SYNTHESIS OF FUNCTIONALIZED INDOLIZINO[8,7-*b*]-INDOLES VIA 1,3-DIPOLAR CYCLOADDITION REACTIONS OF 3,4-DIHYDRO-β-CARBOLINE AZOMETHINE YLIDES WITH OLEFINIC DERIVATIVES

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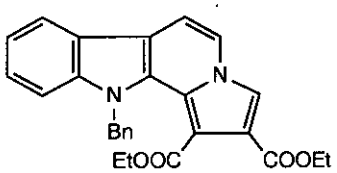
Abstract - The 1,3-dipolar cycloaddition reaction of 3,4-dihydro-β-carboline azomethine ylide **(4)** with dimethyl fumarate **(5)** and fumaronitrile **(5')** is described. The resulting hexahydroindolizine products **(6)** and **(6')** were dehydrogenated stepwise (- H_2, - $2H_2$, - $3H_2$) using $KMnO_4$, MnO_2 and DDQ as oxidants.

As part of a program aimed at the development of multifunctional anticancer agents, we recently synthesized 11*H*-indolizino[8,7-*b*]indoles **(1)** *via* reaction of acetylenic di- (and mono-) carboxylates with



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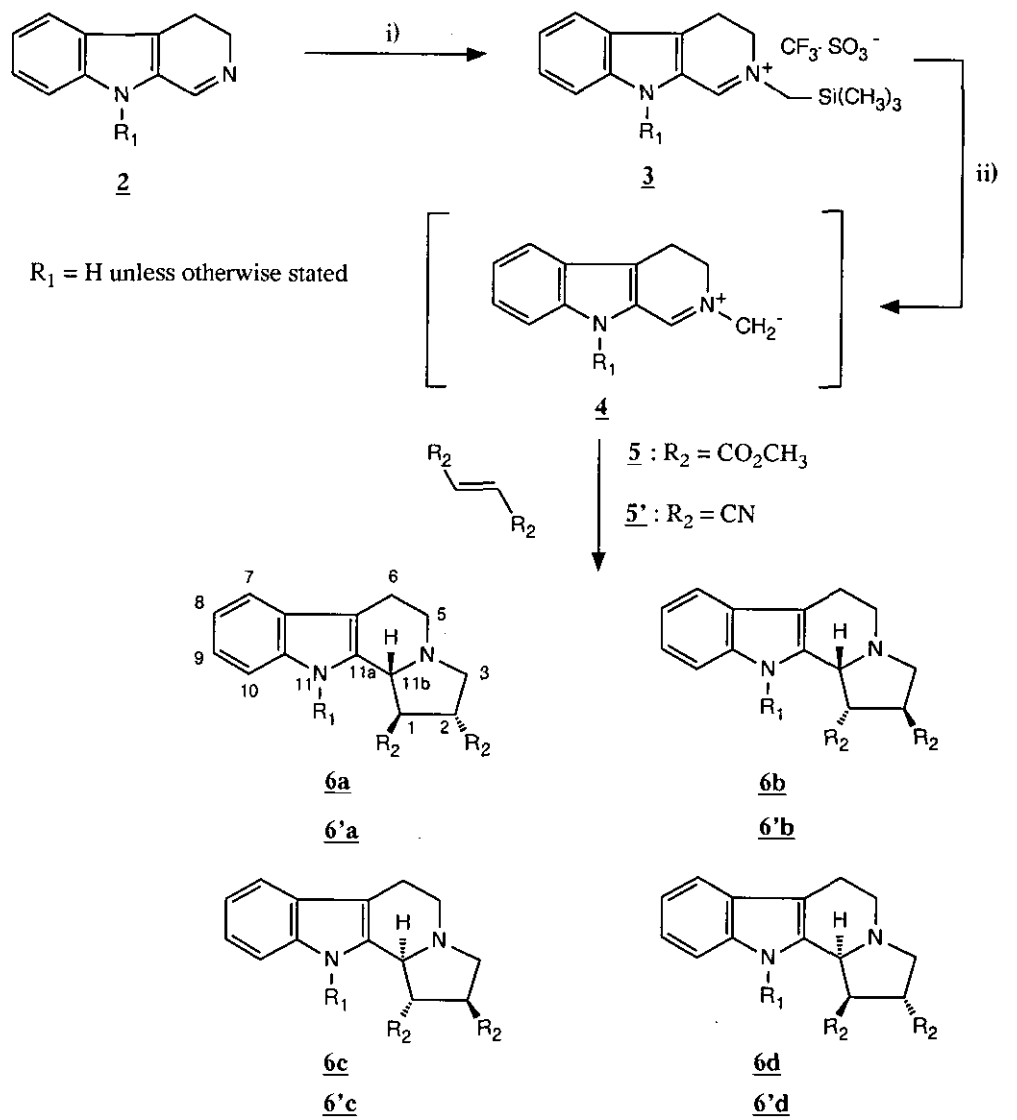
β-carboline azomethine ylides (**4**, R^1 = Bn, Scheme 1).[1] The latter were generated from the trimethylsilylmethyl triflate salts **(3)** (R^1 = Bn) of 3,4-dihydro-β-carbolines **(2)** (R^1 = Bn). In this communication, we now wish to report the 1,3-dipolar cycloaddition reactions of unprotected ylide **(4)** (R^1 = H) with ethylenic dipolarophiles **(5)** (dimethyl fumarate) and **(5')** (fumaronitrile), allowing entry into the hexahydroindolizine analogues of 1 .

Scheme 1



2 **3** **4**

6a **6'a** **6b** **6'b**

6c **6'c** **6d** **6'd**

i) $(CH_3)_3SiCH_2OSO_2CF_3$, CH_2Cl_2 , 25°C ; ii) CsF, DME , reflux , olefin **5** or **5'**

Alkylation of unprotected 3,4-dihydro-β-carboline **(2)** (R^1 = H) with trimethylsilylmethyl trifluoromethanesulfonate[2] in dichloromethane at room temperature gave exclusively the quaternized β-carboline derivative **(3)** (R^1 = H) (73% ; mp 136°C (EtOH)).[3] No alkylation of the indolic N-H by the silyl reagent was observed. Treatment of the triflate salt **(3)** with cesium fluoride in anhydrous dimethoxyethane[2] produced the azomethine ylide **(4)** (R^1 = H). The latter was trapped *in situ* with dimethyl fumarate **(5)** yielding the 1,2,3,5,6,11b-hexahydroindolizino[8,7-*b*]indoles **(6a-d)** as a diastereomeric pair of enantiomers (87% overall yield). A mixture of the enantiomers **(6a)** and **(6c)** was obtained by fractional crystallization of the crude reaction mixture from ethanol (mp 169°C ; 51%). Chromatography of the mother liquor on silica gel using dichloromethane - ethyl acetate (7:3) as developer provided a mixture of **6b** and **6d** in the form of a yellow oil (36% yield).

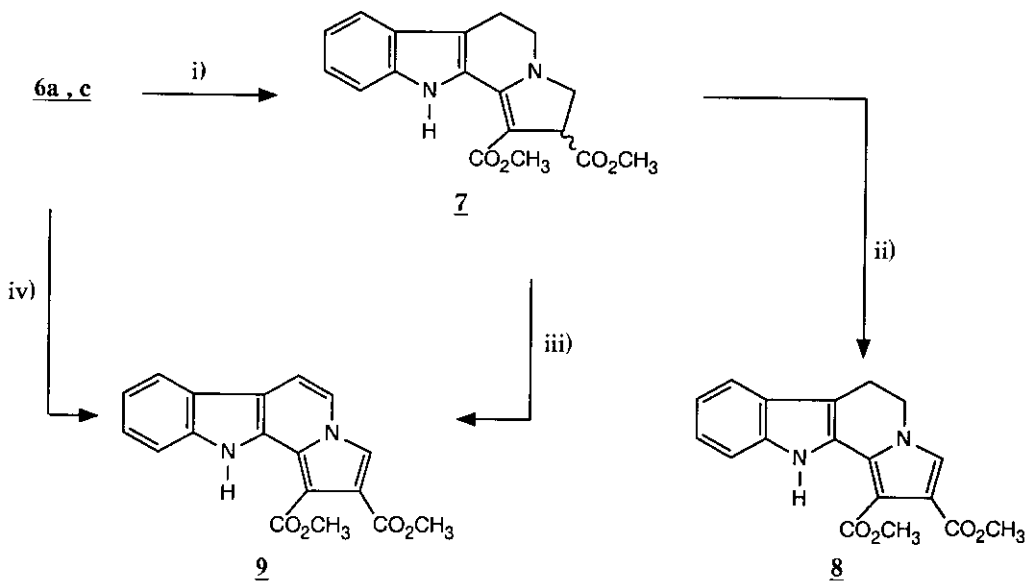
As has been amply demonstrated[2,4] 1,3-dipolar cycloaddition reactions of non-stabilized azomethine ylides with electron-deficient ethylenic dipolarophiles are highly stereospecific, the *cis* (or *trans*) relationship of the latter being maintained in the final products. The reaction of the β-carboline ylide **(4)** with fumarate **(5)** follows this rule, a *trans* arrangement of the ester groups being conserved in the reaction products **(6a-d)**. This was evident from the ^{1}H-^{1}H two-dimensional nmr spectrum of the enantiomeric mixture **(6a)** + **(6c)**, in which $J_{1,2}$ = 7 Hz.[5] A $H_{11b,1}$ coupling constant of 7 Hz was also consistent with a *trans* arrangement of these protons. In the case of **6b** + **6d** , $J_{11b,1}$ was of the order of 9 Hz, indicating a *cis* geometry at these positions while a $J_{1,2}$ value of 7 Hz again pointed to a *trans* relationship of H-1 and H-2.

In similar fashion, reaction of ylide **(4)** (R^1 = H) with fumaronitrile **(5')** in DME gave the mixture of isomers **(6'a-d)** in 64% overall yield. The enantiomeric pair **(6'a)** and **(6'c)** (48%) was separated from their diastereomers **(6'b)** and **(6'd)** (16%) by hplc.[6] The relative configurations of each pair of enantiomers were assigned by 2-D ^{1}H-nmr spectroscopy as for the diester analogues.

The hexahydroindolizines **(6)** and **(6')** could be dehydrogenated progressively (- H_2, - $2H_2$, - $3H_2$) and selectively by use of different oxidants. Thus, treatment of **(6a,c)** with excess potassium permanganate in anhydrous THF[7] for 1 h at 0°C gave the tetrahydro derivative **(7)** (Scheme 2) which was isolated as an oil

in 84% yield after chromatography on silica gel. The pyrroline ring of **(7)** was then transformed, albeit

Scheme 2



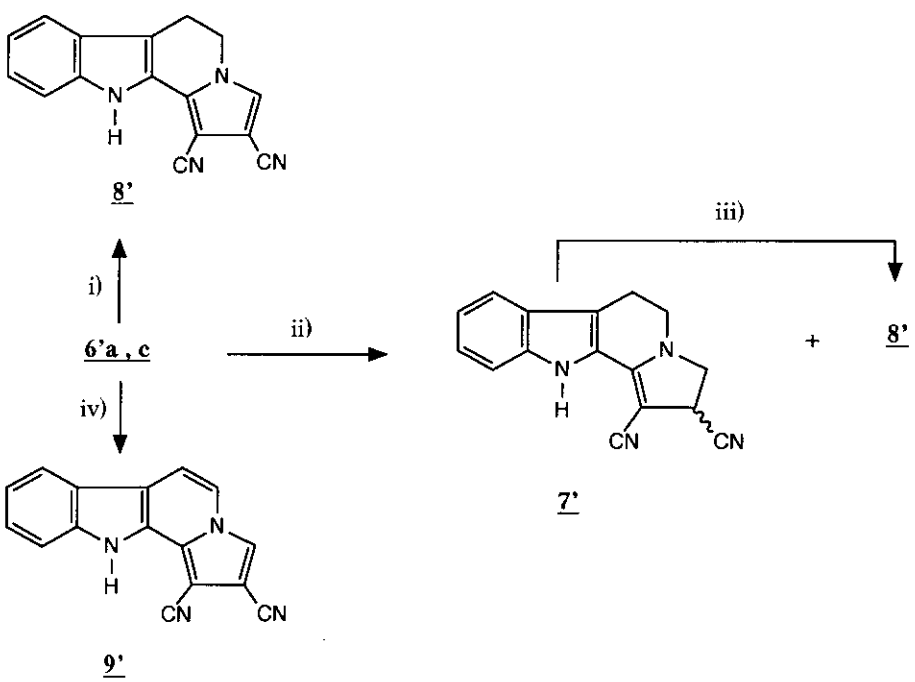
i) $KMnO_4$, THF , 0°C , 1 h ; ii) 1 eq. DDQ , CH_2Cl_2 , 0°C ; iii) 2 eq. DDQ , CH_2Cl_2 , 0°C ; iv) 3 eq. DDQ , CH_2Cl_2 , 0°C or MnO_2 , THF , reflux

in low yield (15%), into the pyrrolidine derivative **(8)** (mp 193°C) by use of 1 eq. of DDQ in dichloromethane at 0°C. The low yield of this reaction is attributable to incomplete reaction ; starting material **(7)** could, however, be isolated by chromatography on silica gel and then recycled. Finally, treatment of **7** with 2 eq. of DDQ or of **6a,c** with 3 eq. of DDQ in THF at 0°C (or with active manganese dioxide in refluxing THF) gave the completely unsaturated derivative **(9)** (mp 163°C) in 70% yields. Compounds **(7)**, **(8)** and **(9)** were characterized by comparison of their spectral properties (uv, ir, ^{1}H-nmr) with those of the previously described[1] N-protected diethyl ester analogues produced by reaction of β-carboline ylides with diethyl acetylenedicarboxylate. In the latter case, the highly electrophilic character of the acetylenic dipolarophiles necessitated protection of the nucleophilic β-carboline N-H

function to avoid competing reactions. The present step-wise oxidation of **6** now allows direct access to the unprotected derivatives.

Stepwise dehydrogenation of the dicyanohexahydroindolizine compounds **(6'a,c)** proved to be more delicate than that of the diester analogues. Thus, under conditions identical to those which led to **7** ($KMnO_4$, THF, 0°C, 1 h), the dicyano derivative **(6'a,c)** gave only the product resulting from loss of $2H_2$, **8'** (65% ; mp 245°C ; Scheme 3). Although **7'** could be detected by tlc when **6'a,c** was treated with 0.5 eq. of DDQ in dichloromethane at 0°C, all attempts to isolate this compound invariably led to formation of **8'** due to air oxidation. The fully aromatic **(9')** could be obtained by treatment of **6'a,c** with 3 eq. of DDQ (60% ; mp 295°C).

Scheme 3



i) $KMnO_4$, THF , 0°C , 1 h ; ii) 0.5 eq. DDQ , CH_2Cl_2 , 0°C ; iii) air ;
iv) 3 eq. DDQ , CH_2Cl_2 , 0°C .

In conclusion, the reaction of unprotected 3,4-dihydro-β-carboline azomethine ylides **(4)** (R^1 = H) with olefinic dipolarophiles **(5)** and **(5')** allows direct access to the new class of hexahydroindolizino[8,7-*b*]indole derivatives in a stereospecific fashion. The ability of the products **(6)** and **(6')** to undergo

controlled, stepwise dehydrogenation will allow evaluation of the optimal geometry necessary to ensure cytotoxic activity.

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