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Synthesis of Cyclopent[*b*]indoles by Formal [3+2]-Addition of Indolylmethyl Cations to Alkenes

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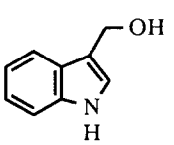
Abstract: *Treatment of indole-2- or 3-methanols with tin(IV) chloride as Lewis acid in the presence of styrenes results in formal [3+2]-addition of the indole stabilised cation to the alkene to give cyclopent[b]indoles with a high degree of stereoselectivity; use of methylcyclohexene as the alkene component gave the cis-fused cyclopent[b]indole* ***17****, which was independently synthesised in enantiomerically pure form from the diketone* ***18****.*

The cyclopent[*b*]indole ring system occurs in a number of indole alkaloids, notably the tremorgenic mycotoxins such as paxilline, paspaline, the lolitrems, penitrems and janthitrems,[1] and the monoterpenoid yuehchukene.[2] We now report a new approach[3] to cyclopent[*b*]indoles based on the formal [3+2]-cycloaddition of the stabilised cation derived from indole-2- or 3-methanols to alkenes.

It is well known that on treatment with acids, indole-3-methanol **1** is readily converted into a stabilised cation **2** which subsequently reacts further to give 3,3'-diindolylmethane.[4] The same product is obtained by reaction of indole itself with formaldehyde,[4] and further examples of 'dimerisation' reactions involving indole stabilised cations (derived from indolemethanols as above or by protonation of vinylindoles) are known.[2a,2d,5]



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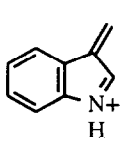
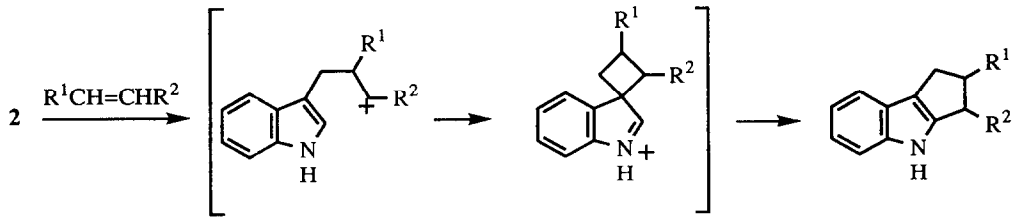


2

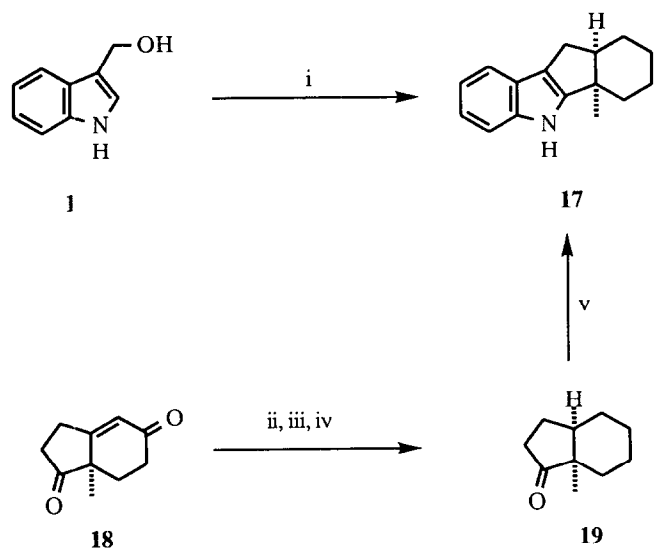
By analogy with the recently reported preparation of dihydroindenes by reaction of benzylic cations with styrenes,[6] it seemed possible that, in the presence of a sufficiently reactive alkene, the 'dimerisation' of indole stabilised cations might be suppressed in favour of a formal [3+2]-addition to the alkene to give cyclopent[*b*]indoles as shown in Scheme 1. This indeed proves to be the case and the reaction provides a simple route to a range of cyclopent[*b*]indoles (Table 1).



Scheme 1

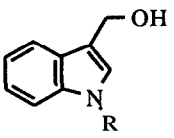
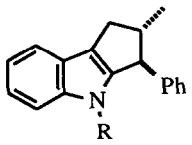
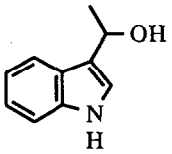
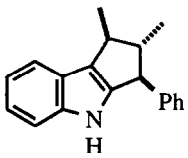
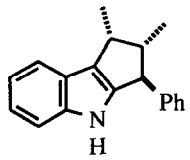
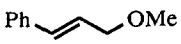
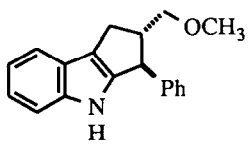
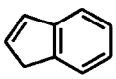
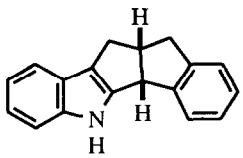
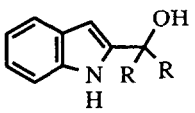
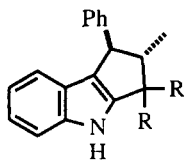
Thus treatment of a mixture of indole-3-methanol **1**, or its *N*-methyl derivative **3**, and β-methylstyrene **4** with tin(IV) chloride at -78°C gave, after aqueous work-up and chromatography, the desired cyclopent[*b*]indoles **5** (55%) and **6** (55%), the *trans*-stereochemistry being proved by NOE difference spectroscopy. The substituted indole-3-methanol **7** reacts similarly with the styrene **4** to give the cyclopent[*b*]indoles **8** and **9** (63% combined) as a 1:10 mixture of diastereomers. Thus, in common with the related reactions involving benzylic cations,[6] the formal [3+2]-addition reactions of indole stabilised cations with alkenes are highly stereoselective; not only is the original alkene stereochemistry preserved, but the new stereocentre at C-1 is also formed stereoselectively. Angle has speculated about the origin of the stereocentre in his related cationic cyclisations,[6] but the exact mechanism remains unknown, although in the case of our indoles we assume that a 4-membered spiroindolenine must be an intermediate (Scheme 1).[7]

The method was extended to other alkenes, (the allylic ether **10** and indene), and to the indole-2-methanols **13** and **14** to give the corresponding cyclopent[*b*]indoles (**11**, **12**, **15** and **16**) stereospecifically albeit in poorer yield (Table 1). Finally, the use of alkenes other than styrenes was investigated. Although no cyclopentindoles could be isolated from reactions involving dihydropyran, 1-diethylaminocyclohexene or allyltri-isopropylsilane, the use of 1-methylcyclohexene gave the octahydroindenoindole **17** in 18% yield (Scheme 2). The structure and *cis*-stereochemistry was confirmed by an independent synthesis of enantiomerically pure (–)-**17**, starting from the known *cis*-fused ketone **19**,[8] prepared by reduction[9] of the enantiomerically pure (R)-diketone **18**[10] (Scheme 2).



Scheme 2. *Reagents*: i, 1-methylcyclohexene, $SnCl_4$, CH_2Cl_2, -78°C; ii, $NaBH_4$, CF_3CO_2H; iii, H_2, Pd-C, EtOH; iv, PCC, CH_2Cl_2; v, $PhNHNH_2$, H^+.

Table 1. Synthesis of cyclopent[*b*]indoles by tin(IV) chloride mediated reaction of indolemethanols with alkenes

Indole	Alkene	Product	Yield (%)
 **1** R = H **3** R = CH_3	 **4** [E:Z = 9:1]	 **5** R = H **6** R = CH_3	**5** 55 **6** 55
 **7**	4	 **8**  **9**	**8+9** 63 [**8**:**9** = 1:10]
1	 **10**	 **11**	22
1		 **12**	19
 **13** R = H **14** R = CH_3	4	 **15** R = H **16** R = CH_3	**15** 27 **16** 17

General Procedure for Cationic Cyclisation

Tin(IV) chloride (4 equiv) was added slowly to a stirred solution of the indolemethanol (1 equiv) and the alkene (2 equiv; 5 equiv in the case of methylcyclohexene) in dry dichloromethane under nitrogen at -78°C. After the addition was complete, the mixture was stirred for 10 min at -78°C, allowed to warm to room temperature, and stirred for a further 40 min (15 h for indolemethanol **13**). The solution was poured into saturated aqueous sodium hydrogen carbonate, and extracted with dichloromethane. The extracts were washed with water, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel to give the cyclopent[*b*]indole.

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