100 / 0
1c	CH_2	1	H	Me	H	CH_3CN	45	56	50 / 50
1d	CH_2	1	H	H	H	CH_3CN	240	0	-
1e	CH_2	1	H	i-Pr	H	CH_3CN	90	14	not det.
3a	O	1	Me	Bz	H	CH_3CN	60	67	100 / 0
3a	O	1	Me	Bz	H	CH_2Cl_2	150	81	100 / 0
3a	O	1	Me	Bz	H	toluene	60	78	100 / 0
3b	O	1	Me	Me	H	CH_3CN	60	66	82 / 18
3b	O	1	Me	Me	H	CH_2Cl_2	90	57	100 / 0
3c	O	1	Me	i-Pr	H	CH_3CN	90	24	100 / 0

[a] isolated chemical yield based on **1** or **3** .

[b] determined by ^{1}H-NMR of the crude product.

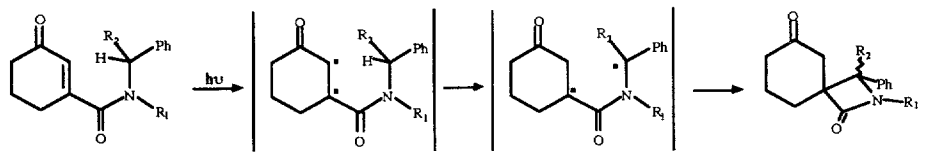
After irradiation and evaporation of the solvent, the two diastereomers formed were easily separated by preparative TLC or flash-chromatography. The ratio **2/2'** and **4/4'** was determined by integration of the signal of the proton in α-position of the phenyl group or by integration of the signals of the two protons near the carbonyl function on the ^{1}H NMR spectrum of the crude product. In the majority of cases only one diastereomer was detected. Attribution of the relative stereochemistry was to date not really clarified. In the case of **1a**, only traces of the corresponding β-lactam was detected even after irradiation over a long time, due probably to the higher energy of the transition state. Moreover, for the secondary oxoamide **1d** cyclisation did not occur, probably due to an unfavorable conformation of the substrate by minimization of steric interactions[17]. Otherwise substitution of the nitrogen by bulky groups such as isopropyl (**1e** or **3c**) hindered the course of the cyclisation and very low yields were obtained. The photochemical behaviour of unsaturated amides[6] such as **5** shows that the presence of the oxo group plays an important role. After longer irradiation than with the oxoamides, the formation of β-lactam **6a** occurred also with photoreduction of the double bond leading to the saturated amide **6b**. This type of adduct was not detected in our case.



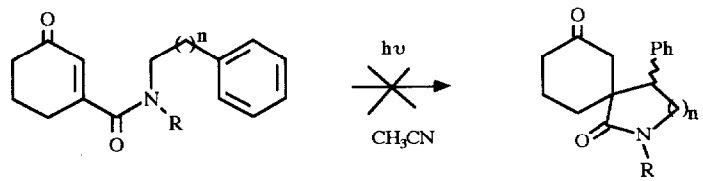
5 (conversion 61%) **6a** (31%) **6b** (5%)

Otherwise the photochemical behaviour of oxoamides **1** and **3** might be compared to those of α,β-unsaturated thioamides which have recently been converted to azetidinethiones by γ-hydrogen abstraction followed by the formation of zwitterionic species [18].

Mechanistically, under irradiation conditions enones are well known to undergo biradical formation [19,20]. Abstraction of one hydrogen at the benzylic position leads to a new biradical intermediate where the two electrons are delocalized, one on the aryl ring and the second stabilized by the proximity of the amide group. Intramolecular coupling leads finally to the product. The zwitterionic intermediate cannot be also excluded.

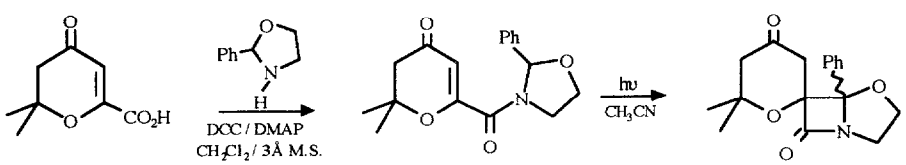


In the hope of obtaining the spiranic γ- or δ-lactams, oxoamides **7**,**9** and **11** were synthetized according to the methodology discussed before and irradiated under the same conditions as for compounds **1**.



7	n=1	R = n-C_5H_{11}	**8**
9	n=1	R = Ph-$(CH_2)_2$-	**10**
11	n=2	R = Ph-$(CH_2)_3$-	**12**

Unfortunately, no cyclisation occured whatever the length (n=1,2) or the nature of the chain and the starting material was either recovered or decomposed after irradiation over a long time. The reaction is also inefficient with N,N-dialkyloxoamides in which no stabilization by delocalisation of the intermediate is possible. We next attempted to transpose the cyclisation process to the more elaborated structure **13**. In this case, cyclisation occured and led to the spiranic oxapenam **14** as a mixture of diastereomers.



3 **13** (47%) **14** (60%)

In conclusion, we have developed a new, efficient and diastereoselective method to β-lactams which possess the unusual spirocyclic framework in the α-position to the carbonyl group. The reaction has been advangeously extended to the synthesis of one spiranic oxapenam. Work is now in progress to apply this method to the synthesis of more functionalized spiranic β-lactams

and to define more precisely the limits of the reaction.

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13 Note: secondary amines were prepared by heating the primary amine and corresponding alkyl halide in the presence of potassium carbonate (1 eq.) in acetonitrile.

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