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NEW DIHYDROQUINOLINES SYNTHESIS VIA TERTIARY AZIDES

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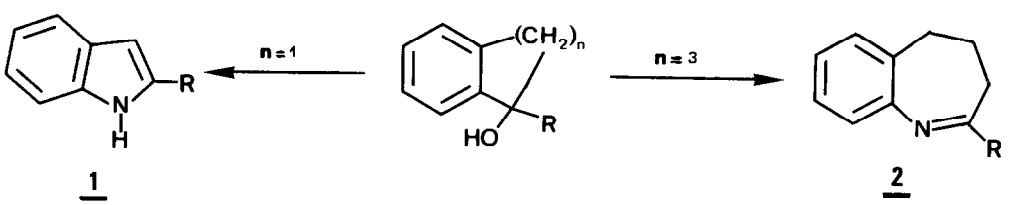
Abstract: When applied to tertiary alcohols of the indane series, the SCHMIDT reaction allows the synthesis of dihydroquinolines substituted on the -2 position. The latter are aromatised in the corresponding quinolines using triphenylmethyl perchlorate.

We have shown that the SCHMIDT reaction applied to benzocyclanic tertiary alcohols leads, after ring expansion, to heterocycles which were all substituted on the carbon atom in the α-position relative to nitrogen (1-3).

In this way, we have previously described a new method for the synthesis of indoles 1 (2) and 3,4-dihydro 5H-benzo (b) azepine 2 (3) both substituted on -2 position (Scheme 1).



1 2

Scheme 1

We describe now the results obtained when this reaction is applied to α-indanols (n = 2, Scheme 1). In this series, only examples relative to fluorenol derivatives are found in the literature (4).

The tertiary alcohols 3(a-c) were prepared by adding Grignard reagents to α-indanone whereas the alcohol 3d (2) was obtained by the addition of (α-picolyl) lithium according to standard procedures.

In order to extend the SCHMIDT reaction to trisubstituted double bonds, the olefins 4a and 4c were prepared by dehydration of the corresponding alcohols 3a and 3c.

An attempt to isolate the 1-azidoindanes 5 by treating corresponding tertiary alcohols 3 with the

HN_3/BF_3-Et_2O/ benzene reagent, was unsuccessful as the main products formed during this reaction were the olefins 4. Similar results (3) have already been obtained in other series, and are due to the great instability of the intermediary azides formed which lead to the very stable olefins 4 by a loss of the azido group complexed by the boron trifluoride (Scheme 2).

However, as we have previously shown (2, 6), it is possible, by directly treating the tertiary alcohols 3 (or trisubstituted olefins 4) with hydrazoic acid and with concentrated sulfuric acid in benzene (conditions of the SCHMIDT reaction), to obtain the same ring expansion products as those obtained by acid-catalysed breakdown of tertiary azides.

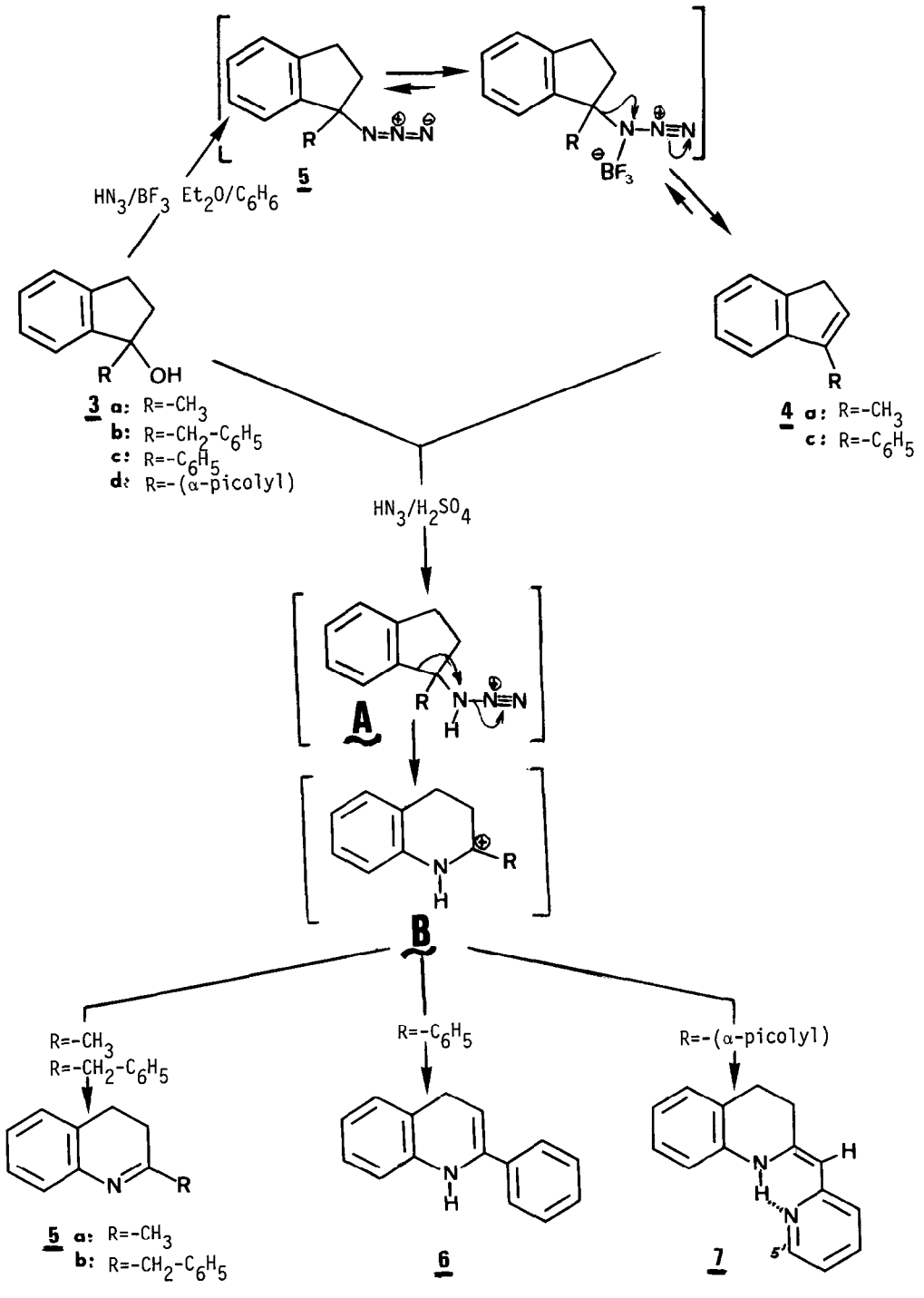
In this way, the treatment of 1-hydroxy 1-methyl indane 3a (7) or of 1-methyl indene 4a with HN_3-H_2SO_4 reagent leads, after usual work-up and acid-base treatment to 3,4-dihydro 2-methyl quinoline 5a (Scheme 3) (Yield: 35%; pale yellow oil; I.R.: ν(C=N): 1640 cm^{-1}; N.M.R. (δ ppm/T.M.S.-$CDCl_3$): (-CH_3-2) 2,10, s, 3H; (-CH_2-3) 2,35, m, 2H; (-CH_2-4) 2,70, m, 2H; (aromatics) from 6,70 to 7,50, m, 4H).

In the same conditions 1-benzyl 1-hydroxy indane 4b (8) gives the 2-benzyl 3,4-dihydro quinoline 5b (Scheme 3) (Yield: 30%; unstable oil; I.R.: ν(C=N): 1640 cm^{-1}; N.M.R.: (-CH_2-3 and -4) from 2,10 to 2,90, m, 4H; (-CH_2 of the substituent) 3,80, s, 2H; (-C_6H_5) 7,25, s, 5H; (aromatics) from 6,80 to 8,10, m, 4H).

However, this reaction does not always lead to an endocyclic imine. In fact, the stabilisation of the intermediary carbocation B by loss of an α-proton results in the most thermodynamically stable product, i.e. with maximum conjugation (Scheme 2). So, 1-hydroxy 1-phenyl indane 3c (8) gives an enamine: the 1,4-dihydro 2-phenyl quinoline 6 (Scheme 3) (Yield: 91%; pale yellow leaflets; F=76-78°C; N.M.R.: (-CH_2-4) 2,85, d (J=2Hz), 2H; (-H-3) 7,15, t (J=2Hz), 1H; (aromatics and NH) from 7,20 to 8,40, m, 10H).

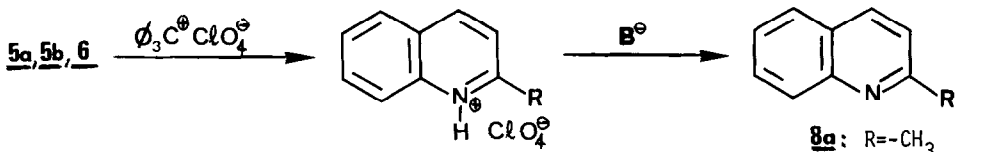
(The structure of this product can be compared to that of 4H-flavene which shows the same coupling constants in N.M.R.)

Finally, treatment of 1-hydroxy 1-(α-picolyl) indane 3d (9) leads by preferential loss of a particularly mobile benzylic proton to an exocyclic enamine: the 2-(α-picolylidene) 1,2,3,4-tetrahydro quinoline 7 (Scheme 2) (Yield: 93%; orange-yellow crystals; F(ether-ethanol) = 155-157°C; I.R.: ν (C=C): 1635 cm^{-1}; absence of N-H band; N.M.R.: (-CH_2-3 and -4) 2,60, m, 4H; (-H ethylenic) 5,05, s, 1H; (aromatics), from 6,60 to 7,10, m, 6H; (-H-8) 7,30, m, 1H; (-H-5') 8,40, m, 1H; (-NH-1) 11,60, s, 1H; the absence of the NH band in I.R., the shape and the chemical shift of the NH signal in N.M.R. and the chemical shift of the proton in 5' suggest an internal chelation between the NH and the pyridinic nitrogen atom of the substituent.


HN3/BF3 Et2O/C6H6
5
3 a: R=-CH3
b: R=-CH2-C6H5
c: R=-C6H5
d: R=-(α-picolyl)
4 a: R=-CH3
c: R=-C6H5
HN3/H2SO4
A
B
R=-CH3
R=-CH2-C6H5
R=-C6H5
R=-(α-picolyl)
5 a: R=-CH3
b: R=-CH2-C6H5
6
7

Scheme 2

In all the examples studied here, the rearrangement observed initiates with the migration of the benzylic bond which is both the most electronegative and transantiperiplanar relative to the azido group.
This is in accordance with an exo position of the azido group (orientated in the less hindered half space) and confirms the mechanism already observed for this kind of rearrangement (1, 2, 3, 11, 12) (Scheme 2).
The structures of the dihydroquinolines 5a, 5b and 6 obtained in this study have been confirmed by quantitative aromatisation in the corresponding quinolines 8a, 8b and 9 using triphenylmethyl perchlorate in boiling acetic acid (Scheme 3). This reagent has already been used successfully to oxidise 4H-chromene into benzopyrylium perchlorate (10).



Scheme 3

In conclusion, the SCHMIDT reaction applied to tertiary alcohols (or trisubstituted olefins) in the indane series allows the regiospecific preparation of dihydro quinolines substituted in the -2 position according to a well established mechanism. In these molecules, the insaturation is oriented to yield the most stable compound.

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