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SYNTHESIS OF NATURAL PRODUCTS VIA TERTIARY AZIDES. II. 2-ALKYL AND 2-ARYL INDOLES.

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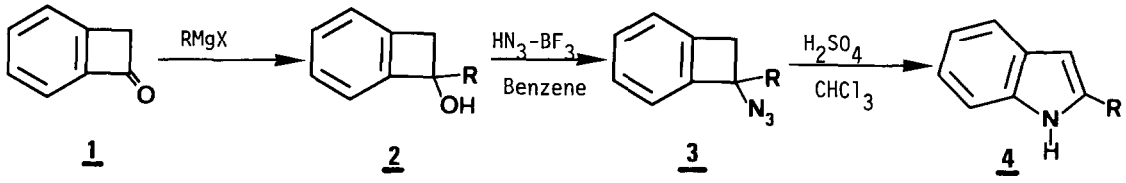
Abstract: A new route to indoles: the acid-catalysed breakdown of 1-azido 1,2-dihydrobenzocyclobutenes.

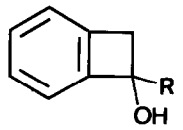
The SCHMIDT reaction applied to tertiary alcohols has been used to the conversion of suitably substitued cyclopentanols to piperidine alkaloids like (±) dihydropinidine and (±) conine (1). This method is now extended to the 1,2-dihydrobenzocyclobutenol series and provides a good and new route to indole derivatives according to the following scheme



1 2 3 4

The synthesis of indoles substitued only on the 2-position is generally difficult because of the great reactivity of the 3-position.

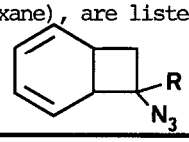
Benzocyclobutenone 1 is obtained by arynic condensation according to DÜRR and al. (2) and reacts easily with Grignard reagents, leading in good yields to the alcohols 2(a-d) described in Table I.

TABLE I 

N°	R	Yield (%)	MP (°C); (lit.)	I.R cm^{-1} ν(OH)	N.M.R. δ ppm/ TMS-$CDCl_3$ R	H-2	CH
2a	$-CH_3$	90	80;(3)	3300	1,55;(s);3H.	3,25;(s);2H.	2,70;(s);1H.
2b	$-CH_2-CH=CH_2$	85	Pale yellow oil	3350	CH_2:2,55;(d);2H $CH=CH_2$:(m) from 4,95 to 6,30; 3H	3,20;(q);2H J_{gem}= 14 Hz.	2,85;(s);1H.
2c	$-CH_2-C_6H_5$	80	Pale yellow oil	3360	CH_2:3,15;(s);2H.	3,30;(q);2H J_{gem}= 14 Hz.	2,35;(s);1H
2d	$-C_6H_5$	75	69-70;(4)	3340	Merging with aromatics.	3,53;(s);2H	2,85;(s);1H.

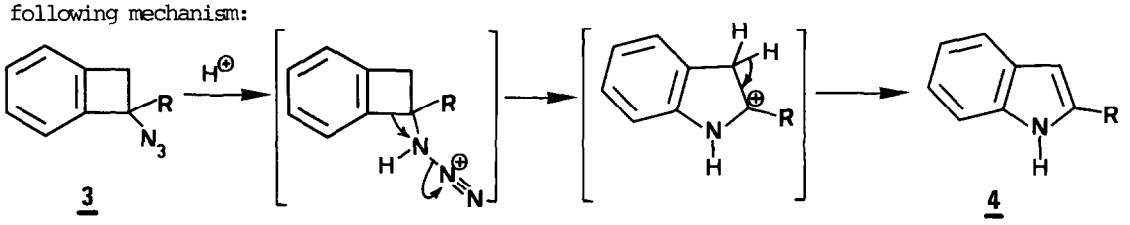
The traitment of benzocyclobutenols 2(a-d) in hydrazoic acid solution by an equimolar amount of boron trifluoride etherate allows quantitative introduction of the azide function by an ion pair mechanism involving the complexation of the hydroxyl by the LEWIS acid (5). The example of the allylic alcohol 2b which gives only the tertiary azide 3b demonstrates the regiospecificity of this reaction; only trisubstitued olefins and tertiary alcohols react with HN_3-BF_3 (9).

The oily thermonabile azides 3(a-d) obtained, purified by column chromatography on neutral silica gel (70-230 mesh; eluent: cyclohexane), are listed in Table II.

TABLE II. 

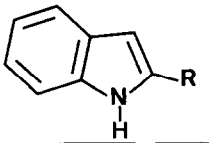
N°	R	Yield (%)	I.R. cm^{-1} ν(N_3)	N.M.R. δ ppm / TMS-$CDCl_3$ H-2	R
3a	$-CH_3$	90	2090	3,35; (m); 2H.	1,65; (s); 3H
3b	$-CH_2-CH=CH_2$	85	2095	3,35; (s); 2H	CH_2: 2,65;(d);J= 6Hz;2H. $CH=CH_2$:4,95 to 6,35;(m);3H
3c	$-CH_2-C_6H_5$	98	2090	3,10; (s); 2H	CH_2: 3,35; (s); 2H C_6H_5: merging with aromatics.
3d	$-C_6H_5$	98	2100	3,65; (s); 2H.	Merging with aromatics.

The acid catalysed breakdown of azides 3(a-d) by concentrated sulfuric acid at 0°C in chloroform leads to 2-substitued indoles 4(a-d) described in Table III according to the following mechanism:



The phenyl group migrates in preference to the ring CH_2, leading to 2-substitued indoles rather than isoindoles. 1-Phenyl 1-azido 1,2-dihydrobenzocyclobutene 3d bearing two quasi equivalent benzylic bonds undergoes only one kind of concerted migration of the trans antiperiplanar bond, the azido group being oriented towards the less hindered half space (10)

TABLE III



N°	R	Yield (%)	Mp (°C) (Lit.)	I.R. cm^{-1} ν(N-H)	N.M.R. δ ppm / TMS-$CDCl_3$ R	H-3	N-H
4a	$-CH_3$	90	61;(6)	3390	2,25; (s); 3H.	6,15;(s);1H.	7,20;(s);1H.
4b	$-CH_2-CH=CH_2$	95	72;(7)	3430	CH_2: 3,40;(d);J=7Hz;2H $CH=CH_2$: (m) from 4,95 to 6,15; 3H.	6,30;(m);1H.	7,60;(s);1H
4c	$-CH_2-C_6H_5$	85	85-86; (8).	3420	CH_2: 3,95; (s); 2H	6,20;(s);1H.	7,55;(s);1H.
4d	$-C_6H_5$	95	187;(6)	3440	Aromatics.	Aromatics.	10,65;(s);1H.

It was also verified that indole compounds 4(a-d) may be obtained by treatment of alcohols 2(a-d) in benzene with a solution of hydrazoic acid and with concentrated sulfuric acid. (SCHMIDT reaction).

2-Allyl indole, cornerstone of the echinulin synthesis, could be prepared by this method without isomerisation of the olefinic bond. The nearly quantitative yields of this reaction are imputed to the decrease of ring strain and to the aromatic character of the indole nucleus.

We have extended this reaction to the synthesis of natural indole alkaloids possessing more than one nitrogen atom. Thus, 1-(α -picolyl) 1-hydroxy 1,2-dihydrobenzocyclobutene 2e (IR: ν(OH)= 3320 cm^{-1}; NMR: 2 CH_2: 3,30 ppm,(s),4H; OH: merging with aromatics; MS M^+ m/e = 211) and 1-(γ -picolyl) 1-hydroxy 1,2-dihydrobenzocyclobutene 2f (IR: ν(OH)= 3210 cm^{-1}; NMR: 2 CH_2: 2 quartets centered at 3,10 and 3,30 ppm,4H; J_{AB}= 14 Hz for each quartet; MS M^+ m/e = 211) are prepared by condensation of α- and γ-picolyl lithium respectively with benzocyclobutenone 1.

The action of the HN_3-BF_3 reagent on these two alcohols 2e and 2f leaves them unchanged. However, 2-(α-picolyl) indole 4e (mp= 94-95°C; lit(11): mp= 95-96°C; NMR: CH_2: 4,20,(s),2H; H-3: 3,65,(m),1H; N-H: 8,30,(s),1H; MS: M^+ m/e = 208) and 2-(γ-picolyl) indole 4f (mp= 142°C; lit(11): mp= 141-142°C; NMR: CH_2: 4,00,(s),2H; H-3: 6,30,(m),1H; N-H: 8,30, (s),1H; MS M^+ m/e = 208) may be obtained directly by treating alcohols 2e and 2f in benzene with a solution of hydrazoic acid and with concentrated sulfuric acid in the conditions of the SCHMIDT reaction.

The extension of this reaction to the synthesis of tetrahydrocarbazoles, quinolines and benzazepines will be reported later.

REFERENCES

(1) : A.ASTIER, M.M.PLAT: Tetrahedron Lett. 1978,2051.

(2) : H.DÜRR, H.NICKELS, L.A.PACALA, M.JONES Jr.: J.org.chem.1980,45,973.

(3) : L.HORNER, P.V.SUBRAMANIAM, K.EIBEN: Liebigs Ann. Chem. 1968,91,714.

(4) : B.J.ARNOLD, P.G.SAMMES, T.W.WALACE: J. chem. Soc.(Perkin Trans I):1980,415.

(5) : A.PANCRAZI, Q.KHUONG-HUU, M.M.JANOT: Tetrahedron 1976,32,447.

(6) : W.MADELUNG: Ber. 1912,45,1128.

(7) : H.PLIENNINGER, H.SIROWEJ: Chem. Ber. 1971,104,1869.

(8) : P.L.JULIAN, J.PIKL: J. amer. chem. Soc. 1933,55,2105.

(9) : Q.KHUONG-HUU, A.PANCRAZI, I.KABOPF:Tetrahedron 1974,30,2579.

(10): A.PANCRAZI, O.KHUONG-HUU: Tetrahedron 1975,31,2049.

(11): M.HOOPER, W.N.PITKETHLY: J. chem. Soc.(Perkin Trans I): 1972,1607.

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