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Two Carbon Ring Expansion by Photochemical Ring Opening of Electrophilic Cyclobutenes

Michel Miesch*, Gaëtan Mislin, Michel Franck-Neumann

* Laboratoire de Chimie Organique Synthétique, associé au CNRS,
Institut de Chimie, Université Louis Pasteur, 1, rue Blaise Pascal 67000 - Strasbourg (France).

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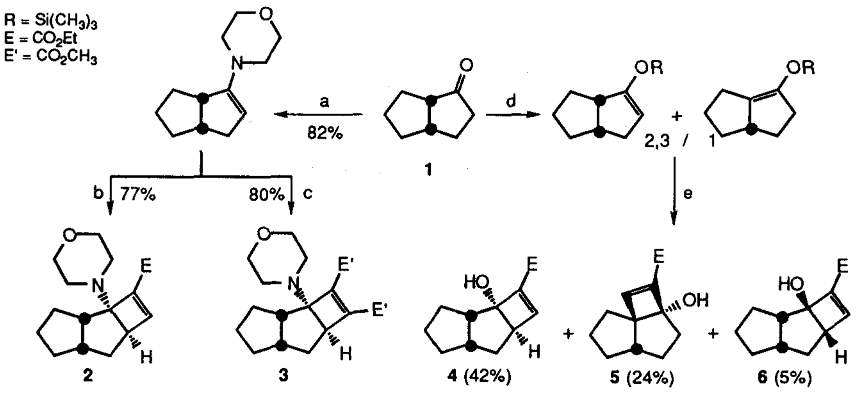
Abstract *:* The photolysis of electrophilic cyclobutenes condensed to a diquinanic moiety and bearing either an amino group or a hydroxyl group at the ring junction leads to the corresponding hydroazulenic derivatives in high yields. © 1997 Elsevier Science Ltd.

The bicyclo [5.3.0] decane (or hydroazulene) skeleton is found in a wide range of natural products[1]. Among the numerous synthetic pathways developed for their synthesis, the two carbon ring enlargment via cyclobutane derivatives (e. g. tricyclodecane → hydroazulene) proved to be a very useful method[2]. The two carbon ring expansion via electrophilic cyclobutenes is, on the contrary, seldom used[3].

In continuation of our interest in small ring chemistry[4], we wish to report our results leading to hydroazulenic derivatives by a two carbon ring expansion reaction using readily available electrophilic cyclobutenes as intermediates.

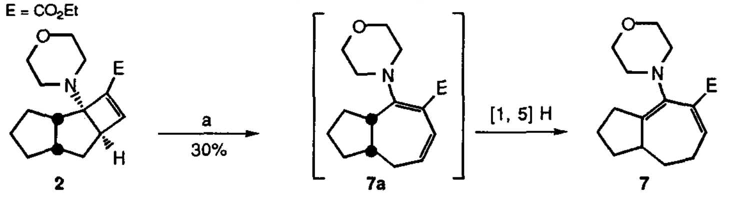
For that purpose, the synthesis of electrophilic cyclobutenes condensed to a diquinanic moiety and bearing either an amino group or a hydroxyl group at the ring junction was undertaken. Thus the thermal [2+2] cycloaddition[5] of acetylenic esters [ethyl propynoate or dimethylacetylenedicarboxylate (ACDM)] with the morpholino enamine derived from bicyclo [3.3.0] octane-2 one **1** gave the corresponding adducts **2** and **3** isolated respectively in 77 % and 80 % yield. On the other hand, the thermal $ZrCl_4$ catalyzed [2+2] cycloaddition[4] of ethyl propynoate with the trimethyl silyl enol ether (2 regioisomers; ratio : 2.3/1) derived from diquinanone **1** led to the corresponding electrophilic cyclobutenes **4**, **5** and **6**, easily separable by chromatography over silica gel (overall yield : 71 %).

✆ : (33) 03.88.41.68.12 - Fax : (33) 03.88.60.42.48 - Email : miesch@chimie.u-strasbg.fr



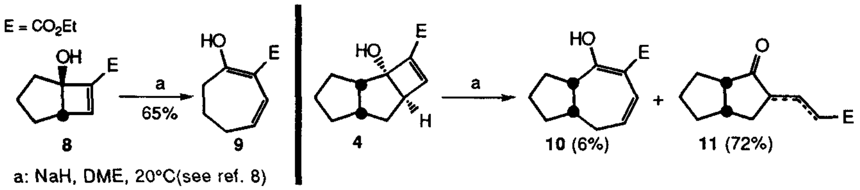
a: morpholine, pTsOH cat., toluene reflux; b: ethyl propynoate, dioxane, 20°C; c: ACDM, dioxane, 20°C;
d: TMSOTf, NEt_3, CH_2Cl_2, reflux; e: ethyl propynoate, $ZrCl_4$, CH_2Cl_2, Et_2O, 20°C.

To obtain hydroazulenic derivatives, we first tried to run a thermal two carbon ring expansion starting from compounds **2** and **3**. Indeed, it is known that the thermal ring opening of 3-amino cyclobutenes normally takes place easily and the reasons for that facile ring opening have been well discussed in the literature[6]. However, in our hands and despite the results obtained by Froborg et al. for similar compounds[3], the hydroazulenic derivative **7** was isolated in only 30 % yield when compound **2** was heated for 12h in xylene at reflux. Compound **7** probably results from the primary adduct **7a** which undergoes a [1,5] hydrogen shift[6]. Moreover, the same thermal treatment applied to compound **3** led only to unidentified products[7].



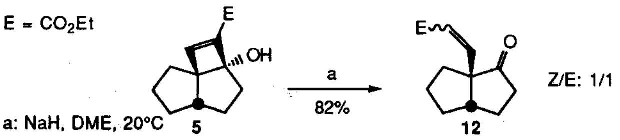
a: xylene, reflux, 12h

Being unable to obtain hydroazulenic derivatives in good yields by this route, we next turned our attention towards the hydroxycyclobutenes **4** and **5**. Indeed, it had been shown that basic treatment (NaH, DME, 20° C) of the hydroxycyclobutene **8** led to the β-ketoester **9** resulting from ring opening reaction[8]. However, when compound **4** was subjected to the same conditions, the hydroazulenic derivate **10** was isolated in only 6 % yield along with the ketoester **11** resulting from a retro-aldol type reaction.



a: NaH, DME, 20°C(see ref. 8)

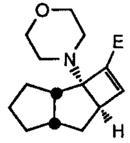
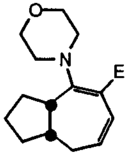
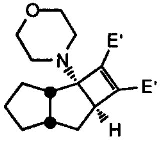
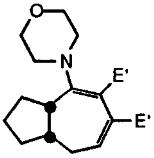
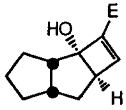
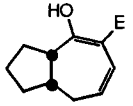
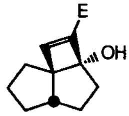
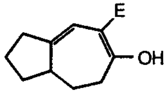
In the same conditions, the angularly fused cyclobutene **5** opened readily at room temperature to give exclusively the retro-aldol product **12** (Z/E mixture : 1/1) isolated in 82 % yield.



These results and the fact that the Woodward-Hoffmann rules predict that the disrotatory ring opening of cyclobutenes is photochemically allowed[9], prompted us to explore the photochemical behaviour of the electrophilic cyclobutenes **2**, **3**, **4** and **5**.

The photolysis of these compounds was carried out in a quartz photoreactor with a medium pressure Philips HPK-125 Hg lamp using hexane as solvent (concentration range : 2,5mM/l-25mM/l). In each case, the desired two carbon ring expansion reaction took place very cleanly leading to the corresponding hydroazulenic derivatives **7a**, **13**, **14** and **15** isolated in high yields (see table I)[10]. In general, the time required for the irradiation is relatively short but not for compound **4**. In this particular case, the best results were obtained when the Hg lamp was plugged to a power supply of only 150V. This voltage lowering transforms apparently the emission spectrum of the medium pressure lamp into the spectrum of a low pressure lamp. If the lamp was supplied with 220V, several unidentified photoproducts were obtained after a 2 hours irradiation.

Table I (E= CO$_2$Et; E'= CO$_2$Me)

Entry λ max (ε)	Time required for the photolysis	Hydroazulenic derivative	Yield (%)*
 **2** 286 nm (970) ; 218 nm (6300)	10 min.	 **7a**	90[11]
 **3** 300 nm (1000) ; 220 (6900)	20 min.	 **13**	83
 **4** 213 nm (6400)	2 h	 **14**	79**
 **5** 218 nm (6300)	5 min.	 **15**	75

* The yields are based on chromatographed material ; ** 8% of starting material is recovered.

In summary, this two carbon ring expansion via a photochemical ring opening of electrophilic cyclobutenes leads to differently substituted hydroazulenic derivatives. This method applied to appropriately substituted cyclobutenes should lead to valuable intermediates for the synthesis of natural products bearing a bicyclo [5.3.0] undecanic skeleton. We are currently investigating further application of the photochemical method outlined here for the total synthesis of natural bioactive compounds.

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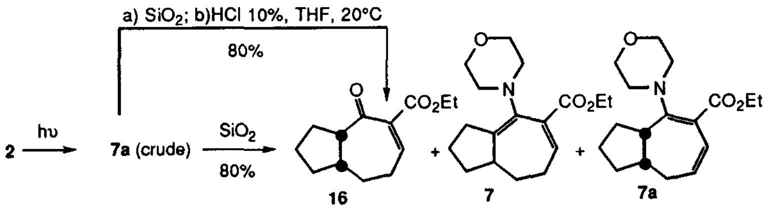
11. The yield refers to the crude photolysis product. If the hydroazulenic derivative **7a** is chromatographed over SiO_2, the β-ketoester **16** is obtained along with compounds **7** and **7a** (ratio: 10/2/1; overall yield: 80%). This result could be explained by the fact that compound **7a** undergoes a [1,5]H shift giving compound **7** which is partially hydrolysed into compound **16**. The sole β-ketoester **16** can however be isolated in 80% yield when the crude photolysis product is chromatographed over SiO_2 and then treated in acidic conditions (HCl 10%, THF, 20°C).



The cis ring junction of compound **16** was secured by COSY and NOESY spectra.

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