PHOTOCHEMISTRY OF POLYHALOGENATED HETEROCYCLIC ENAMINONES: COMPETITION BETWEEN CYCLIZATION AND DEHALOGENATION

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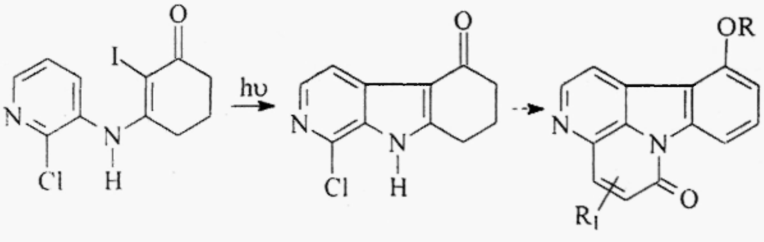
Abstract- Photochemistry of polyhalogenated enaminones is described under various conditions to give functionalized tetrahydroazacarbazolone (**9**, **15**). Starting enaminones (**2**, **7**, **14**) also underwent competitive dehalogenations creating a set of secondary products. Mechanistic aspect of the reactions are considered .

INTRODUCTION

As a part of our program concerning the elaboration of analogs of natural compounds of biological interest, (1) we are interested in the photochemistry of heterocyclic enaminones. In this context, we have previously described a general and convergent route to tetrahydro β-and δ-carbolin-5-ones (2) and α-carbolin-5-ones (3) based on the photocyclization of enaminones **1** (4). Use of *N*-(halogenopyridinyl)enaminones derived from aminopyridines was shown to be the most efficient path for the elaboration of the pyridoindolic framework such as β-carbolines. However, in each case, the cyclization occurred with abstraction of the chlorine atom. As a continuation of our investigations concerning the synthesis and biological activities of natural compounds, we are interested in the preparation of derivatives of amarorine (a β-carboline alkaloid extracted from the bark of *Amaroria soulameides*(5)). This compound is related to the general class of canthin-6-ones which possess various biological properties in respect to their substituents (6). Retrosynthetic analysis showed that a C-1 halogenated β-carbolin-5-one is an interesting synthetic intermediate which can be implicated in the elaboration of diverse analogs of amarorine modified on rings C and D (scheme 1).

Scheme 1



Amarorine derivatives

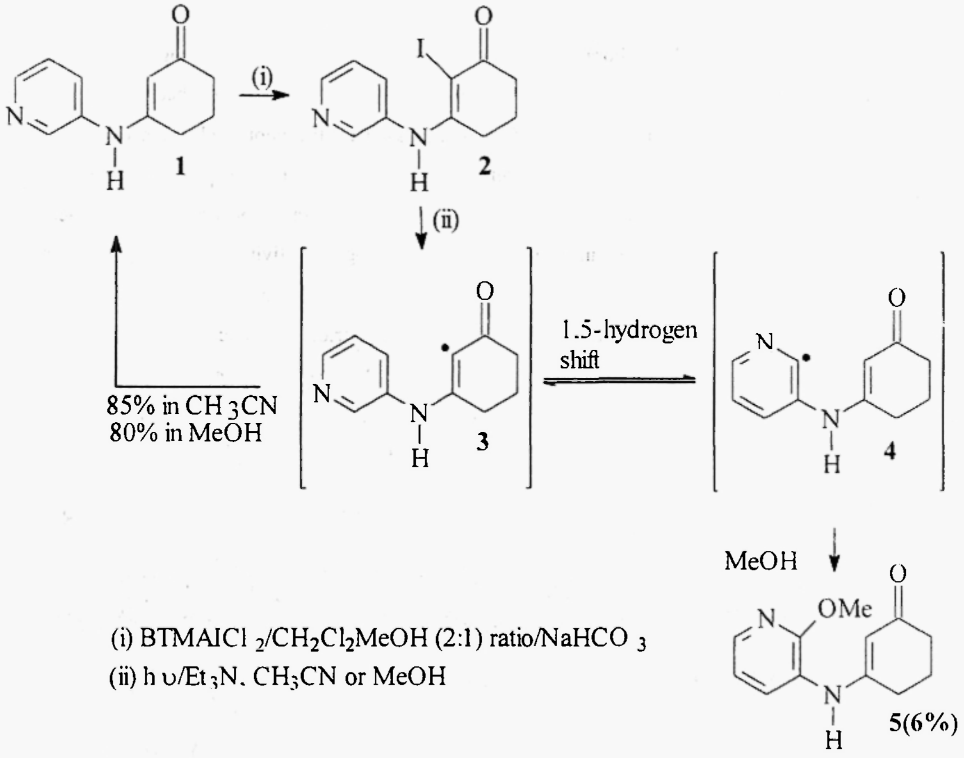
Since the reactivity of tertiary α-iodoenaminones has recently been described as giving radical cyclization by a photoinduced electron transfer (PET), our synthetic strategy resides in the use of dihalogenated enaminones such as **7** to give selective photocyclizations.

The major difficulty of this strategy resides in the presence of two halogens in the starting enaminone. However, considering the differences in strength of the C-Cl and C-I bonds, we could reasonably suppose that a judicious choice of the wavelength and irradiation conditions should lead to a selective photocyclization. In this paper, we report our results concerning the selective reactivity of such enaminones in different conditions.

RESULT AND DISCUSSION

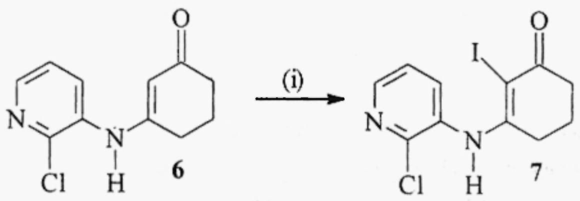
We first examined the reactivity of the α-iodoenaminone **2** under triethylamine mediated PET conditions or by direct homolysis of the C-I bond. This compound **2** was obtained quantitatively from the known enaminone **1** (2) by iodination using benzyltrimethylammonium dichloroiodate (8,9) Subsequent irradiation of **2** using a Pyrex immersion well apparatus and a medium pressure mercury UV lamp (150 W) using acetonitrile as solvent with 10 equivalents of triethylamine (10) did not give any cyclization product, but led to a simple deiodination to recover starting enaminone **1** in 85% yield. Using methanol , the same reduction was observed, but in this case, the methoxy derivative **5** was formed in 6% yield. Formation of **5** is probably performed by the radical species **3**, which can undergo a 1,5-hydrogen shift (11) to give the radical species **4**, which furthermore can be trapped by the nucleophilic solvent (scheme 2). This hypothesis of a 1,5-hydrogen shift was supported by the following experiments. When irradiating enaminone **1** in methanol for 4 hours, no reaction occurred and starting material was recovered unchanged. When irradiating **1** in acetonitrile with 2 equivalents of iodine, compound **2** was obtained in 80% yield . In methanol, the same result was observed (in these conditions, formation of **5** was also detected by tlc).

Scheme 2



Next, reactivity of the chloroiodoenaminone was examined. Compound **7** was obtained in 92% yield from **6**' by iodination using benzyltrimethylammonium dichloroiodate (scheme 3).

Scheme 3



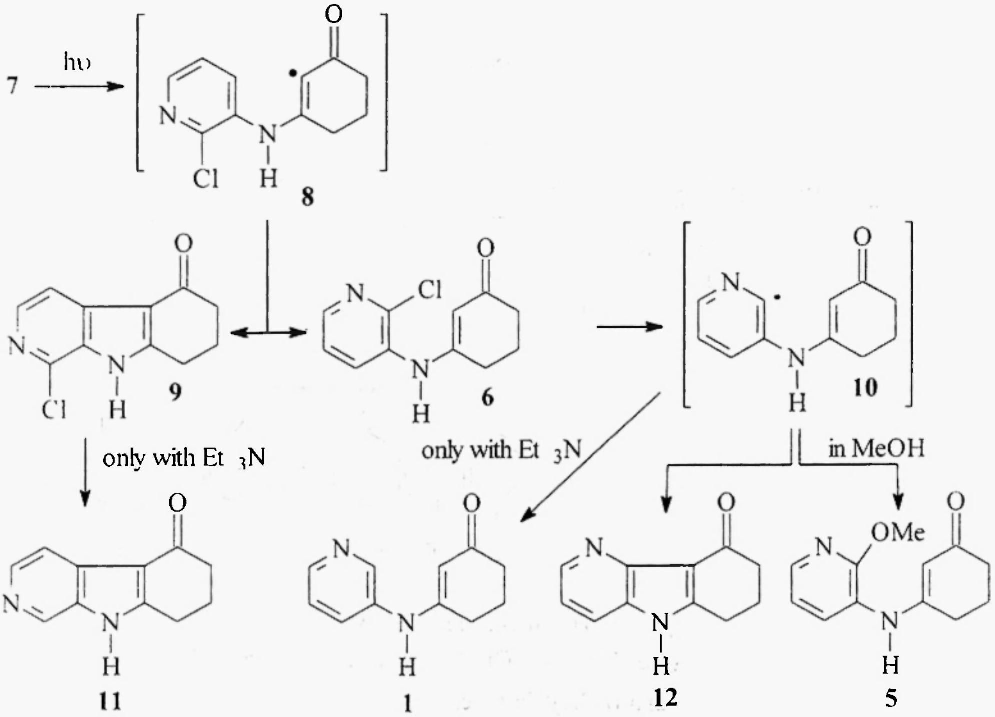
(i): BTMAICl $_2$/CH$_2$Cl$_2$-MeOH (2-1)/ NaHCO$_3$

Compound 7 was then subjected to a set of irradiations in different conditions which are summarized in Table 1.

Table 1 : irradiation of compound 7 under various conditions

Conditions\compounds	1	5	6	9	11	12
$h\nu$/CH$_3$CN/NEt$_3$/Pyrex (5 h)	30%	-	26%	13%	8%	20%
$h\nu$/CH$_3$CN/Pyrex (5 h)	-	-	21%	42%	-	13%
$h\nu$/CH$_3$OH/Pyrex (5 h)	-	24%	8%	15%	-	18%
$h\nu$/THF/Pyrex (5 h)	-	-	30%	16%	-	40%
$h\nu$/CH$_3$COCH$_3$/Pyrex (5 h)	-	-	40%	21%	-	20%

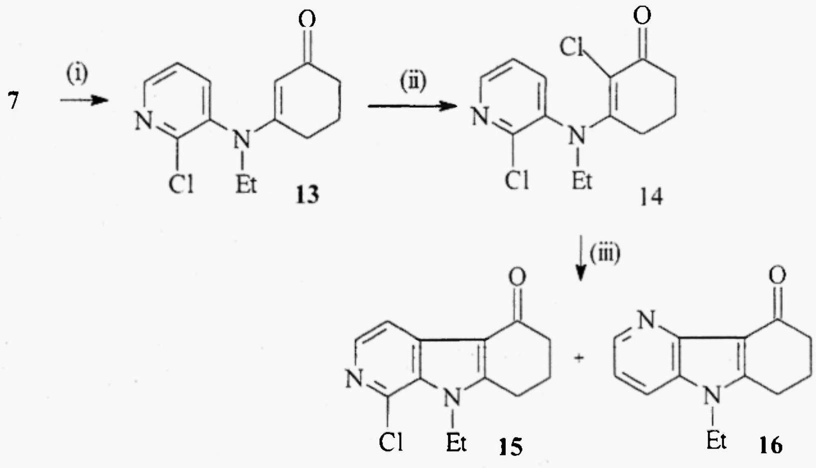
Scheme 4



These results indicate that the photocyclization of α-iodoenaminone **7** is greatly controlled by the experimental conditions. When the reaction was conducted with triethylamine, the expected carboline **9** was obtained, admixed with **6** which resulted from a simple deiodination of **7**. However in these conditions, further abstraction of the chlorine atom occured too, resulting in the formation of a set of secondary products, such as the β-carboline **11** (2), δ-carboline **12** (2) and enaminone **1**. When the reaction was conducted without triethylamine, compound **9** was obtained in 42%. Formation of the dehalogenated carboline **11** did not occur in these conditions while the dehalogenation of the enaminone still occured. This result clearly indicates that formation of **11** is the result of a dehalogenation of carboline **9** (probably achieved through an initial electron transfer from triethylamine to **9**), and not from a photocyclization of **6**.(12) Furthermore, radical species **10** was formed from enaminone **6**, (13) leading regioselectively to the δ-carboline **12**, and in presence of triethylamine, to the dehalogenated enaminone **1**. Influence of the solvent was also investigated and was shown to have great importance in the evolution of reactions. Methanol, tetrahydrofuran and acetone were used. In each cases, yield of **9** was lower than with acetonitrile. In methanol, radical species **10** was trapped by the solvent to give **5** (11). In THF, the reaction resulted firstly in the formation of **6**, followed by **12** (40%), while in acetone, the enaminone **6** is quite stable and isolated in 40% yield.

In order to evaluate the scope of the photocyclization of tertiary enaminones, and considering the results of Sha and coll. (7) who reported the high reactivity of *N*-protected enaminones in photocyclizations promoted by a PET process, we turned our interest to the access and reactivity of *N*-ethyl derivatives of enaminone **7**. Attempts of alkylation of the iodo derivative **7** under different conditions failed to give the expected *N*-ethyl-α-iodoenaminone. Using triethylamine or sodium carbonate in dichloromethane, *N*-ethylation was unsuccessfull, recovering starting materials admixed with the deiodo compound **6**, while the use of sodium hydride in toluene or THF led to the formation of **13**.[2] Subsequent halogenation of **13** with BTMAICl$_2$ was finally conducted to give the α-chloroenaminone **14** (8). Photochemistry of this derivative was then performed in the same conditions as used for **7**, to give the β-carboline **16** (2) as the major compound (41% yield) and the expected 1-chloro-β-carboline **15** in only 6% yield. This result clearly indicates that the tertiary enaminone **14** primarily undergoes a dehalogenation process to recover the derivative **13**, which can finally undergo a photocyclization.

Scheme 5



(i) a) NaH,toluene, b) EtI, reflux
(ii)BTMAICl $_2$, CH_2Cl_2-MeOH (2-1), $NaHCO_3$
(iii) h υ/CH_3CN/Pyrex

In conclusion , we reported the synthesis and reactivity of α-chloroenaminones in view of the synthesis of functionalized tetrahydro-β-carbolines. Photocyclizations were investigated in different conditions showing the impact of the conditions and reagents. The results obtained showed that the photocylizations are better performed with the secondary enaminones. In this case, the reactions were conducted in classic conditions and in photoinduced electron transfer conditions. In PET conditions, the 1-chloro-β-carboline 9 gave a C-Cl bond cleavage leading to the carboline **11**. Finally, when compared to our previous results, interest of this methodology resides in the obtention of 5,6,7,8-tetrahydro-1-chlorinated-β-carbolin-5-ones as new synthons for elaboration of natural products.

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9. Typical procedure for iodination of enaminones with BTMAICl$_2$: 9.0 mmol of the appropriate enaminone 1, 6 and 16, 3 g (9.0 mmol) of BTMAICl$_2$, and 5 g (56 mmol) of NaHCO$_3$ were added to an anhydrous solution of MeOH-CH$_2$Cl$_2$ (60 mL-120mL), and the mixture was stirred under a nitrogen stream for 30 min at room temperature. The resulting mixture was filtered and the solvents were evaporated to give the crude 2-halogenoenaminones **2**, **7** and **14** which were then purified by chromatography on alumine eluted with dicholomethane.

10. **Typical procedure for irradiation of enaminones.** A medium pressure mercury lamp was used (150W, TQ 150) with a quartz reactor, allowing emissions lower than 290 nm. A solution of the appropriate enaminone **2**, **7**, **14** (1.6 mmol) in 400 ml of freshly distilled and degased appropriate solvent with or without 10 equivalents of triethylamine was irradiated for 5 hours. The solvents were then evaporated under reduced pressure. Purifications were performed by flash chromatography of the residual oils on silica gel using a CH$_2$Cl$_2$/MeOH mixture as eluent (95/5).

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