A NEW SYNTHESIS OF 3,4,5-TRIHYDROAZEPINO[2,3-b]INDOLES

R. Balamurali & K.J. Rajendra Prasad*
Department of Chemistry, Bharathiar University
Coimbatore - 641 046, India.

Abstract : The Schmidt reaction of 1-oxo-1,2,3,4-tetrahydrocarbazoles, 1a-e, with sodium azide in the presence of anhydrous polyphosphoric acid at 100°C yielded the respective 3,4,5-trihydroazepino[2,3-b]indoles, 2a-e. All the newly synthesized compounds were characterized by IR, NMR and mass spectral means. The plausible mechanism for the product 2 formation was also proposed.

Introduction

Extensive reports are available on antitumour[1], antiinflammatory[2], antibacterial[3], antifungal[4] and antituberculosis[4] activities of indole derivatives. As well, azepine derivatives such as imipramine and molinate were reported to have antidepressent and herbicidal properties respectively[5,6]. Keeping above facts in mind, in our present investigation on carbazole alkaloids[7-9], we herein report a new synthetic route for the hitherto unknown 3,4,5-trihydroazepino[2,3-b]indole derivatives 2.

Experimental

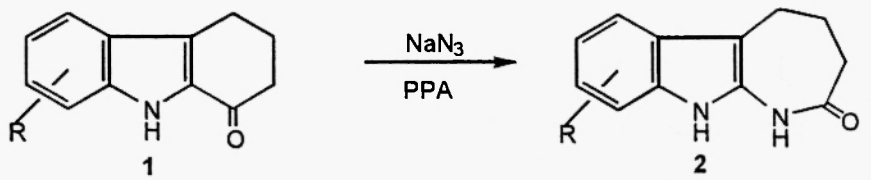
Schmidt reaction of 1-oxo-1,2,3,4-tetrahydrocarbazoles 1

To a solution of 1-oxo-1,2,3,4-tetrahydrocarbazole (1, 0.003 mol) in anhydrous polyphosphoric acid (21.6 gms of P_2O_5 in 12 gms of H_3PO_4) maintained at 100°C sodium azide (0.003 mol) was added in portionwise (Scheme-1). Heating was further carried out for 8 hrs. The resulting mixture was cooled, poured into ice water. The product thus obtained was extracted with chloroform. Evaporation of the solvent yielded the crude product, which was purified by passing through a column packed with silica gel using peteroleum ether-ethyl acetate (4:1) mixture as eluant. The product was further recrystalised from the same solvent mixture.

Results and discussion

6-Methyl-1-oxo-1,2,3,4-tetrahydrocarbazole 1a was subjected to Schmidt reaction[10-12] by treating with sodium azide in presence of excess of PPA at 100°C for 8 hrs. After work up it yielded a single product on tlc., which melted at 198°C. Absorptions, at 1627 cm^{-1} and 3211 cm^{-1} in its IR spectrum were ascribed to amide carbonyl and N-H stretching vibrations respectively. The proton NMR spectrum displayed three multiplets at δ 3.48, δ 3.11 and δ 2.19 ppm for C_5, C_3 and C_4 protons, a three proton singlet for C_7-CH_3 at δ 2.45 ppm, two one proton broad singlets at δ 6.50 and δ 9.32 ppm for a -NH proton

SCHEME 1



1a: R = 6-CH_3
b: R = 7-CH_3
c: R = 8-CH_3
d: R = 6-Cl
e: R = H

2 a: R = 7-CH_3
b: R = 8-CH_3
c: R = 9-CH_3
d: R = 7-Cl
e: R = H

SCHEME 2

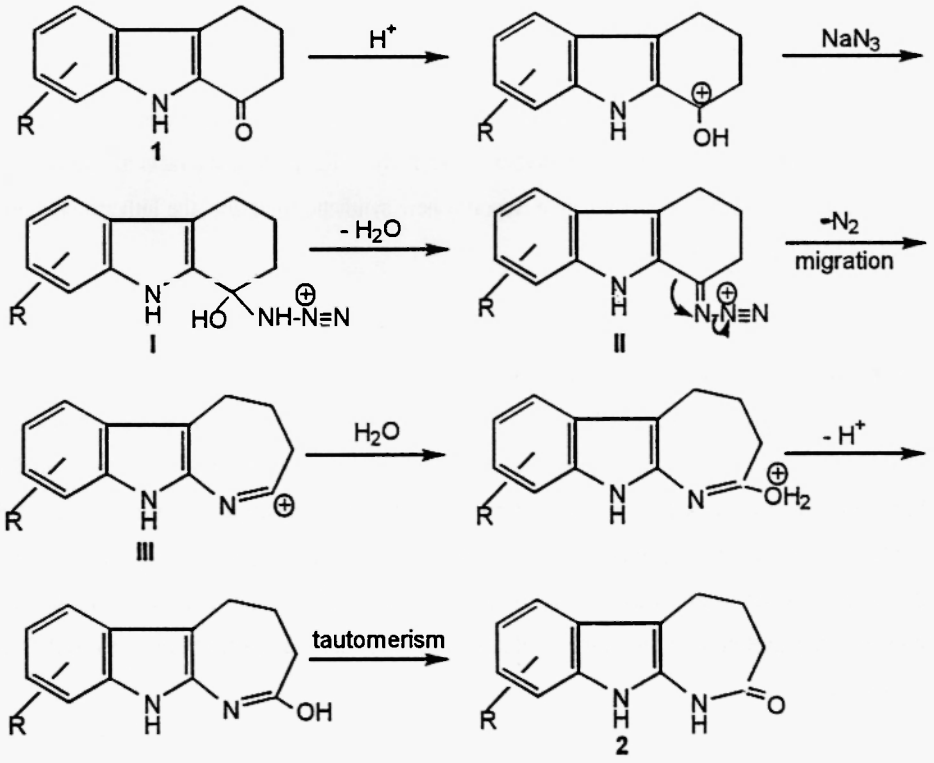


Table. I. Physical and spectral data of 3,4,5-trihydroazepino[2,3-b]indoles 2

Componnd	M.P (°C)[a] solvent	Yield (%)	IR[b] (ν)	MS (eV)[c] m/z (M^+)	Molecular formula	Analysis[d] Calcd	Found	^{1}H – NMR[e]
2a	198 PE-EA	49	3280, 3211, 1627	214	$C_{13}H_{14}N_2O$	C 72.87 H 06.59 N 13.07	72.55 06.51 12.98	2.19 (m, 2H, C_4-H_2), 2.45 (s, 3H, C_7-CH_3), 3.11 (m, 2H, C_3-H_2), 3.48 (m,2H, C_5-H_2), 6.50 (b s, 1H, NH), 7.14 (d, 1H, C_8-H, J_{ortho} = 8.4 Hz, J_{meta} = 1.2Hz), 7.30 (d, 1H, C_9-H, J_{ortho} = 8.4 Hz), 7.37 (s, 1H, C_6-H) and 9.32 (b s, 1H, indole NH)
2b	184 PE-EA	44	3388, 3199, 1629	214	$C_{13}H_{14}N_2O$	C 72.87 H 06.59 N 13.07	72.66 06.48 13.01	2.21 (m, 2H, C_4-H_2), 2.49 (s, 3H, C_8-CH_3), 3.14 (m, 2H, C_3-H_2), 3.49 (m,2H, C_5-H_2), 6.26 (b s, 1H, NH), 7.26 (m, 3H, C_6-H, C_7-H and C_9-H) and 9.03 (b s, 1H, indole NH)
2c	216 PE-EA	58	3318, 3212, 1624	214	$C_{13}H_{14}N_2O$	C 72.87 H 06.59 N 13.07	72.70 06.44 13.03	2.22 (m, 2H, C_4-H_2), 2.51 (s, 3H, C_9-CH_3), 3.15 (m, 2H, C_3-H_2), 3.50 (m,2H, C_5-H_2), 6.29 (b s, 1H, NH), 7.31 (m, 3H, C_6-H, C_7-H and C_8-H) and 9.07 (b s, 1H, indole NH)
2d	225 PE-EA	57	3282, 3197, 1645	234	$C_{12}H_{11}N_2OCl$	C 61.53 H 04.72 N 11.94	61.24 04.64 11.88	2.20 (m, 2H, C_4-H_2), 3.08 (m, 2H, C_3-H_2), 3.49 (m,2H, C_5-H_2), 6.79 (b s, 1H, NH), 7.23 (d, 1H, C_8-H, J_{ortho} = 10Hz, J_{meta} = 2.8Hz), 7.35 (d, 1H, C_9-H, J_{ortho} = 10Hz), 7.55 (d, 1H C_5-H) and 9.73 (b s, 1H, indole NH)
2e	213 PE-EA	45	3286, 3201, 1624	200	$C_{12}H_{12}N_2O$	C 71.98 H 06.04 N 13.99	71.69 05.98 13.99	2.20 (m, 2H, C_4-H_2), 3.15 (m, 2H, C_3-H_2), 3.50 (m,2H, C_5-H_2), 6.52 (b s, 1H, NH), 7.29 (m, 4H, C_6-H, C_7-H, C_8-H and C_9-H) and 9.30 (b s, 1H, indole NH)

PE-EA : Petrolen n Ether – Ethyl acetate

a : Uncorrected, measured using Mettler FP5 apparatus and Boetius microheating table

b : Recorded on a Shimadzu FTIR 8201 (PC)s spectrometer

c : Recorded on a Jeol JMS – D 300 Mass spectrometer

d : Satisfactory microanalysis were obtained on Carlo Erba 1106 and Perkin Elmer Model 240 CHN analyser

e : NMR spectra were recorded on Varian AMX 400 MHz spectrometer in $CDCl_3$ using tetramethylsilane as imernal standard.

singlet for C_7-CH_3 at δ 2.45 ppm, two one proton broad singlets at δ 6.50 and δ 9.32 ppm for a -NH proton and indole -NH proton respectively. In the aromatic region resonance appeared as two doublets at δ 7.30 ppm, (J_{ortho} = 8.4 Hz) and δ 7.14 ppm (J_{ortho} = 8.4 Hz, J_{meta} = 1.2 Hz) for C_8 and C_9 protons, a singlet at δ 7.37 ppm for the C_6 proton. In its mass spectrum, the appearance of the molecular ion peak at *m/e* 214 (100%) and the elemental analysis: C: 72.55%, H: 06.51%, N: 12.98% agreed well with the molecular formula $C_{13}H_{14}N_2O$. Based on the above spectral and analytical data, the structure of the product was found to be 7-methyl-3,4,5-trihydroazepino [2,3-b]indole, 2a. Further in the mass spectrum the fragment peaks at *m/e* 213 (M-H), 199 (M-CH_3), 186 (M-CO) and (M- CH_2=CH_2), 143 (M-cyclobutanone, $H^{\cdot}$) attest the above assigned structure.

A similar series of compounds 2b, 2c, 2d and 2e were realized with 1b, 1c, Id, and 1e (Scheme 1 and Table 1). The plausible mechanism for the formation of product 2 from 1 has also been proposed (Scheme - 2). Under acidic condition, the carbonyl group gets protonated follwed by the addition of sodium azide to give the intermediate I. It then losses a water molecule to yield the intermediate II, in which the aryl group migration and elimination of the nitrogen molecule take place synchronously leading to the formation of the intermediate III. This further underoges nucleophilic substitution and tautamerism to yield the final product 2.

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