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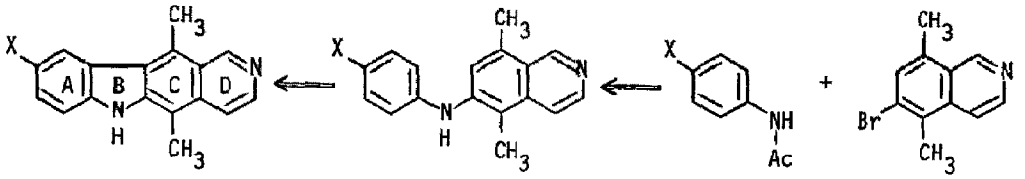
A GENERAL SYNTHESIS OF 6-H-PYRIDO[4,3-b]CARBAZOLE ALKALOIDS

R. Bryan Miller* and Thomas Moock
Department of Chemistry, University of California, Davis, California 95616

Summary. A general and versatile synthesis of the 6-H-pyrido[4,3-b]carbazole alkaloid ellipticine is described; the approach employs the coupling of an acetanilide with a bromoisoquinoline followed by heterocyclic ring formation to give ellipticine.

Recently several members of the 6-H-pyrido[4,3-b]carbazole class of alkaloids, notably ellipticine (1) and 9-methoxyellipticine (2), have shown significant anticancer activity.[1] As a result, a great deal of interest has been generated in synthetic approaches to these alkaloids.[2] Unfortunately most of these approaches do not allow easy access to a wide variety of derivatives and thus the need for a general and versatile synthetic approach is still present.

In an attempt to maximize versatility, our analysis of the problem indicated that ring A and the isoquinoline portion (rings C and D) should be kept separate until the latter stages of the synthesis. After bonding these two portions together, ring B should be formed in the final step. A description of one such approach (see Scheme I) is given in this paper.

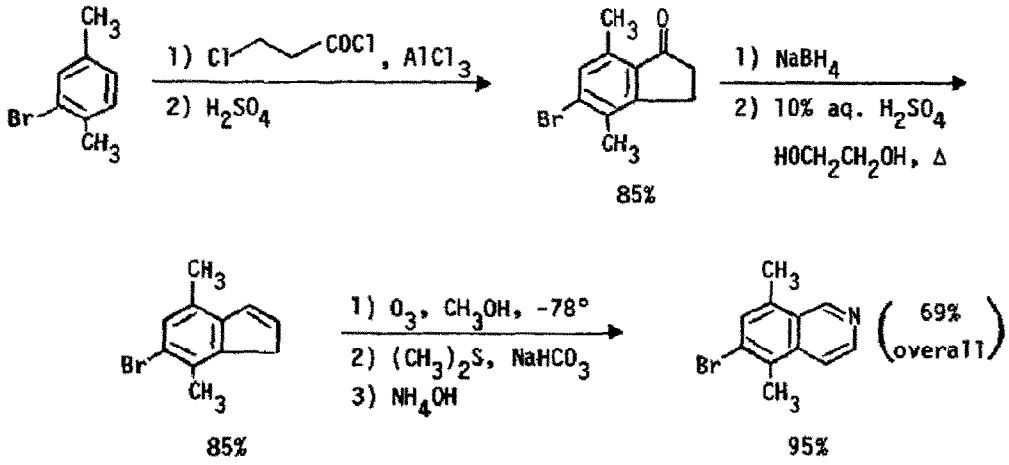


1, X = H
2, X = OCH_3

Scheme I

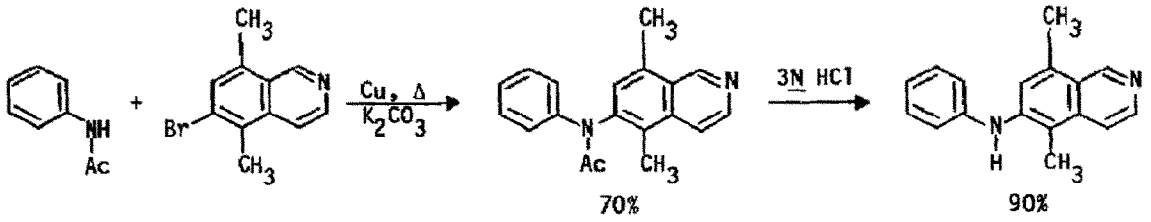
The proposed synthesis of ellipticine has three key elements to it: (1) production of the proper halogenated isoquinoline, (2) coupling with an appropriate acetanilide, and (3) indole formation by either photolytic or palladium-induced cyclization. Synthesis of the 6-bromo-5,8-dimethylisoquinoline[3] proceeded along standard lines previously developed in our laboratories in connection with a general isoquinoline synthesis.[4] This approach is shown in Scheme II and has as its key step the ozonolysis of an indene to give an intermediate homophthalaldehyde which is directly reacted with ammonium hydroxide in a "one pot" procedure to

give the fully aromatic isoquinoline.



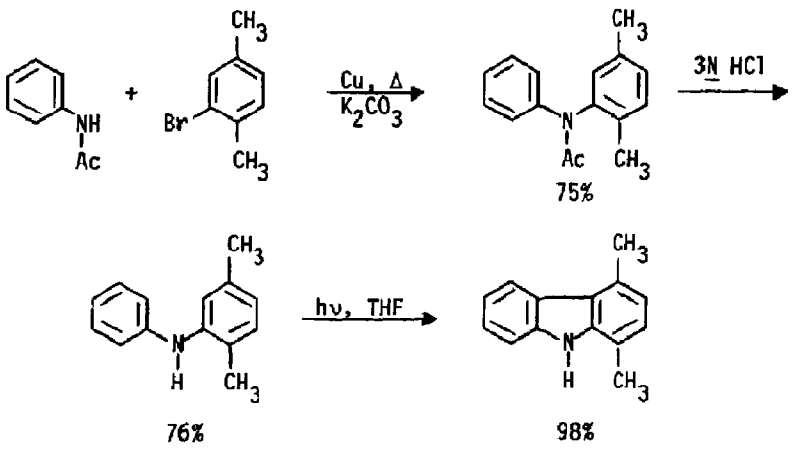
Scheme II

The next reaction in the sequence was the coupling of the bromoisoquinoline with an acetanilide which was carried out using the Goldberg modification of the Ullmann coupling reaction The diarylamide product was then hydrolyzed under acidic conditions to give the desired 6-anilino-5,8-dimethylisoquinoline[3] (see Scheme III).



Scheme III

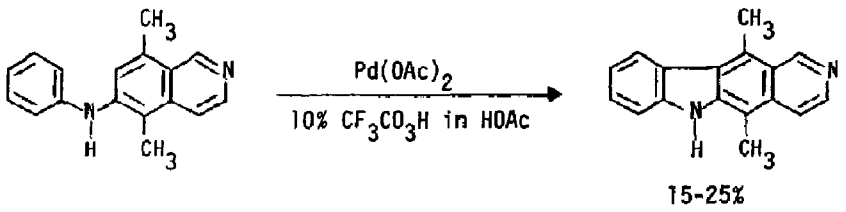
The last step of the sequence involved indole cyclization of the aryl isoquinoline amine to give ellipticine. Initially photochemical cyclization was investigated. It was known that diarylamines gave carbazoles upon photolysis[6] and in fact a model study was carried out to insure that the dimethyl substitution would not be a problem (see Scheme IV). Thus 2-anilino-p-xylene[3] was photolyzed to give 2,5-dimethylcarbazole[3] in excellent yield. Unfortunately when 6-anilino-5,8-dimethylisoquinoline was photolyzed no ellipticine was observed.[7] A control experiment showed that ellipticine was photochemically unstable to the reaction conditions



Scheme IV

needed for significant amounts of the amine to begin to disappear. Thus it is not clear that even if ellipticine were formed during the photolysis reaction it would have been detected.

Next indole cyclization was attempted using palladium acetate.[8] This approach proved to be successful although the yields were not outstanding. It was found that the anilinoisoquinoline could be cyclized using one or two equivalents of palladium acetate in a trifluoroacetic acid, acetic acid solvent system.



(46% based on recovered starting material)

Although the yield of the final step is only moderate, the overall yield of ellipticine[3] is competitive with other synthetic approaches and should allow preparation of a large number of derivatives.

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References and Notes

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8. For formation of carbazole from diphenylamine, see B. Akermark, L. Eberson, E. Jonsson, and E. Pettersson, *J. Org. Chem.*, 40, 1365 (1965).

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