A New Approach to 4-(2-Aminoethyl)indoles *via* Claisen *ortho*-Amide Rearrangement of 3-Hydroxy-2-methoxyindolines

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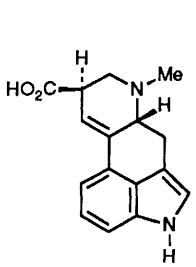
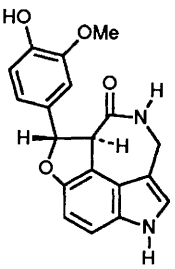
Reaction of 3-hydroxy-2-methoxyindoline (**4**) with the amide acetal (**5**) gives 4-carbamoylmethyl-indoline (**7**) and -indole (**8**), which are converted into 4-(2-aminoethyl)indole (**10**) by treatment of the indoline (**7**) with hydrogen chloride followed by sodium hydroxide to form the indole (**8**), and then by reduction of the indole (**8**) with lithium aluminium hydride.

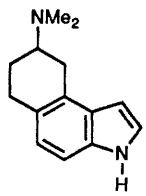
The 4-(2-aminoethyl)indole system is a key structural feature of many biologically active indoles, such as the well known ergot alkaloids [*e.g.*, lysergic acid (**1**)],[1,2] the recently isolated serotobenine (**2**),[3] and synthetic dopamine agonists [*e.g.*, (**3**)].[4] Although the direct introduction of the substituent into the indole 4-position using the intermolecular reaction is difficult to achieve with few exceptions,[5] the intramolecular reaction of 3-substituted indoles and indolines is more effective for accomplishing functionalisation at the indole 4-position.[6] Examples involve cyclisation such as the intramolecular alkylation,[7] photoalkylation,[8] and Friedel–Crafts acylation reactions.[9] To date, however, no approach has utilised the rearrangement of the 3-substituted indole and indoline; the only known attempt to carry out the Cope rearrangement of 3-allylindolines was unsuccessful.[2] We now report a new approach to the 4-(2-aminoethyl)indole system which involves the Claisen *ortho*-amide rearrangement of the 3-hydroxy-2-methoxyindoline (**4**) with the amide acetal (**5**).



(1)

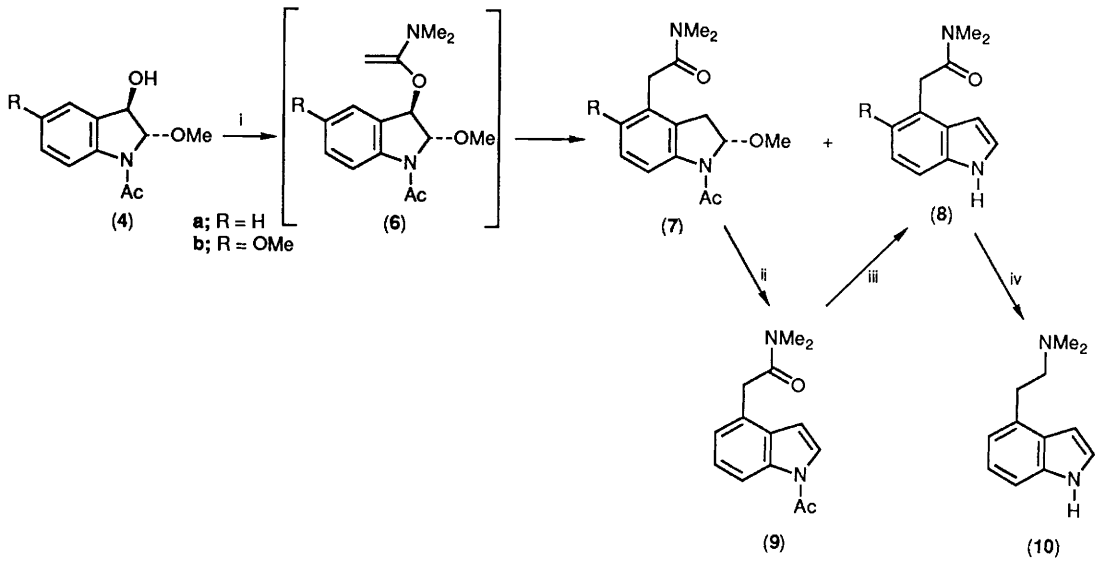


(2)



(3)

The indolines (**4a, b**) were readily obtained by our previously described method,[10] and the amide acetal (**5**) was prepared by Meerwein's method.[11] When the indoline (**4a**) was treated with the amide acetal (**5**) in refluxing *o*-dichlorobenzene for 14 h, the Claisen rearrangement of an inter-



Scheme 1. *Reagents and conditions*: i, $MeC(OEt)_2NMe_2$ (**5**), *o*-dichlorobenzene, reflux, 14 h; ii, HCl, $CHCl_3$, room temp., 2 h; iii, NaOH, MeOH, room temp., 2 h; iv, $LiAlH_4$, THF, reflux, 22 h.

mediary 3-vinyloxyindoline (**6**) occurred to give 4-carbamoylmethyl-indoline (**7a**) and -indole (**8a**) in 11 and 33% yields.† The indoline (**7a**) was smoothly converted into the indole (**8a**). Thus, treatment of (**7a**) with hydrogen chloride in chloroform gave 1-acetylindole (**9**) in 84% yield, which was deacetylated with sodium hydroxide in methanol to the indole (**8a**) (90%). Similar Claisen *ortho*-amide rearrangement of the 5-methoxyindoline (**4b**) with (**5**) afforded 4-carbamoylmethylindoline (**7b**) and the indole (**8b**) in 27 and 18% yields. Reduction of the indole (**8a**) with lithium aluminium hydride ($LiAlH_4$) in tetrahydrofuran (THF) gave the 4-(2-aminoethyl)indole (**10**) in 63% yield.

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† All new compounds gave satisfactory elemental analyses and spectral data.