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C-2 SIDE CHAIN ALKYLATION OF 2-METHYL-3-ALKYLINDOLES VIA 3-METHOXYINDOLENINES:

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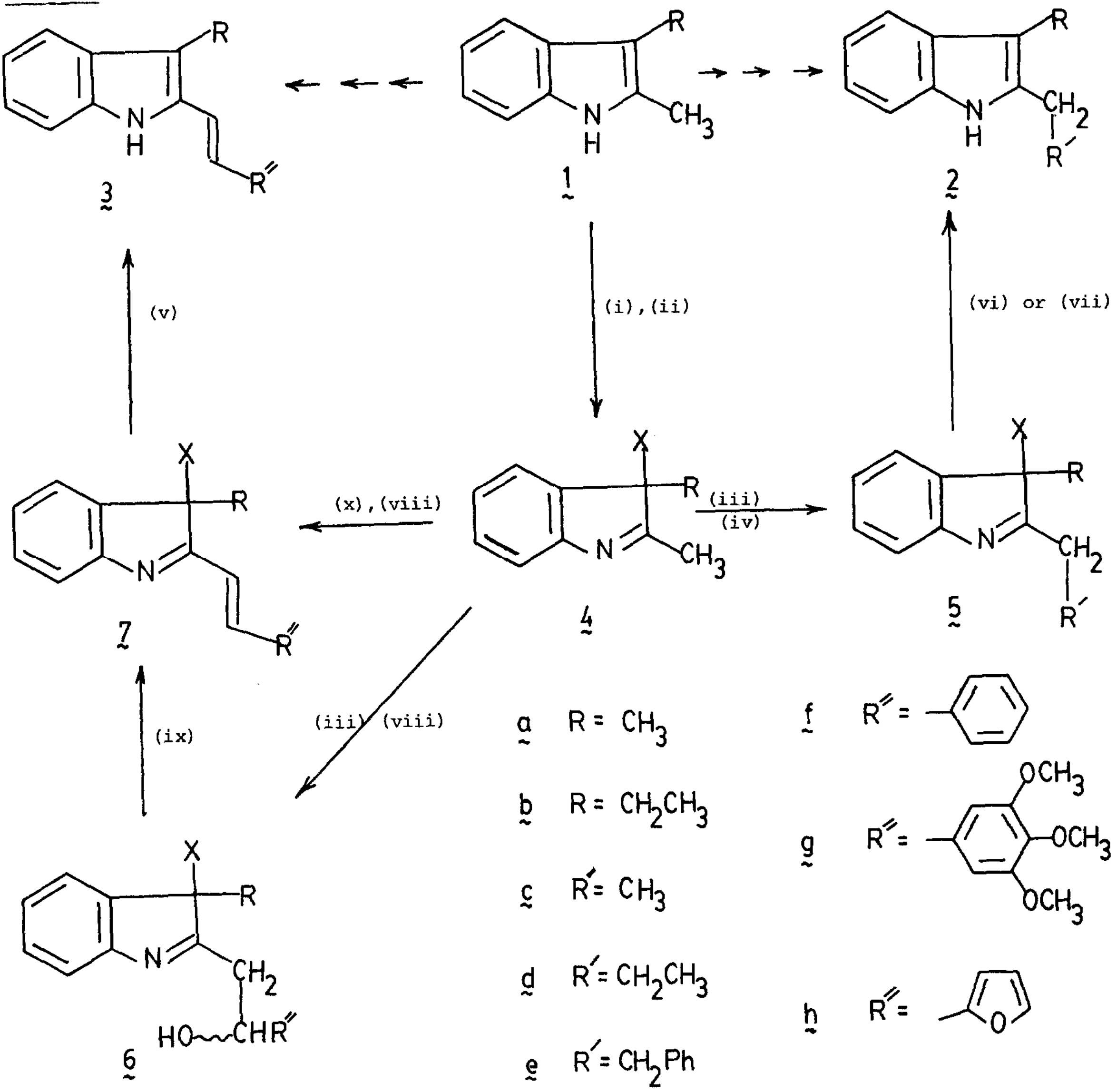
3-Methoxyindolenines derived from 2-methyl-3-alkylindoles by bromination-methanolysis undergo base induced alkylations and aldol condensations at the C-2 methyl group. The modified indolenines can be efficiently converted to C-2-side chain alkylated indoles by reduction with lithium-aluminum hydride or zinc.

2-Methyl-3-alkylindoles are readily available from methylalkyl ketones by the Fischer indole synthesis[1]. During the course of synthetic studies in our laboratory it occured to us that a method of alkylation at the α-carbon at C-2 of such indoles would be a very useful approach to other 2,3-dialkylindoles not readily available by direct methods. Herein, we describe and illustrate a synthetic methodology for effecting such transformations.

Our strategy involves conversion of the indole system, 1, reversibly to a corresponding indolenine 4. As a result of this transformation, the hydrogens on the α-carbon at C-2 are rendered sufficiently acidic that base-catalyzed alkylation to give 5 or aldol condensation to give 7 via 6 at this site becomes feasible. Reductive regeneration of the indole system would then complete the cycle to give 2 or 3. In order that such a reaction sequence be successful the substituent X must be stable to the strongly basic conditions of the alkylation or aldol condensation steps and also be able to undergo facile elimination as HX in the reductive steps leading to 2 or 3.

With this strategy in mind, we have recently developed an efficient method for the conversion of 2,3-dialkylindoles to the corresponding 3-methoxyindolenines 4 ($X = OCH_3$)[2,3]. Treatment of a solution of 4a with lithium diisopropylamide in dry THF at -78° yielded the corresponding carbanion which upon treatment with an appropriate alkyl halide yielded the C-2-side chain alkylated indolenine 5. Reduction of 5 with lithium aluminum hydride in THF yielded, after workup and chromatography, the C-2 side chain alkylated indole 2. The overall yields (see the Table) of 2 from 1 are in the range of 39 to 64%. In one case (2ac) an improved yield of alkylated indole was obtained by the use of sodium borohydride in methanol as the reducing agent. Under these conditions the intermediate methoxyindoline

SCHEME 1:



Reagents:

(i) $Br_2/Et_3N/CH_2Cl_2$; (ii) CH_3OH/p-TSA; (iii) LDA/THF; (iv) R'I/THF; (v) Zn (activated)/ $NaOH/H_2O$/Et OH; (vi) LAH/THF; (vii) {(a) $NaBH_4$/MeOH, (b) excess $HOAc/CH_2Cl_2$}; (viii) R"CHO; (ix) HOAc; (x) $NaOH/H_2O$/MeOH/reflux.

SCHEME 2:

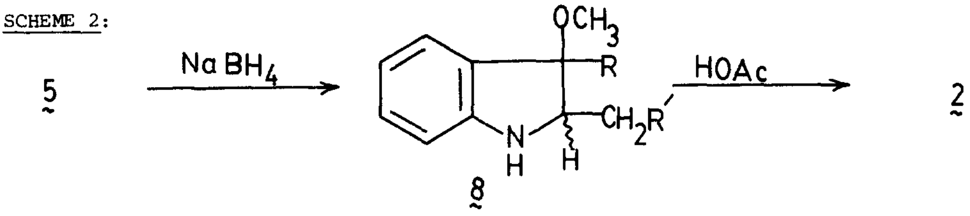
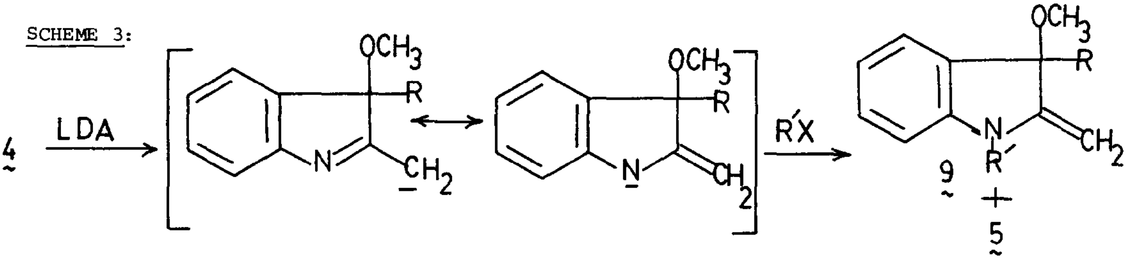


TABLE:

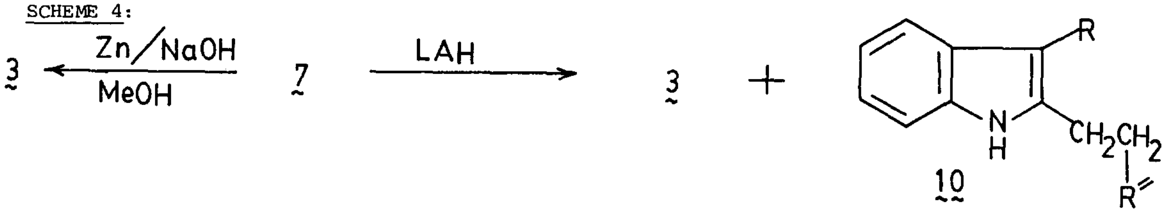
Starting Material	Product	Overall % Yield
1a	2ac	64^a, 73^b
1a	2ad	64^a
1a	2ac	39^a
1b	2bc	43^a
1a	3af	75^c, 72^d
1a	3ag	64^c
1a	3ah	0^c, 64^d

(a) via LAH reduction; (b) via Na BH_4 reduction; (c) via equilibrium aldol condensation conditions; (d) via 6.

SCHEME 3:



SCHEME 4:



8 was obtained as a mixture of diastereomers and was converted to the indole by brief treatment with acetic acid. In other cases the indole products appeared to be unstable to the acidic conditions used and pure products could not be obtained.

It should be noted that 2ad, 2ac and 2bc are not available by simple Fischer indole synthesis. In the case of 2ad and 2bc the overall yields quoted are significantly improved over those reported for the preparation of these indoles from skatole (28%)[4] and 3-ethylindole (< 30%)[5] respectively. N-alkylation (see Scheme 3) becomes a significant side reaction (∿5-10%) when alkyl bromides are utilized in the place of alkyl iodides, presumably reflecting the tendency of the harder electrophiles[6], the alkyl bromides, to react with the harder nucleophilic site, nitrogen, of these ambident nucleophiles (see Scheme 3).

In addition, we have found that the methoxyindolenines, **4**, react readily with aromatic aldehydes in refluxing methanolic sodium hydroxide to give the dehydrated crossed-aldol products, **7af** and **7ag**, in good yield (each in 79% yield from **1a**)[7]. Under the same conditions, furfural underwent extensive decomposition and no aldol product was obtained. However, the carbanion generated from **4a** with LDA condensed with furfural at -40° with warming to room temperature to give the unstable aldol product **6ah** as a mixture of diastereomers. Treatment of **6** with acetic acid yielded **7ah** in **71**% overall yield from **1a**. Similarly, benzaldehyde was converted to **7af** by this two step procedure in 76% yield.

Reduction of these indolenines with LAH yielded mixtures of the indoles **3** and the saturated side chain system **10** (see Scheme 4). However, conversion of these indolenines, **7**, to the indoles **3** could be effected smoothly with activated zinc[8] in refluxing methanolic sodium hydroxide (see the Table).

Continuing studies in this laboratory are concerned with the application of this synthetic methodology to the synthesis of indole containing natural products.[9]

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REFERENCES:

1. R.K. Brown in "Indoles" Part 1, W.J. Houlihan, Ed., Wiley-Interscience, New York, N.Y., 1972; R.J. Sundberg, "The Chemistry of Indoles", Academic Press, New York, N.Y., 1970.
2. G.I. Dmitrienko, Heterocycles, 12, 1411 (1979); G.I. Dmitrienko, E.A. Gross and S.F. Vice, Can. J. Chem., 58, 808 (1980); E.A. Gross, S.F. Vice and G.I. Dmitrienko, Can. J. Chem., 59, 635 (1981).
3. For other preparations of 3-methoxyindolenines see: P.G. Gassman, G.A. Campbell, and G. Mehta, Tetrahedron, 28, 2749 (1972); R.J. Owellen, J. Org. Chem., 39, 69 (1970).
4. A.H. Jackson and P. Smith, Tetrahedron, 24, 2227 (1968).
5. A.H. Jackson and A.E. Smith, Tetrahedron, 21, 989 (1965).
6. W.J. le Noble and H.F. Morris, J. Org. Chem., 34 1969 (1969); G. Brieger and W.M. Pelletier, Tetrahedron Lett., 3555 (1965).
7. For a different approach to 2-(2-arylvinyl) indoles and comments on their potential synthetic utility see: J.A. Eenkhorn, S.O. de Silva and V. Snieckus, Can. J. Chem., 51, 792 (1973).
8. K. Tsuda, E. Ohki, and S. Nozoe, J. Org. Chem., 28, 783 (1963).
9. For elegant applications of indolenine reactivity in the synthesis of indole natural products see: M.E. Kuehne, T.H. Matsko, J.C. Bohnert, and C.L. Kirkemo, J. Org. Chem., 44, 1063 (1979) and references cited therein.

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