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A New Efficient Synthesis of Pyridocarbazoles

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A general synthesis to give a carbazole with an aldehyde or keto functionality at the 3-position is described; these can be converted into pyridocarbazoles, such as olivacine and 1-demethylolivacine.

Pyridocarbazoles are potential anti-cancer compounds¹ and devising efficient syntheses for them continues to be important. We report below a short and general synthesis of pyridocarbazoles, using readily available starting materials, which proceeds in good yields. The syntheses of olivacine (**6b**) and 1-demethylolivacine (6a) are used to illustrate this method.

Indole 3-acetic acid can be readily converted² by BF_{3-} Et₂O-acetic anhydride into the diene (3). The Diels-Alder reaction of (3) with maleic anhydride is known² to be



complicated, as the initial adduct (7) can readily decarboxylate to the diene (8) which can undergo a further Diels-Alder reaction. However, when a chloroethylene, activated by a CN, CHO, or COMe group, was used as the dienophile[†] along with a dehydrohalogenating base in tetrahydrofuran (THF) solvent[‡] at 80 °C the expected thermal decarboxylation was followed by elimination of HCl to give compound (4). In this reaction it was necessary to use a hindered base such as collidine. If a base like dimethylaniline was used, the preferred reaction was the cleavage of the lactone ring to furnish (2; R = Me) (after aqueous workup).

The reaction of (3) with $CH_2=C(Cl)CN$ gave (4a) in 82—85% yield. The CN group of this compound could be converted into CHO in one step using $SnCl_2$ -HCl-diethyl ether or (EtO)₃LiAlH. The yields, however, were poor (5 and 13% respectively). The longer route of hydrolysis of CN to CO_2H (KOH-EtOH-water) followed by reduction to CH_2OH (B₂H₆-THF) and further oxidation to CHO (pyridinium chlorochromate-CH₂Cl₂), provided (4b) in 60% overall yield. In later experiments, (4b) was directly obtained in 76% yield by using the readily available $CH_2=C(Cl)CHO^3$ as the dienophile. Similarly $CH_2=C(Cl)COMe$ (obtained by chlorination of methyl vinyl ketone followed by dehydrochlorination) gave (4c) in 78% yield.

The aldehyde (4b) was converted into 1-demethylolivacine (6a) by the well known procedure,⁴ which involved conversion into the tosyl (Ts) derivative (5a) followed by cyclisation with aqueous HCl-dioxane (72% yield). Under similar conditions the ketone (4c) gave olivacine (6b) only in poor yields. It was noted that in this case, unlike the case of the aldehyde, when the tosyl derivative (5b) was treated with aqueous HCldioxane, no precipitate was obtained. However, when the water content was reduced, a good amount of precipitate could be obtained. The tosyl derivative (5b) was then successfully cyclised to olivacine in 65% yield when only four drops of aqueous HCl was used in dioxane solvent.

It may be noted that, in the above synthesis, R and R' can be varied conveniently.

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⁺ Reaction of chloroethylenes with collidine in THF under identical experimental conditions gave 90% recovery of the starting material, excluding acetylenes as intermediates in the Diels-Alder reaction.

 $[\]ddagger$ When the reaction was carried out in neat collidine (80 °C) a regioisomeric mixture of (4) and (9) was obtained, in 42 and 38% yields respectively.