An Efficient Synthesis of 3-[1-(3-Pyridyl)ethyl]indoles

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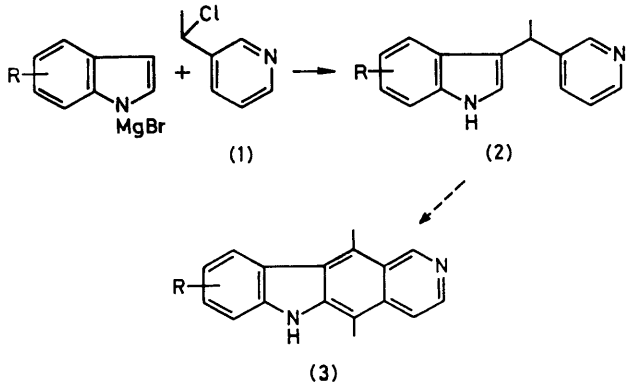
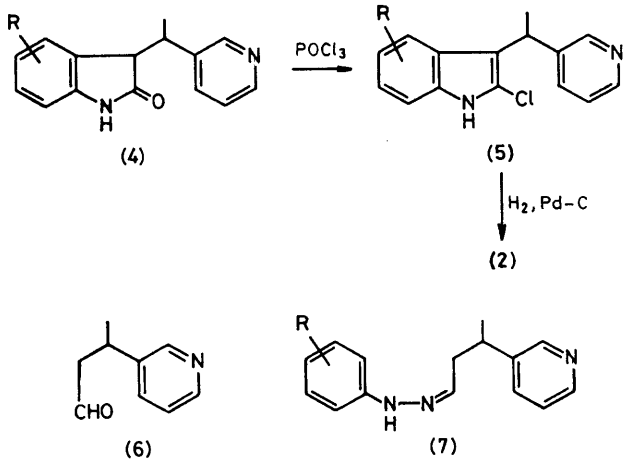
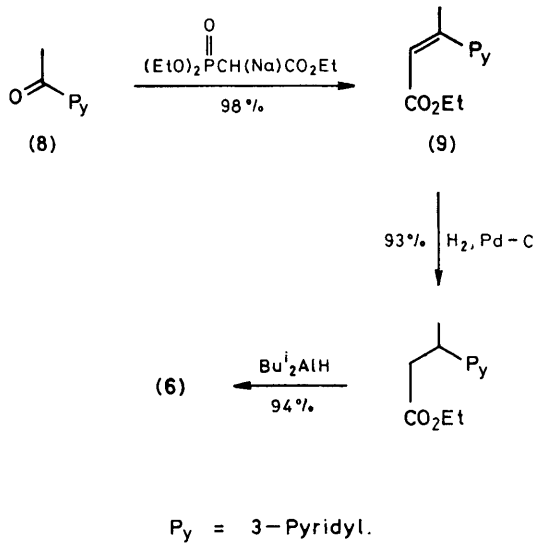
Summary An efficient and versatile synthesis of 3-[1-(3-pyridyl)ethyl]indoles is described; these compounds are important starting materials for the synthesis of ring-A substituted ellipticines.

OUR synthesis of substituted ellipticines from pyridylethylindoles (**2**) → (**3**)[1] is a high-yielding, mild, and versatile process marred only by the relative inaccessibility of the starting materials. Despite much effort[2] we have not been able to improve the productivity of the usual approach, namely reactions between indolylmagnesium halides and the pyridylethyl chloride (**1**). Yields are typically only 10—30% and to this must be added the problem of making substituted indoles themselves.



Kubo and Nakai[3] report that the two-step conversion of oxindoles into pyridylethylindoles [(**4**) → (**5**) → (**2**)] is a practical alternative, but in our hands the route has proved to be unsatisfactory and very expensive in terms of catalyst. A solution to these difficulties lies in the indolisation of hydrazones (**7**) and for this an expeditious synthesis of the aldehyde (**6**) from commercially available 3-acetylpyridine is necessary. We have achieved this through an Emmons–





P_y = 3-Pyridyl.

Wadsworth reaction[4] between 3-acetylpyridine (**8**) and triethyl phosphonoacetate giving the unsaturated ester (**9**) which on hydrogenation at atmospheric pressure over 5% palladium on charcoal and reduction with 1·5 mol. equiv. of Bu^i_2AlH affords the aldehyde (**6**) in 86% yield for the three-step sequence.

The aldehyde (**6**) may be combined with various hydrazines and cyclised under Fischer indolisation conditions to give the required pyridylethylindoles (**2**; R = alkyl, alkoxy, halogen) in high yields, typically 65—80% (in the case of 3-substituted hydrazines both 4- and 6-substituted indoles are formed, the 6-isomers predominating).

A number of new ellipticines, *e.g.* 7-chloro-7-fluoro-, and 7-methyl- have already been synthesised from the appropriate indoles, and others based on the 8- and 10-positions are in preparation.

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[2] D. Watkins, University of Bath, unpublished results.
[3] A. Kubo and T. Nakai, *Synthesis*, 1980, 365.
[4] W. S. Wadsworth, *Org. React.*, 1977, **25**, 73.