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Intramolecular [2+2] Photocycloaddition of Oxoesters and Oxoamides

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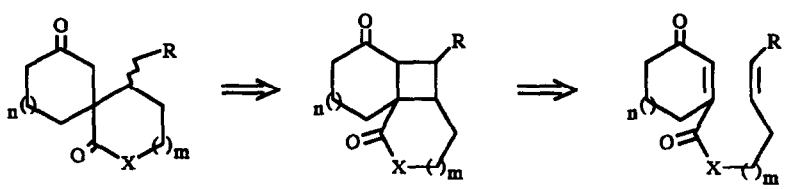
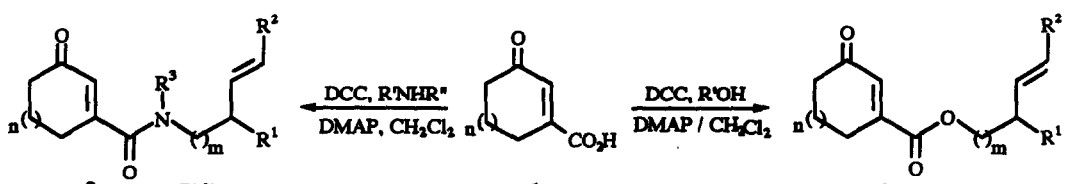
Key words: [2+2] Photocycloaddition; unsaturated oxoester; unsaturated oxoamide; lactone; lactame.

Abstract: *α,β-unsaturated oxoesters and oxoamides bearing an alkenyl chain have been photolyzed and lead to the expected lactone and lactam cycloadducts with very high regio- and diastereoselectivity. These compounds constitute valuable precursors for spirolactones by treatement with TMS-I or polycyclic structures by reduction with Li-ammonia.*

[2+2] Photocycloaddition represents a very promising reaction for the construction of polycyclic structures [1] and the control of regio- and diastereoselectivity has been shown to be high when the approach of the unsaturated addends is intramolecular [2,3]. With the aim of obtaining spirocyclic lactones and lactams, we have considered the intramolecular [2+2] photocycloaddition of unsaturated oxoesters and oxoamides bearing an alkenyl chain. Up to date, only intermolecular processes of α,β-unsaturated oxoesters have been studied[4,5] and applied in total synthesis[6]. After irradiation, the intramolecular cyclized products would be expected to undergo ring opening to compounds which contain the interesting spiro framework. These structures constitute very useful subunits for the total synthesis of numerous products such as nitramine[7] (X= NR') or bakkenane[8] analogues (X=O).



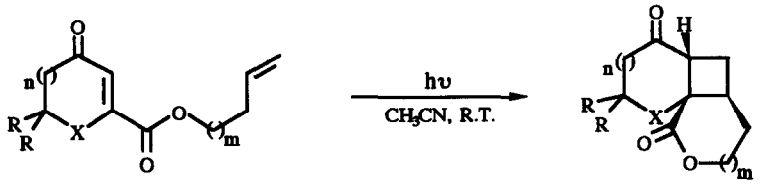
In this communication, we report that the expected cycloadducts are produced with very high selectivity from the corresponding oxoesters or amides which are easily obtained from the known oxoacids 1 using the oxalyl chloride - DMF[9] or even better the DCC activation[10].



3 c.y. > 70% **1** **2** c.y. = 92-97%

The unsaturated oxoesters **2** have been submitted to irradiation at 313nm or 366nm, in acetonitrile. The results are shown in the following table.

Table 1 : Irradiation of unsaturated oxoesters **2**

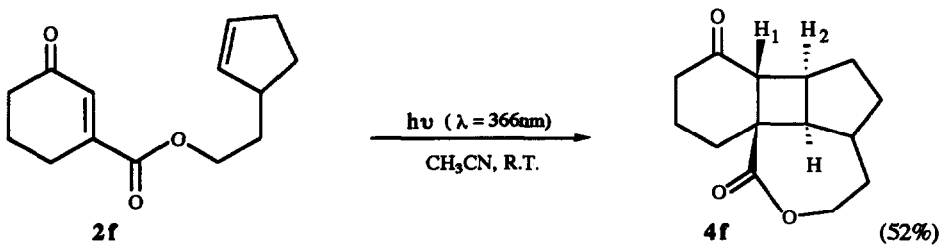


2 **4**

oxoester					cycloadduct		
2	n	X	R	m	**4**	c.y. [a,c]	c.y. [b,c]
2a	1	CH_2	H	0		0%	-
2b	1	CH_2	H	1	**4b**	47%	47%
2c	1	CH_2	H	2	**4c**	61%	62%
2d	0	CH_2	H	2	**4d**	59%	-
2e	1	O	Me	2	**4e**	71%	92%

(a) reaction performed at 313nm. (c) yields of isolated pure material.
(b) reaction performed at 366 nm.

Irradiation of the oxoesters **2** leads in a few hours to the cyclized products in moderate to good yields, except for those bearing an allylic chain. In the case of **2a** (m=0), the chain is not long enough to allow a favourable approach of the alkenyl group towards the excited enone system. The only products observed arise from intermolecular cycloadditions. When the length of the chain increases (m=1,2), only one regioisomer is isolated in moderate to good yields. According to the ^{1}HNMR spectrum and in respect with the "rule of five"[1,2,11] only one regioisomer is obtained and this corresponds to one diastereoisomer; the selectivity of the reaction is thus very impressive. Unfortunately in the cases of **4b-4d**, the determination of the relative configuration of the cyclobutane system was difficult to achieve by ^{1}H NMR or ^{13}C NMR. This problem was resolved by examining the proton spectrum of **4f**; in this case, the value of the vicinal coupling constant between the two protons H_1 and H_2 of the cyclobutane is very low ($J_{1\text{-}2}$ = 4.5Hz) and can be compared to previous results in the literature[12] for which the relative stereochemistry is *cis / anti / cis*.



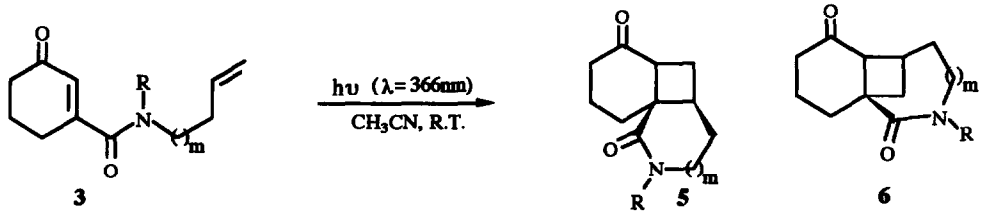
2f **4f** (52%)

Moreover, this relative configuration has already been reported for the unique stereoisomer obtained during [2+2] photocycloaddition of enones subtituted by an alkenyl chain in the β-position[2,13]. These results are also supported by the examination of molecular models which demonstrates that the approach leading to the *cis* /

syn / cis adduct is considerably less favorable than the other diastereoisomeric approach. Consequently, the relative configuration *cis / anti / cis* has been attributed to all the cycloadducts **4b-4d** obtained. Finally this process has been generalized to more functionalized esters, such as **2e** with high efficiency.

For the oxoamides **3** (table 2), photocycloaddition occurs efficiently at 366nm. In contrast with the oxoesters **2**, cyclization takes place even with an allylic chain (m = 0); however, in this case, a mixture of the two regioisomers **5** and **6** was also observed. In all other examples, compounds **5** are isolated exclusively, and display a very high diastereoselectivity. The relative *anti* configuration has been attributed to this diastereoisomer by analogy with the corresponding lactones **4**. Otherwise, the nature of the substituent on the nitrogen atom is of great importance. When R is a hydrogen atom (**3a**) no intramolecular cyclization occurs, probably due to an unfavourable conformation [14]. If this group is benzyl, a competitive reaction takes place: the abstraction of benzylic hydrogen atom by the excited enone moiety, leading to a mixture of the expected [2+2] cycloadducts but also to the very unusual spiranic β-lactams [15].

Table 2 : Irradiation of unsaturated oxoamides **3**

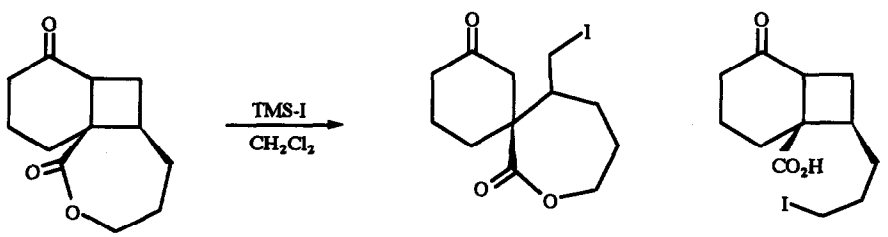


3 **5** **6**

oxoamide			cycloadduct	
3	m	R	c.y. [a]	ratio **5 / 6**
3a	0	H	0%	-
3b	0	Me	75%	**5b / 6b** 60 / 40
3c	0	Allyl	61%[b]	**5c / 6c** 60 / 40
3d	1	n-Pentyl	83%	**5d / 6d** 100 / 0
3e	2	n-Pentyl	76%	**5e / 6e** 100 / 0

(a) chemical yields of pure isolated material. (b) reaction performed at 313 nm.

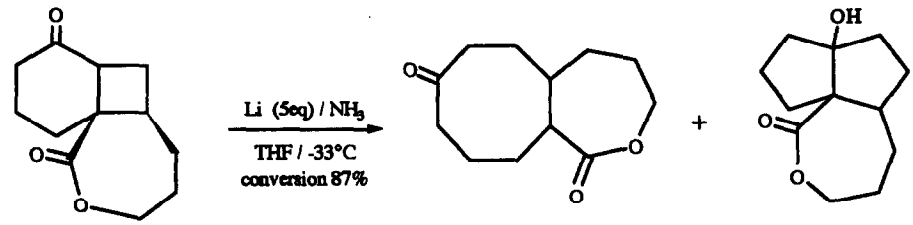
We have then performed the ring-opening of the cycloadducts by the use of trimethylsilyl iodide [16]. For example, the cycloadduct **4c** leads respectively under these conditions to a mixture of the expected iodospirolactone **7** and of the iodocarboxylic acid **8**, obtained by cleavage of the lactone ring[17].



4c **7** (39%) **8** (60%)

Interestingly, when the same substrate is submitted to the action of lithium in ammonia[18], a ring expansion occurs with formation of the bicyclic lactone **9** and consecutively **10**. The last compound results

from an intramolecular aldolisation of **9** [19].



4c **9** (24%) **10** (18%)

In conclusion we have developed new access to spirolactones and bicyclic polyfunctionalized compounds by the opening of cyclobutane derivatives formed in a very high regio and diastereoselective process. Work is now in progress, to apply this methodology to the total synthesis of natural products.

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Note: All the new products have been caracterized by ^{1}H and ^{13}C-NMR; IR; MS and/or microanalysis.

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