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Intramolecular [2+2] Photocycloaddition of N-Alkenoyl β - Enaminones

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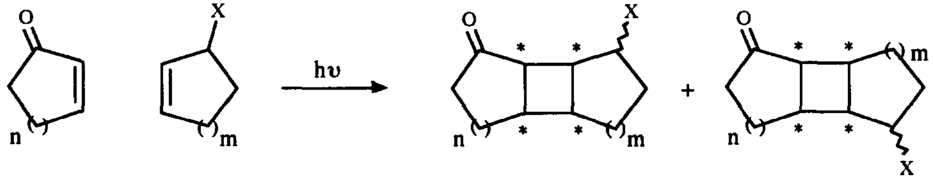
Key words: [2+2]photocycloaddition; β-enaminones; cyclobutanes; ring enlargement; photochemistry.

***Abstract:** Intramolecular cycloaddition of N-alkenoyl β-enaminones occurs with high regioselectivity and diastereoselectivity leading to interesting synthons for the total synthesis of triquinanes or various sesquiterpenes.*

The great importance of [2+2] photocycloadditions and cyclobutanes as synthons in the total synthesis of natural products has been recently reviewed[1,2]. Conversion of these interesting intermediates into polycyclic compounds has been used in syntheses of guaianolides[3], polyquinanes [4] or taxanes[5]. The reaction can create in one step up to 4 new asymmetric centers and 32 stereoisomers, but unfortunately, the regio and stereoselectivities are usually modest.

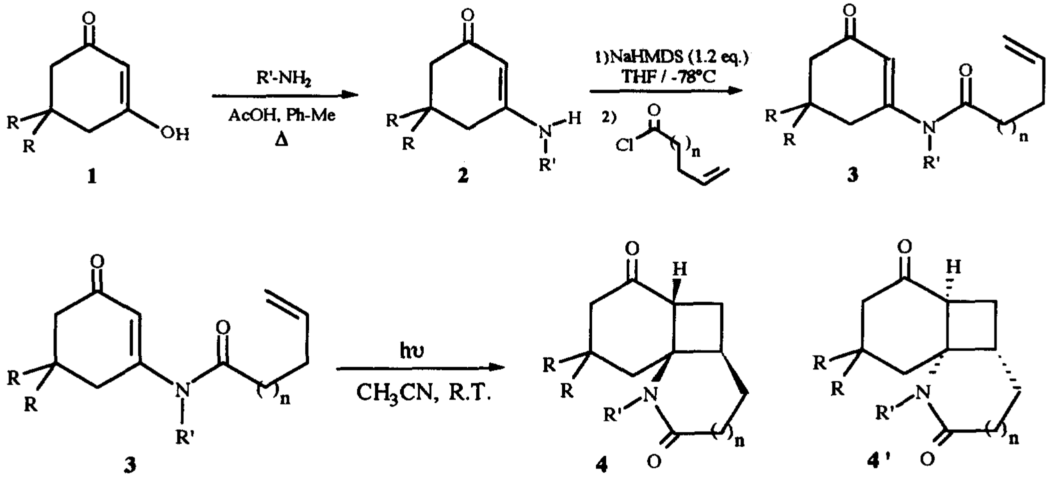


In part of a program on the access to natural products using [2+2] photocycloadditions, we decided to examine the intramolecular photocycloadditions of N-alkenyl cyclohexenones. The mechanism of the reaction indicates that such an addition might lead regioselectively and stereoselectively to the corresponding cyclobutane derivatives. Furthermore, the presence on the side chain of one nitrogen atom might enable us to control the chirality of all the new asymmetric centers and lead to versatile structures, useful for synthetic applications.

We decided to study first the N-alkenoyl 3-aminocyclohex-2-enones to check if the conformation of the amido chain was compatible with the cycloaddition and to determine if the cyclization [6,7] could be preferred to side reactions such as the Photo-Fries rearrangement [8] or intramolecular abstraction processes [9,10].

β-Enaminones **2** obtained in high yields from the commercialy available 1,3-diones **1** [11,12] were transformed into the required N-alkenoyl β-enaminones **3** by deprotonation at low temperature in THF using NaHMDS as base, followed by addition of the convenient unsaturated acid chloride, easily prepared according to standard procedure[13].

Table: Synthesis and irradiation at 313 nm of N-alkenoyl, β-enaminones **3**:



Substrate					Cycloadduct		
3	n	R	R'	Yield (a)	**4/4'**	Yield (a)	
a	1	H	H	51%		no reaction	
b	1	H	Benzyl	67%	**b**	60%	
c	1	Me	n-C_6H_{13}	75%	**c**	95%	
d	1	Me	Benzyl	84%	**d**	87%	
e	2	Me	Benzyl	63%	**e**	66%	
f	1	Me	N-Piperidino	55%	**f**	39%	
g	1	Me	(S)-1-Phenylethyl	46%	**g**	35%	(60/40) [b]

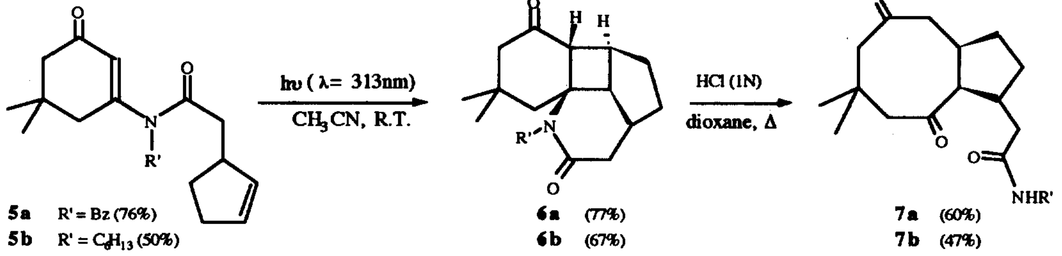
(a) chemical yields of pure isolated material.

(b) ratio of the two diastereoisomers **4** and **4'** determined by ^{1}H-NMR on the crude product.

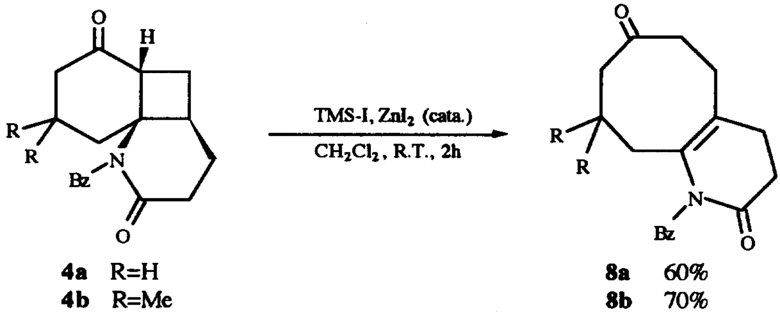
When **3a** was irradiated in Argon flushed acetonitrile solution, at 313 nm (pyrex vessel, medium pressure lamp), no reaction could be detected over a long time. This lack of reactivity can be attributed to an unfavourable conformation of the exocyclic chain as has already been described for unsaturated oxoamides [14] or in radical cyclisation processes [15]. Substitution of the nitrogen atom by alkyl substituents was expected to modify the conformational behaviour of the starting β-enaminones. Thus, [2+2] cycloadducts **4** were now isolated from **3b-3g** in good yields. In all cases, and according to the proton spectra [16], only one regioisomer was observed. The [2+2] photocycloaddition can be generalized to more highly substituted N-alkenoyl β-enaminones **5** with the same efficiency and high diastereoselectivity. As reported for intramolecular processes, the cyclisation obeys the rule of five defined by Baldwin [1a,17] and already observed for numerous substrates[18] . According to previous work in this field and studying molecular models, the relative configuration *anti* has been assigned to the only product observed. Furthermore, in the case of **3g** bearing a removable chiral group, asymmetric induction occurs, but unfortunately with a relative low diastereomeric excess (20%).

The opening of the cyclobutane ring can be obtained easily and selectively by treatement of adducts **6a** and

6b, with HCl in aqueous dioxane[19]. Under these conditions, the [6.3.0] undecane structures **7a,b** formed can be considered as precursors of triquinanes or asteriscane analogues[20].



Furthermore, ring-opening of the cyclobutane adducts by trimethylsilyliodide [21] in methylene chloride gives selectively the fused bicyclic compounds **8** in good yields.



In conclusion, intramolecular [2+2] cycloaddition of N-alkenoyl β-enaminones represents an efficient and highly regio- and diastereoselective process. The cycloadducts are of particular interest for the synthesis of bicyclic compounds, precursors of natural products. Work to improve the control of the asymmetric induction of intramolecular photocycloaddition and application of this methodology to syntheses in the field of triquinanes are now in progress.

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16 Selected data for compound **3d**: RMN ^{1}H: 1.00 (s, 6H); 2.20 (s, 2H); 2.40 (s, 2H); 2.40-2.50 (ma, 4H); 4.80 (s, 2H); 4.95-5.10 (ma, 2H); 5.75 (s, 1H); 5.80 (ddt, 1H, J= 17-12.5-6.6 Hz); 7.15 -7.35 (m, 5H). RMN ^{13}C : 27.92 (q); 29.31 (t); 33.45 (s); 34.12 (t); 43.62 (t); 50.28 (t); 50.69 (t); 115.66 (d); 123.50 (d); 127.34 (d); 127.67 (d); 128.70 (d); 136.47 (s); 136.72 (d); 159.67 (s); 171.75 (s); 199.09 (s). $C_{20}H_{25}NO_2$: calc. : C: 77.13; H: 8.09; N: 4.49; found : C: 76,90; H: 8,23; N: 4,46.

Compound **4d** : RMN ^{1}H : 1.09 (s, 3H); 1.10 (s, 3H); 1.70-1.80 (ma, 3H); 2.00-2.20 (ma, 2H); 2.25 (s, 2H); 2.30 -2.40 (ma, 2H); 2.50 (dt, 1H, J=16,4.4 Hz); 2.70 -2.80 (ma, 2H); 4.10 (d,1H, J=16Hz); 5.05 (d, 1H, J=16Hz); 7.20-7.41(m, 5H). RMN ^{13}C : 26.30 (t); 27.20 (q); 27.98 (t); 30.58 (t); 33.08 (q); 33.91 (s); 37.43 (d); 44.98 (d); 45.90 (t); 46.42 (t); 53.00 (t); 66.95 (s); 126.10(d); 127.00 (d); 127.60 (d); 138.40 (s); 172.91 (s); 211.85 (s). $C_{20}H_{25}NO_2$: calc. : C: 77.13; H: 8.09; N: 4.49; found : C: 76.71; H: 7.95; N: 4.38.

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