Regioselective Claisen Rearrangements in Indoles

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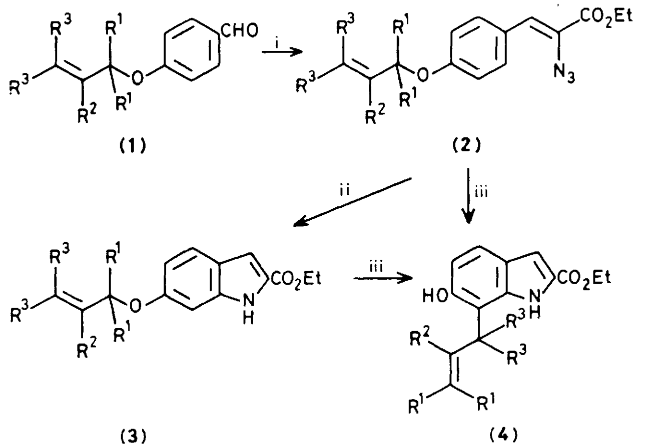
Heating the 6-allyloxyindoles (**3**), readily prepared from the benzaldehydes (**1**), gives the corresponding 7-allylindoles (**4**) by regioselective Claisen rearrangement; the 7-linalylindole (**10**) is prepared from 4-geranyloxybenzaldehyde by a similar sequence.

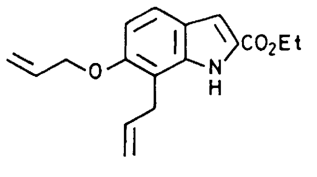
Regioselectivity in the Claisen rearrangement[1] has been known for many years, although recently it has been the subject of renewed interest.[2,3] Although thermal rearrangements of heteroaromatic allyl ethers are known,[1,4] there is only one report of Claisen rearrangements in the benzene ring of indoles, in which 5-allyloxyindole and ethyl 5-allyloxyindole-2-carboxylate gave the 4-allyl-5-hydroxyindoles regioselectively on heating.[5] It has now been shown that rearrangement of 6-allyloxyindole-2-carboxylates proceeds selectively to the 7-position, in a reaction which can be extended to the preparation of 7-prenyl- and 7-linalyl-indoles.

The requisite 6-allyloxyindole-2-carboxylates† are easily prepared in two steps (40—60%) from the corresponding known 4-allyloxybenzaldehydes (**1**) by base condensation with ethyl azidoacetate followed by thermolysis of the resulting azidocinnamates (**2**) in boiling toluene (Scheme 1).[6] Claisen rearrangement of the indole (**3a**) occurred readily in boiling bromobenzene (156 °C) to give the 7-allyl-6-hydroxyindole (**4a**) (71%). No products resulting from rearrangement to the 5-position were isolated. That rearrangement had occurred selectively to the 7-position was immediately clear from the ^{1}H n.m.r. spectrum which showed the vicinal protons 4-H and 5-H as two doublets (*J* 9 Hz). The fact that rearrangement to the 5-position is strongly disfavoured, by what has been variously described in other systems as aromatic bond fixation, mesomeric, or partial resonance effects,[3] was further demonstrated when the allyl ether (**5**), prepared from (**4a**), was recovered unchanged after heating in bromobenzene. Prolonged heating caused a slow decomposition, from which no recognisable products were obtained. Thus, in exact parallel to the well known regioselective Claisen rearrangement of 2-allyloxynaphthalene, the transition state leading to the intermediate (**6**) which retains some aromatic stabilisation must be substantially favoured over that leading to (**7**).

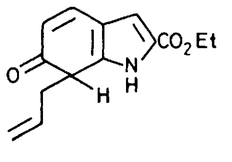


a; $R^1 = R^2 = R^3 = H$
b; $R^1 = R^3 = H, R^2 = Me$
c; $R^1 = Me, R^2 = R^3 = H$
d; $R^1 = R^2 = H, R^3 = Me$

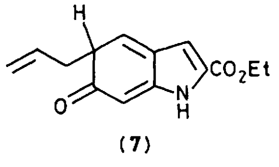
Scheme 1. *Reagents:* i, $N_3CH_2CO_2Et$, NaOEt, EtOH, −10 °C; ii, PhMe, reflux; iii, PhBr, reflux, or see text.



(**5**)



(**6**)

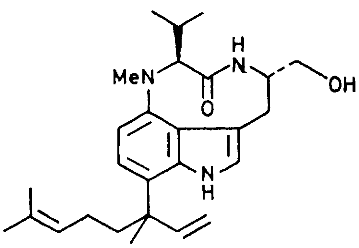


(**7**)

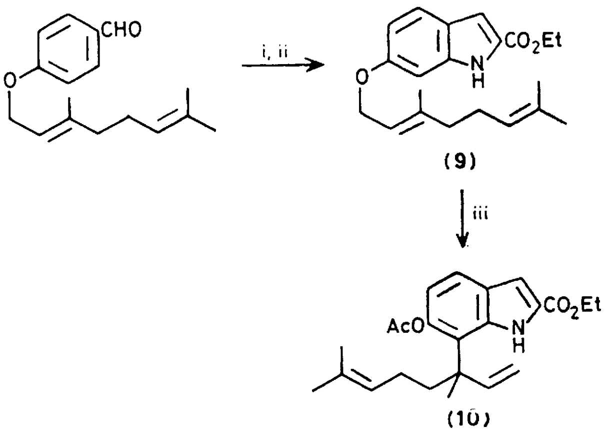
When the azide (**2a**) was heated in boiling bromobenzene, concomitant indole formation and Claisen rearrangement occurred to give the indole (**4a**) (78%). Similarly, thermolysis of the azides (**2b**) and (**2c**) in bromobenzene resulted in concomitant indolisation and rearrangement to give the corresponding 7-methallyl- and 7-prenyl-indoles (**4b**) (65%) and (**4c**) (61%) respectively. Subsequently it was found that Claisen rearrangement of the isoprenyl ether occurred at lower temperature, and the unrearranged indole (**3c**) could not be isolated even after short refluxing of the azide (**2c**) in toluene.

Since Claisen rearrangements of ethers which bear γ-alkyl substituents on the allyl group are often complicated by further rearrangements of the initial product (the so-called abnormal Claisen rearrangement[1]), the rearrangement of the 6-prenyloxyindole (**3d**) was carried out differently. Thus, heating the indole (**3d**) in a mixture of acetic anhydride‡ and *N,N*-dimethylaniline (1 : 1 v/v) gave only the normal Claisen product, the 7-isoprenyl-6-hydroxyindole (**4d**) (89% as its *O*-acetate).

To extend the scope of the indolisation–Claisen rearrangement sequence, and in connection with synthetic studies on lyngbyatoxin A (**8**), a highly toxic marine indole alkaloid,[10]



(**8**)



Scheme 2. *Reagents:* i, $N_3CH_2CO_2Et$, NaOEt, EtOH, −10 °C; ii, PhMe, reflux; iii, Ac_2O, $PhNMe_2$, reflux.

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† The structure of all new compounds was supported by spectroscopic methods, and with the exception of azides, by elemental microanalysis.

‡ The use of acetic anhydride to intercept the initial phenolic Claisen rearrangement product was first reported by Fieser *et al.* (ref. 7). Various modifications have subsequently been used (*e.g.* refs. 8 and 9).

the conversion of 4-geranyloxybenzaldehyde[11] into the indole (**10**) was investigated (Scheme 2). Condensation of the aldehyde with ethyl azidoacetate, followed by thermolysis of the resulting azide gave the indole (**9**) which, without further purification, was heated in acetic anhydride-*N*,*N*-dimethylaniline to give the indole (**10**) (32% from 4-geranyloxybenzaldehyde) containing the required 7-linalyl substituent, the introduction of which forms a key step in any approach to (**8**). Since, in principle, the additional 2- and 6-substituents may be removed if necessary, although the corresponding aza- and thia-Claisen rearrangements might lead to more useful compounds for this latter transformation, the regioselective Claisen rearrangement provides a useful route to a range of 7-allylindoles.

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