ALKYLATION OF N-HETEROCYCLES VIA THEIR α-AMINO CARBANION

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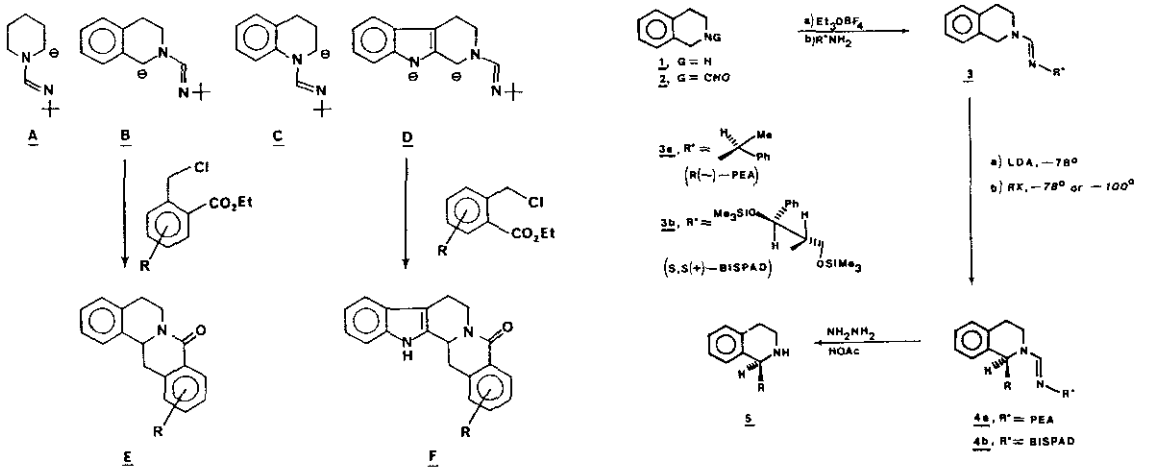
The ability of formamidines to increase the kinetic acidity[1] of a proton α- to an amino group has led to a highly useful route for elaboration of saturated heterocycles.

In this fashion the carbanions A-D have been generated (LDA, S-BuLi, or t-BuLi) and alkylated with a variety of electrophiles[2,3]. In addition to those above, other heterocyclic systems have also been studied (pyrrolidines, thiazolidines, thiazines, indolines) and found to proceed in a similar manner. A number of useful transformations have been uncovered[4] which include rapid entry into the protoberberine (E) and yohimbane (F) nucleus.

Furthermore, we have succeeded in utilizing this heterocyclic C-C bond forming reaction into one which proceeds with simultaneous chirality[5].

Thus, transformation of the tetrahydroisoquinoline 1 into the chiral formamidine 3 gave, after metalation and alkylation, the elaborated formamidine 4. Removal of the chiral auxiliary led to 1-substituted isoquinolines 5 in 90-99% enantiomeric excess (R=Me, Bu, $PhCH_2$). The application of this new, unprecedented C-C bond forming reaction with simultaneous chirality should have far reaching importance in the synthesis of many biologically active substances and this work is being vigorously pursued. Also, we are examining the mechanistic aspects of this formamidine metalation-alkylation and have found a number of very unusual stereoelectronic effects which must be satisfied[6]. Thus, the nature of the process, as well as its synthetic utility is one of great concern to us.



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