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A NEW INDOLIZIDINE SYNTHESIS

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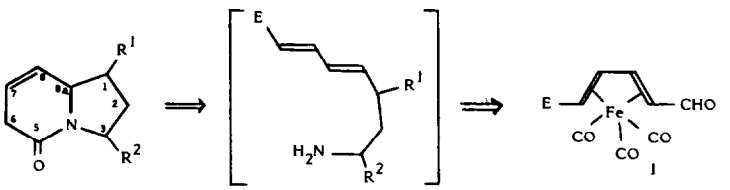
Abstract - The intramolecular 1,6 Michael type addition of a primary amine to an electrophilic diene occurs under very mild conditions ; it is the key step for a new preparation of indolizidines.

The indolizidine alkaloids are compounds of much current interest due especially to their potent biological properties. Although many approaches have been described for the preparation of indolizidines, only a few of them can be efficiently applied to chiral synthesis : the use of carbohydrates as starting materials [1] or the chiral dihydropyridine equivalents[2] appear as the two most promising methods.

As part of our program concerned with the use of butadiene iron tricarbonyl complexes in organic synthesis [3], we describe here a new strategy for the elaboration of the indolizidine skeleton (scheme I) : an intramolecular 1,6 Michael type addition of a primary amine



R^1 = OH ; R^2 = H
R^1 = H ; R^2 = CH_3

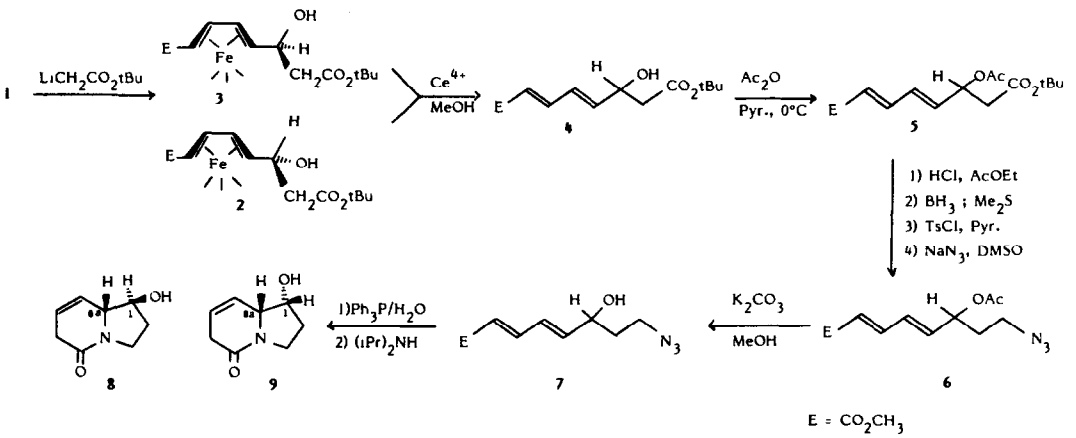
E = CO_2CH_3

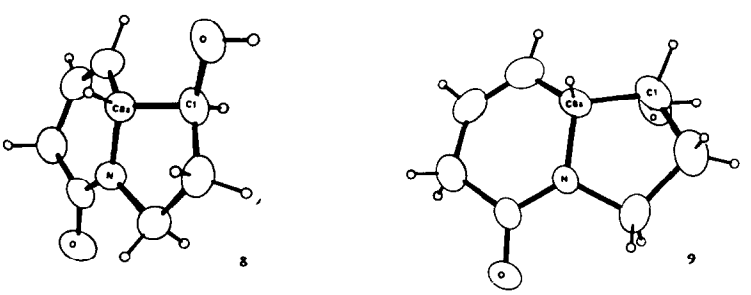
Scheme I

on an electrophilic diene followed by a second cyclisation on the ester group leads to an indolizidine conveniently substituted for further transformations. This approach, described here on two examples, appears not only versatile but could also be extended to chiral synthesis since the starting complex I has been resolved [4].

I - Hydroxy-1 indolizidines

The scheme II describes the different steps of this synthesis. The reaction of the lithium enolate of tertiobutylacetate with **1** leads to a 2/1 mixture of alcohols **2** and **3** easily separated by flash chromatography (94 % overall yield). The "Ψ exo" structure was attributed to the more polar isomer **2** by analogy with the literature[5] and precedent work in this laboratory[6]. The decomplexation of each isomer (Ce^{4+}, MeOH, -15°C, 87 %) gives the diene **4** [7] whose alcohol function is protected (Ac_2O, Pyr, 0°C, 97 %). The azidodiene **6** is then obtained after a four step sequence : cleavage of the tertiobutylester [8], selective reduction of the acid, tosylation of the alcohol and nucleophilic substitution with NaN_3 (31 % overall yield). The key intermediate **7** is obtained after deprotection of the alcohol (70 %) and the azide reduced chemoselectively (Ph_3P and H_2O in THF)[9] : *the intermediate primary amine could not be detected spectroscopically ; it cyclises spontaneously at room temperature or below.* After removal of Ph_3PO, the crude reaction mixture is refluxed in benzene in the presence of $(iPr)_2NH$ leading to a 80/20 mixture of indolizidines **8** and **9** which are easily separated by chromatography (35 % overall yield from **7**).





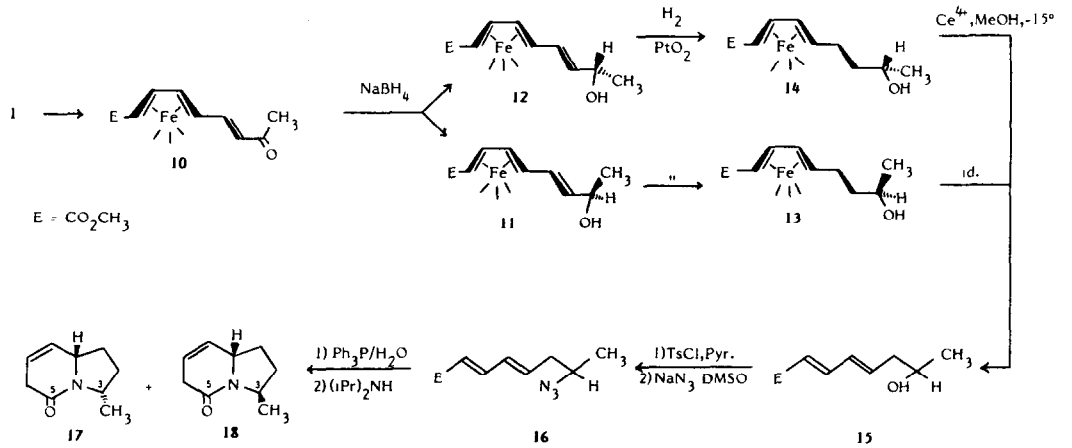
Scheme II

From the X-Ray structures of **8** and **9** [10], it is worth noting that these compounds are diastereoisomers ; the major one having H_1 and H_{8a} in trans relationship. The double bond is not conjugated with the amide and the nitrogen atom is almost planar.

It is important to point out here that this double cyclisation procedure occurs not only under very mild conditions but also with a good diastereoselectivity in agreement with preceeding results concerning the 1,4 mode [11]. Furthermore, these indolizidines seem to be useful intermediates for the synthesis of important alcaloïds such as castanospermine [12] or slaframine [13].

II - Methyl-3 Indolizidines

The same basic strategy with a 1,6 Michael type addition was used for the synthesis



Scheme III

of **17** and **18**. A different route was however designed for the preparation of the key intermediate **16** (scheme III). The olefin **10** is prepared by a Wittig-Horner reaction starting from **1** (85 % yield) [14] ; the reduction of the ketone gives a 1/1 mixture of **11** and **12** separated by flash chromatography (71 % overall yield). The presence of the complex allows a selective reduction of the free double bond in **11** and **12** leading to **13** and **14** respectively (PtO_2, H_2, 5 bars, yields > 95 %). After decomplexation (81 % yield) the alcohol **15** is transformed into the azido diene **16** (50 % overall yield). Under the same conditions as before, it gives a 57/43

mixture (NMR control) of **17** and **18** (33 % overall yield from **16**). These are easily separated by chromatography and their structure has been attributed by analogy of their spectral data with those of **8** and **9**. The stereochemistry at C_3 is supported by the presence of a coupling constant $J_{2a3e} \neq 0$ Hz in the case of **18** [15].

It is interesting to note here that such an approach could be useful for the synthesis of alcaloïds disubstituted in positions 3 and 5 like monomorine or gephyrotoxine 223 AB [2].

References and notes

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7 - For racemic synthesis, this alcohol may be obtained directly by condensation of the lithium enolate of tertiobutylacetate with the uncomplexed diene corresponding to **1** (97 % yield).

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10 - Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K..

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14 - To a THF solution of **1** are added 3 eq. of the Wittig-Horner reagent and Na_2CO_3 (1 M solution, 2 eq.). Then heating of the reaction mixture at 50°C for 1 h and usual work-up lead to **10** (m.p. = 112°C, yield : 85 %).

15 - After irradiation of the methyl signal H_3 appears as a triplet (J = 7,2 Hz) in the case of **17** and as a doublet (J = 8,2 Hz) for **18**. The examination of molecular models and X Ray data of **8** and **9** shows that the NMR results only fit with the indicated structures.

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