Efficient Synthesis of Organometallics of Pyridines, Quinolines and Diazines: New Synthetic Methodologies for Azaaromatic Biomolecules

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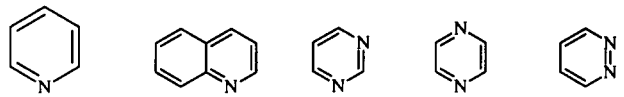
I. Scope of the Reaction.

I.1. Introduction.

Here will be described the scope of an efficient synthesis of organometallics of azines (pyridines, quinolines, diazines) by directed lithiation of these compounds. The word metallation is used only for the hydrogen lithium exchange by a strong base and not for the exchange of bromine by lithium.



The main interests of the lithiation of π-deficient heteroaromatic derivatives are:

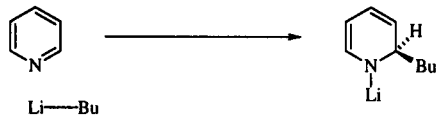
- The pyridine series is the second aromatic one.
- A great number of pharmaceutical and natural products have these structures.
- Reactions are generally difficult:
  - Organometallics are not easy to prepare:
  - RMgX are rarely used.
  - RLi were prepared only by Br → Li exchange.

Very little information was known about metallation of azines two decades ago. In the reference review of Gschwend and Rodriguez in Organic Reactions (1979) [1] there was only around twenty lines, the main of which being:

Metallation of Pyridines is Not a Practical Reaction.

I.2. So one can wonder why it is so difficult to metallate azines while it is so easy with benzene derivatives and how this could be achieved?

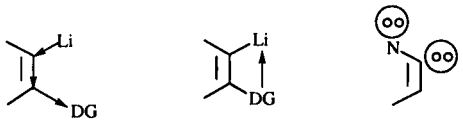
Benzenic compounds that can be metallated have p*K*a lying between 38 and 40 [2]. These derivatives are generally metallated with *n*-, *sec*-, *tert*-butyllithium (p*K*a are around 45). But it is well known that alkyllithiums add to azines very fast, even at low temperature.



We observed that this nucleophilic addition is correlated with orbital interactions between the lowest unoccupied molecular orbital (LUMO) of the pyridine derivative and the highest occupied molecular orbital (HOMO) of the base, this could explain why the nucleophilic addition is so fast with many azines added to the low electron density of azines.

So to prevent addition reaction a solution is to try lithium amides which are less nucleophilic but their drawback is that they are also weaker bases (p*K*a = 35.7 for lithium diisopropylamide (LDA) and 37.3 for lithium tetramethylpiperidide (LTMP). This can be effective if the p*K*a of the azine derivatives are much lower than those of benzene derivatives owing to the electron withdrawing effect of nitrogen. The p*K*a is depending on three thermodynamic factors: electron withdrawing effect of the *ortho* directing group, chelation of lithium with the *ortho* directing group and electronic repulsion between the carbanion and the lone pair of the *ortho* nitrogen.

Thermodynamic Control: 3 Main Factors

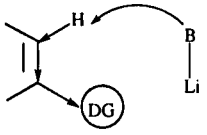


This thermodynamic control occurs generally with lithium amides which p*K*a are close to those of the compounds to be metallated.

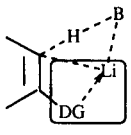
Another solution is to try to get a kinetic control of the reaction by the use a lithium alkyl as bases. The rate of the metallation is depending on two mechanisms.

Kinetic Control, Two Mechanisms:

1) Acid-Base



2) Chelation in Transition State



The kinetic control occurs generally with alkyllithiums and one must use the most electron withdrawing and the most chelating groups.

So with some *ortho* directing groups (OR, NHCO*t*-Bu) which are Electron Donating Groups (EDG) the LUMOs are higher and the nucleophilic addition is slower and occurs at a higher temperature (3-OMe pyridine can be metallated by BuLi in tetrahydrofurane (THF) at -40°; 2,3,4-pivaloylaminopyridines at 0°).

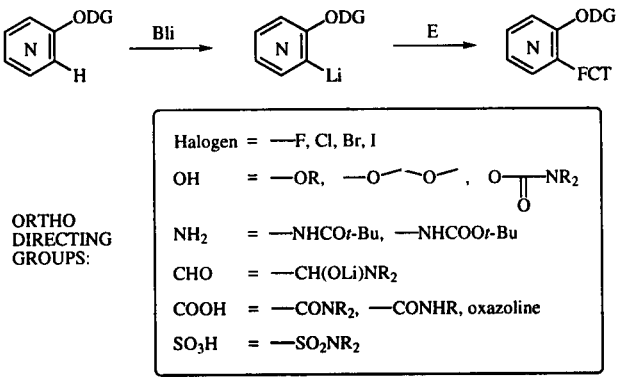
With *ortho* directing groups, that are Electron Withdrawing Groups ($OCONEt_2$, $CONi\text{-}Pr_2$, CONH*t*-Bu,...) or are essentially chelating groups one has to slow down the rate of the nucleophilic addition of alkyllithum (by lowering the temperature and increasing the steric hindrance of the base (*s*- or *t*-BuLi)) while speeding up the metallation step by increasing the electron withdrawing effect of the *ortho* directing group or the chelating effect (OMOM, OMeM, OSeM, $OCONEt_2$, NHCO*t*-Bu, NHCOO*t*-Bu, $CH(OLi)NMeCH_2CH_2NMe_2$).

By a careful use of these factors many metallation of azines can be performed.

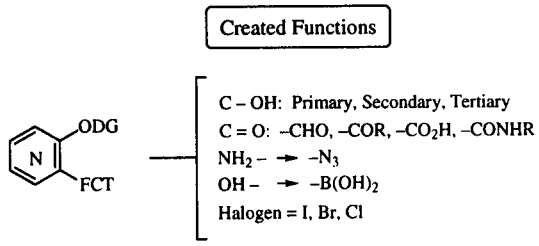
I.3. Scope.

Nowadays, so many results have been obtained that could be written two reviews entitled: "Directed Metallation of π-Deficient Azaaromatics. Strategies of Functionalization of Pyridines, Quinolines and Diazines" [3] and "Metallations of diazines" [4].

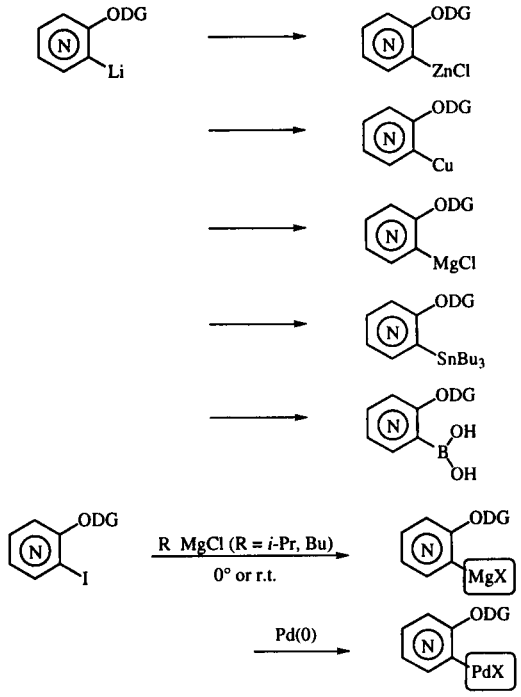
The scope of the metallation of azines is now wide and the main functions (halogen, OH, NH_2, CHO, COOH, SO_3H) can be used as ODG after activation and protection.



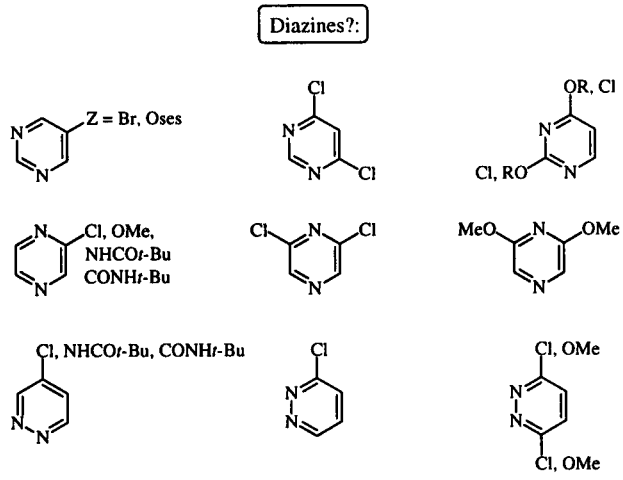
The synthetic potential of these organometallics has been widely developed and the main functions can also be created regioselectively in *ortho* position (halogen, OH, NH_2, alkyl, CR_1R_2OH, CHO, COOH, metals).



These new lithiations also allows the synthesis of many other organometallics:

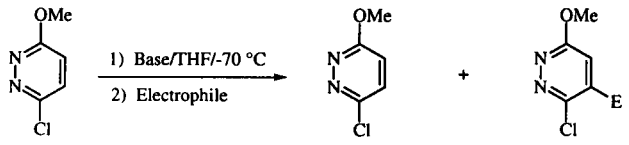


In spite of the greater difficulty of the metallation of diazines (due to their lower LUMOs) compared to that of pyridines, it has also recently been widely developed.

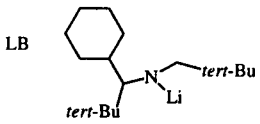


I.4. Some Original Characteristics of the Metallation of Diazines Can Be Mentioned.

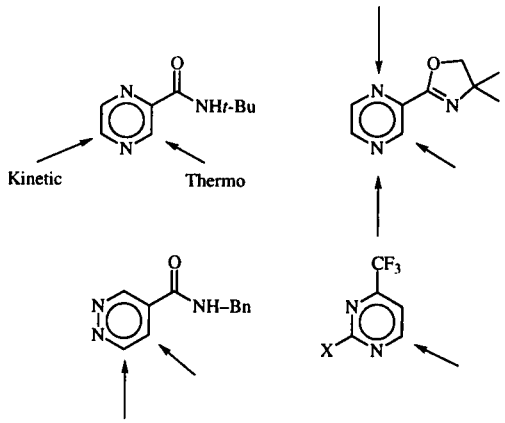
I.4.1. The Regioselectivity Can Be Improved by Use of More Crowded Bases, for example:

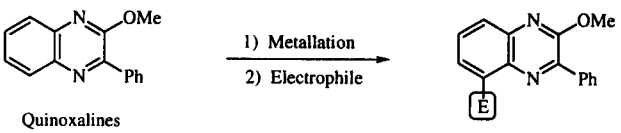


Base	Yield	%	
LDA	85%	60	40
LTMP	86%	80	20
LB	90%	98	[2]

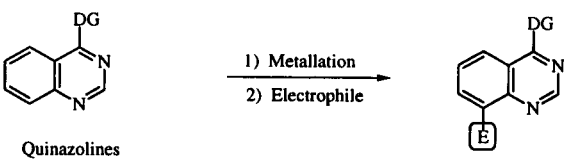


I.4.2. "Long Range Metallations".



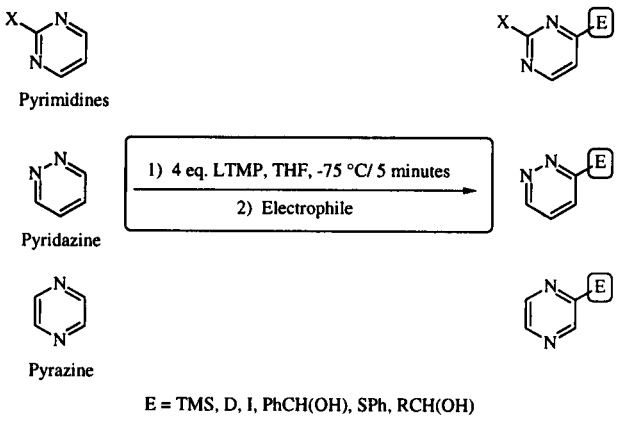


Quinoxalines



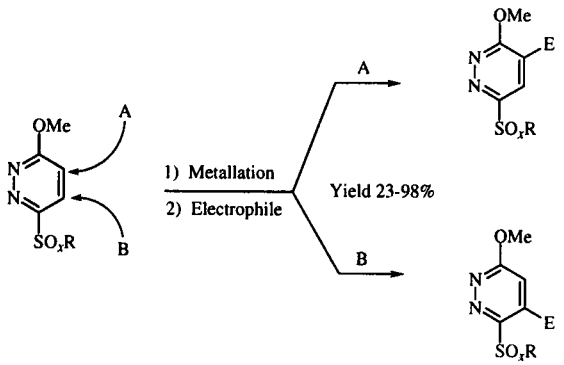
Quinazolines

I.4.3. Metallation Without *ortho* Directing Group!



E = TMS, D, I, PhCH(OH), SPh, RCH(OH)

1.4.4. New Sulfur O.D.G for Pyridazines Can Be Used.



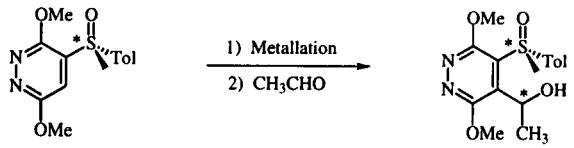
Electrophiles: RCHO, MeI, I_2

x = 0 Thioethers ⟹ A

x = 1 Sulfoxides ⟹ B

x = 2 Sulfones ⟹ A + B

I.4.5. Enantioselective Induction by a Chiral Sulfoxide.



Diastereoisomeric excess 98%

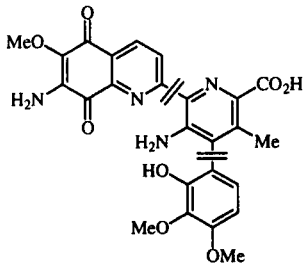
I.5. Applications to New Synthetic Methodologies.

All these synthetic breakthroughs in the field of azines open the field to new methodologies for total synthesis of biomolecules even more than synthesis of biomolecules from metallation of homoaromatic compounds.

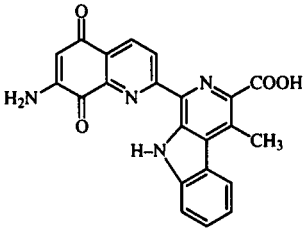
The metallation can be used along with other methodologies: hetaryne formation, halogen migration, aromatic nucleophilic substitution, nucleophilic radical substitution, cross coupling reaction.

I.5.1. For Pyridines.

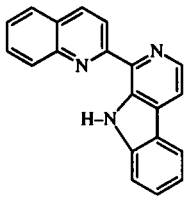
New synthetic methologies for more than 40 biomolecules have been devised [3,5]. Below are biomolecules for which we have found new synthetic strategies based on metallation of pyridines [5].



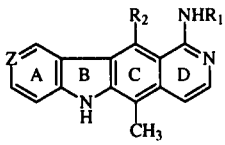
Streptonigrine



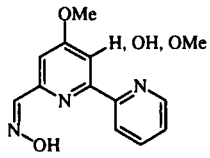
Lavendamycine



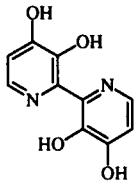
Nitramarine



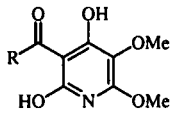
Ellipticines



Caerulomycines

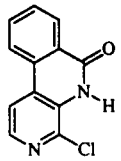


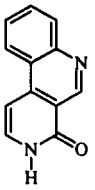
Orelline



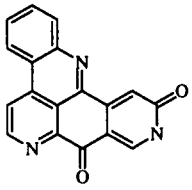
Atpenine B
Harzianopyridone

Azaphenanthridines

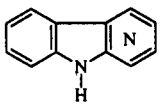




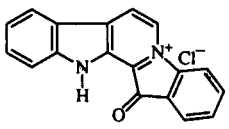
Perlolidine



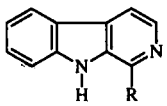
Amphimedine
Marine Alkaloids



Azacarbazoles



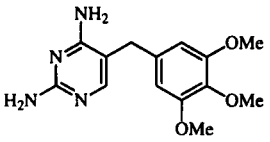
Fascaplysin



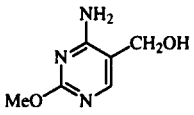
R = Me Harmane
R = Et
R = Vinyl Pavettine

I.5.2 Diazines.

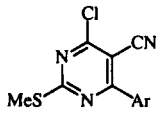
New methodologies based on organometallic derivatives of diazines which were out of reach before could be devised [5].



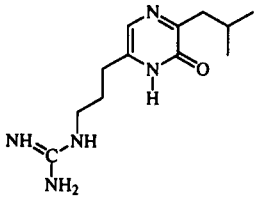
Trimethoprim



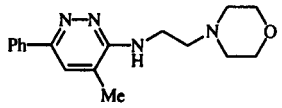
Bacimethrins



Leshmaniacids

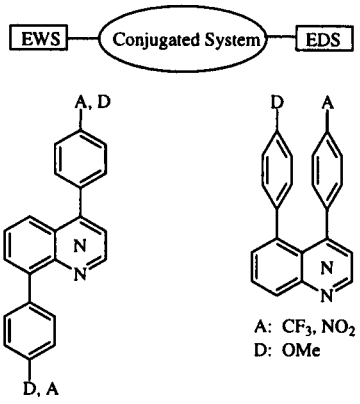


Arglecin



Minaprine

I.5.3. With Benzodiazines.



Molecules with electro-optical properties

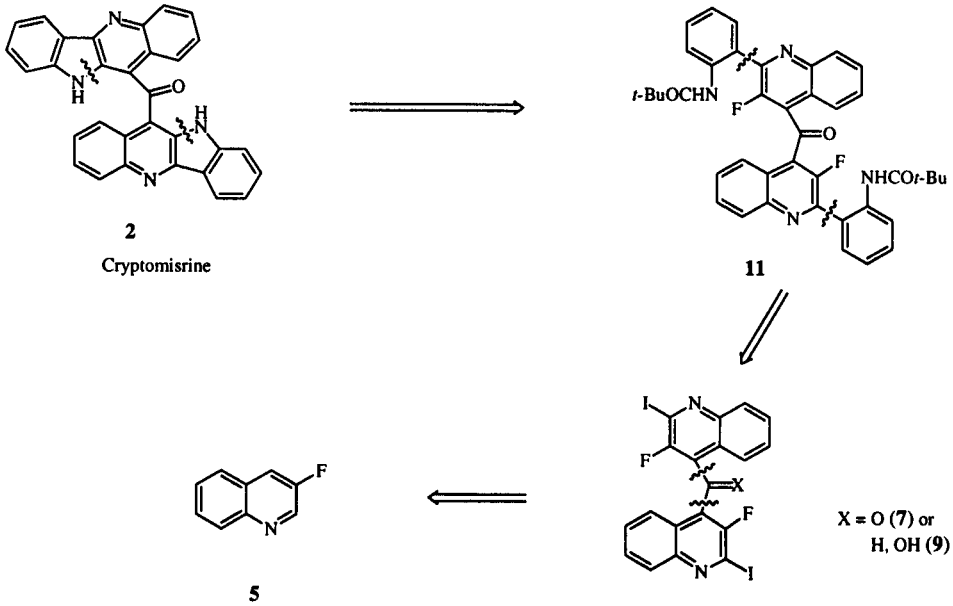
I.6. First Total Synthesis of Cryptomisrine **2** [6].

Compound **2** is an alcaloid recently isolated from *Cryptolepis sanguinolenta*. It has biological activities, such as antimuscarinic, antibacterial, antiviral, antiplasmodial and antihyperglycemic activities.

We devised a retrosynthetic scheme (Scheme I) based on a construction of the indole ring by nucleophilic substitution and cross coupling. The trisubstituted quinoline is synthesized by metallation and halogen scrambling from **6** [6].

Compound **6**, after metallation, halogen migration, and reaction with ethyl formate leads to compound **8**. By addition of the preceding lithio derivative of **6** compound **9** is obtained.

Scheme I

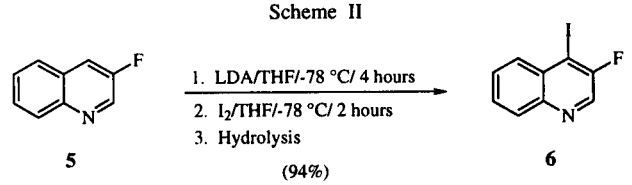


2
Cryptomisrine

11

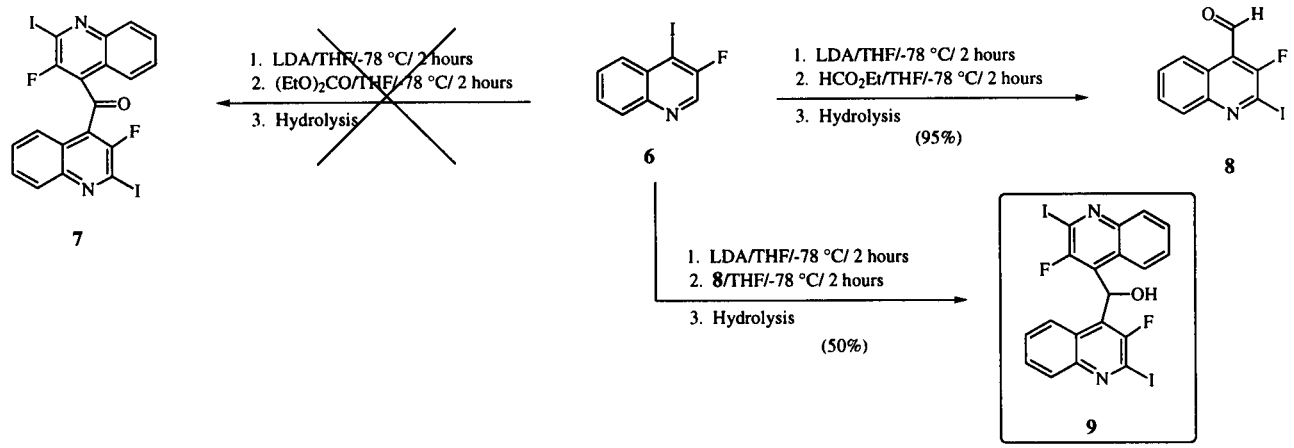
5

Scheme II



5 6

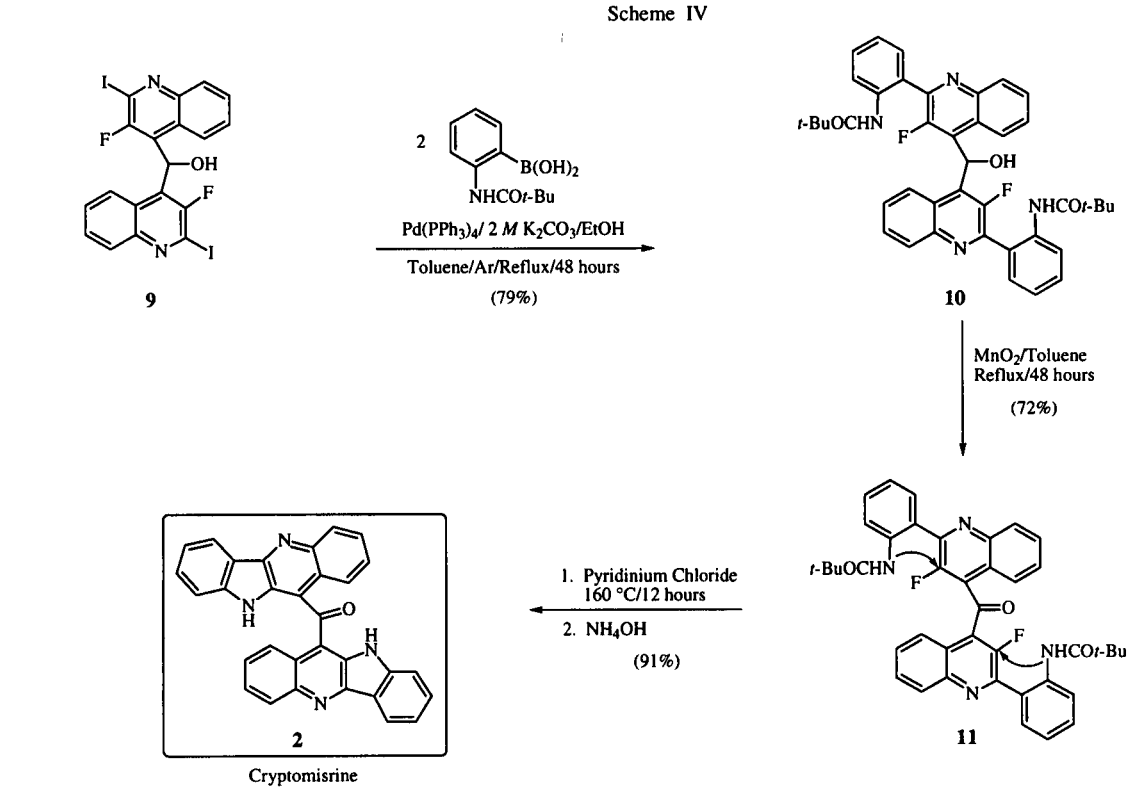
Scheme III



7 6 8 9

Then the indole rings are synthesized by cross coupling and nucleophilic substitution in pyridinium chloride.

Scheme IV



9 10 11 2

Cryptomisrine

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REFERENCES AND NOTES

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[4] A. Turck, N. Plé, G. Quéguiner, *Heterocycles*, **37**, 449 (1994).

[5] A. Godard, F. Marsais, N. Plé, F. Trécourt, G. Quéguiner, *Heterocycles*, **40**, 1055 (1995).

[6] E. Arzel, P. Rocca, F. Marsais, A. Godard and G. Quéguiner, *Tetrahedron*, **55**, 12149 (1999).