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A NEW SYNTHESIS OF 1,2-DISUBSTITUTED CARBAZOLES. ELECTROPHILIC CYANATION WITH VIEHE'S REAGENT.

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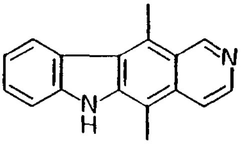
ABSTRACT: Reaction of 2-ethylindole and 2-benzylindole with methyl vinyl ketone gives 1,2-dimethylcarbazole and 2-methyl-1-phenylcarbazole respectively. On thermolysis of the salt 11, obtained from the reaction of 2-(2-methylpropenyl)indole (7a) with Viehe's salt (10), the corresponding nitrile 13 is formed.

The interest in the chemistry of carbazoles and related condensed systems has continued to grow.[1] Among the many alkaloids with a carbazole moiety some are known to possess profound physiological activity. Ellipticine (1)[2], rebeccamycin (2)[3] and staurosporine (3)[4] are just a few. Other carbazole alkaloids are of considerable taxonomic importance as they have a substitution pattern exclusively found in some genera of one plant family *e.g.* the 3-methylcarbazoles from the *Rutaceae*[5]. The recently isolated[6] alkaloid dihydroxygirinimbine (4) is one example.



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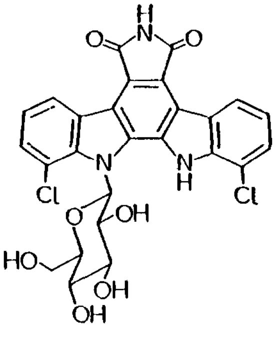

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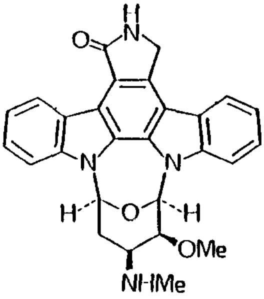

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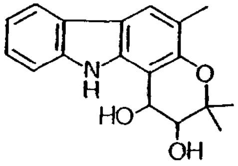
Hyellazole (5)[7], carbazomycine A (6a)[8] and the antibiotic carbazomycine B (6b)[8] can be considered as hydroxylated and/or methoxylated 1,2-disubstituted carbazoles, but in spite of their relative simplicity and the multitude of carbazole syntheses[1], no general synthetic route to 1,2-disubstituted carbazoles from simple and inexpensive starting materials is available.



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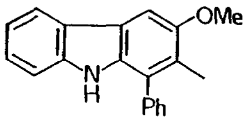

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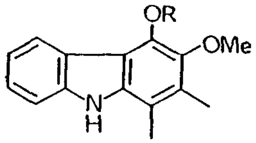
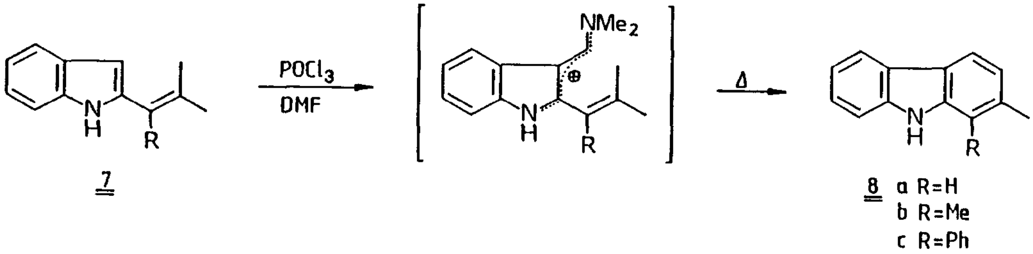


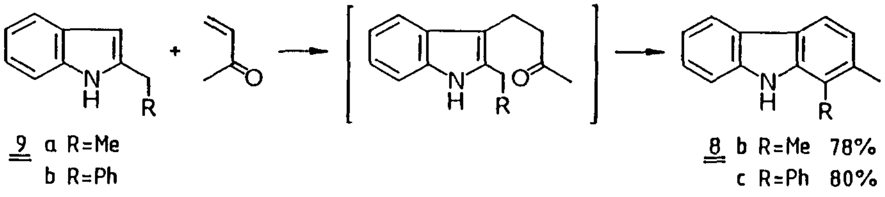
6 a R=Me
b R=H

In a previous paper[9], we reported the synthesis of 2-methylcarbazole (8a) from 2-(2-methylpropenyl)indole (7a) and the Vilsmeier reagent, $POCl_3$/DMF (Scheme 1). Unfortunately only low yields of the analogs 8b and 8c could be obtained from 7b and 7c[10] by this method.



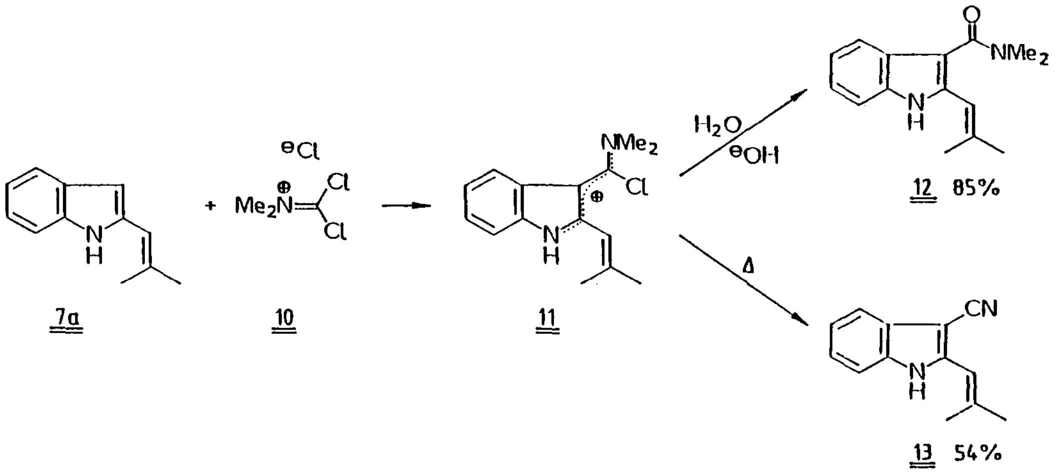
Scheme 1

The difficulties in obtaining larger amounts of 8b and 8c were overcome by using a different approach. Indoles will react at their 3-position in a 1,4-addition process with α,β-unsaturated ketones, and under suitable reaction conditions the 2-(3-indolyl)ketones thus formed will cyclize[11] to carbazoles (Scheme 2). Refluxing 2-ethylindole (9a) or 2-benzylindole (9b)[12] with methyl vinyl ketone in acetic acid containing a catalytic amount of palladium on charcoal gave good yields of 8b and 8c. The use of appropriately substituted methyl vinyl ketones in combination with hydroxylation/methoxylation methods as a synthetically viable route to the alkaloids 5 and 6 is now under investigation.

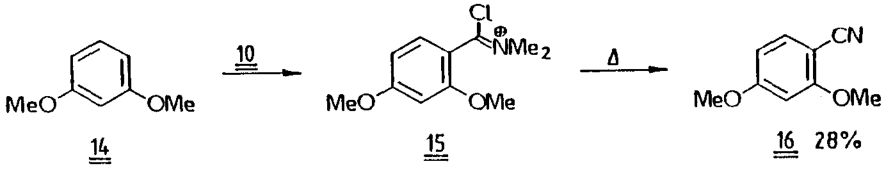


Scheme 2

To examine whether the reaction of 2-vinylindoles with "C$_1$-units" other then those mentioned above would give 4-hetero-substituted carbazoles, **7a** was treated with dichloromethylene dimethylimmonium chloride (Viehe's salt, **10**).[13] The salt **11** formed could be isolated[14] or readily hydrolyzed[14] to the corresponding amide **12** (Scheme 3). On thermolysis (reflux in 1,2-dichlorobenzene) the intermediate **11**, instead of cyclization, lost two equivalents of MeCl[15] giving the nitrile **13**. This reaction could be extended to other indoles as well as to other aromatic (*e.g.* 1,3-dimethoxybenzene **14**) and heteroaromatic (*e.g.* pyrrole) systems, and thus constitutes a new nitrile synthesis.[16] It should be noted that **14** is giving the corresponding nitrile **16** under much milder reaction conditions (reflux in MeCN) than those necessary for the indole systems, reflecting the larger resonance stabilisation of **11** as compared to **15** (Scheme 4).



Scheme 3



Scheme 4

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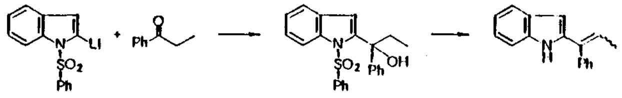
10. (a) 7c was formed directly (no intermediate was obtained)[10b] when 1-benzenesulfonyl-2-lithioindole (i) was treated with isobutyrophenone. For other examples of *in situ* debenzenesulphonylation of lithiated indoles and pyrroles *cf.* refs. 10c and 10d.

(b) The reaction of i with propiophenone is reported[7a] to give an adduct ii which had to be deprotected/dehydrated to give the 2-vinylindole iii.



i ii iii

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12. (a) 9b was obtained by an $EtAlCl_2$- (or better PPA-) catalyzed rearrangement of 3-benzylindole, *cf.* refs 12b and 12c.

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15. (a) This known[13b,15a] phenomenon has not been utilized for a general nitrile synthesis. For a related synthesis of nitriles involving loss of alkyl chlorides from transient imidoyl species, *cf.* ref. 15c.

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16. (a) For leading references concerning electrophilic cyanations, see Y. Tamura, M. Adachi, T. Kawasaki, H. Yasuda and Y.Kita, *J. Chem. Soc., Perkin I*, 1132 (1980).

(b) In this connection Lohaus'[16c] and Vorbrüggen's[16d] nitrile synthesis is of interest. This method involves electrophilic attack of chlorosulphonyl isocyanate on suitable aromatic systems, *e.g.* indole, followed by treatment with DMF or triethylamine.

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