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ADDITION OF PHTHALIMIDONITRENE TO SUBSTITUTED INDOLES

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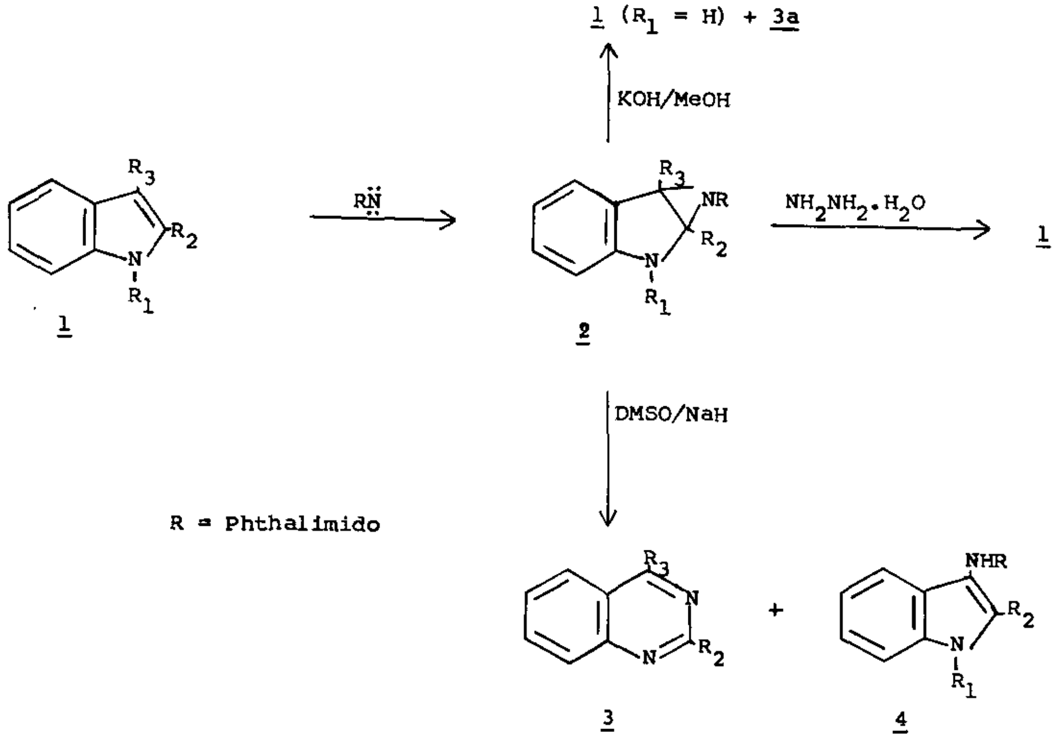
Abstract - The aziridine 2a obtained by the addition of phthalimidonitrene to N-phenylsulphonylindole was treated with methanolic potassium hydroxide to give desulphonated indole and quinazoline. The aziridine 2b and 2c derived from phthalimidonitrene and 2-methylindole or 2-phenylindole were treated with dimsyl anion to give 2-methylquinazoline and 2-phenylquinazoline. However the nitrene adducts 2d and 2e derived from 1,2,3,4-tetrahydrocarbazole and 1-oxo-1,2,3,4-tetrahydrocarbazole afford carbazole and 1-hydroxycarbazole under similar conditions. Hydrazinolysis of the nitrene adducts 2a, b, c, d and e regenerated the parent indole.

Phthalimidonitrene generated by the oxidation of N-aminophthalimide with lead tetraacetate undergoes facile cycloaddition with a variety of olefins[1]. The aziridines derived by the cycloaddition of phthalimidonitrene to substituted indoles could be used as a potential synthon for the construction of substituted heterocyclic systems. However, sulphonylnitrene with indoles did not result in the formation of aziridine[2]. The following report explores the synthetic utility of phthalimidonitrene for the construction of quinazoline ring system.

N-Phenylsulphonylindole is stable towards lead tetraacetate and therefore the nitrene adduct derived from it could be used as synthon for quinazoline synthesis. The yellow crystalline adduct 2a derived by the cycloaddition of phthalimidonitrene to N-phenylsulphonylindole showed the presence of phthalimido carbonyls and sulphonyl absorption in ir, and ^{1}Hnmr spectrum of 2a exhibits the aziridine protons as one proton doublet each at δ 2.178 and 2.046 in addition to the signal for aromatic protons. As one of the aziridine protons is flanked by two nitrogen atoms, it is relatively shielded and hence appears high field. The proposed structure 2a received further support by the appearance of molecular ion peak at m/z 417 in the mass spectrum. When the aziridine 2a was treated with methanolic potassium hydroxide quinazoline (20%) and indole (80%) were obtained. The yield of quinazoline is suppressed because of the preferential attack of potassium hydroxide at the carbonyl function.

Addition of phthalimidonitrene to 2-methylindole afforded the aziridine 2b in 55% yield. The reaction of the aziridine 2b with dimsyl anion at 0°C under nitrogen yielded 2-methylquinazoline (30%) and N-phthalimido-3-amino-2-methylindole (10%). The potentiality of the above synthetic route was further explored with the aziridine 2c derived from phthalimidonitrene and 2-phenylindole. Oxidation of N-aminophthalimide with lead tetraacetate in presence of 2-phenylindole in dry methylene chloride resulted in the formation of the aziridine 2c, recrystallised from ethylacetate-petrol as bright red crystalline solid (mp 245°C). Treatment of 2c with dimsyl anion afforded 2-phenylquinazoline (70%) and N-phthalimido-3-amino-2-phenylindole (10%). An extension of the above procedure for the construction of quinazoline ring from the aziridine 2d derived from 1,2,3,4-tetrahydrocarbazole and phthalimidonitrene could result in the formation of 8,9-benzo-7,10-diazobicyclo(4.3.1)deca-1,6-diene. However treatment of the aziridine 2d with dimsyl anion gave carbazole (85%). The cycloaddition of phthalimidonitrene to 1-oxo-1,2,3,4-tetrahydrocarbazole afforded the aziridine 2e (mp 145°C) in 67% yield. Interaction of the aziridine 2e with dimsyl anion in dry dimethylsulphoxide did not furnish any bicyclic compound but resulted in the formation of 1-hydroxycarbazole in 70% yield. The formation of 1-hydroxycarbazole can be explained by a sequential elimination and enolisation process.

The reaction of the aziridine 2c with hydrazine hydrate in ethanol at 50°C led to the formation of a viscous oil which on chromatographic purification over neutral alumina using petrol : ethylacetate (1:5) as eluent afforded 2-phenylindole (90%). The formation of 2-phenylindole could result either by a thermal cycloreversion route or through an intermediacy of unstable N-aminoaziridine. Since the aziridine 2c has been found to be thermally stable, the intermediacy of N-aminoaziridine was investigated. Hydrazinolysis of the aziridine 2c with hydrazine hydrate at -10°C in ethanol furnished a dark blue coloured solid which in its ir displayed the presence of νNH_2 mode at 3380 and 3350 cm^{-1} in addition to the indole N-H absorption at 3400 cm^{-1} and the absence of phthalimido carbonyls. The N-aminoaziridine on heating underwent cycloreversion to give the parent indole. Similarly, the aziridines 2a, 2b, 2d and 2e gave N-phenylsulphonylindole, 2-methylindole, 1,2,3,4-tetrahydrocarbazole and 1-oxo-1,2,3,4-tetrahydrocarbazole respectively. The reaction sequence is summarised in the following scheme.



a; $R_1 = SO_2Ph$, $R_2 = R_3 = H$

b; $R_1 = R_3 = H$, $R_2 = CH_3$

c; $R_1 = R_3 = H$, $R_2 = Ph$

d; $R_1 = H$, R_2 & $R_3 = -(CH_2)_4-$

e; $R_1 = H$, R_2 & $R_3 = -\underset{\underset{O}{\|}}{C}-(CH_2)_3-$

EXPERIMENTAL

Melting points are uncorrected. Ir spectra were recorded in KBr on Perkin-Elmer 598 spectrometer. ^{1}Hnmr spectra were obtained on Varian EM 390 (90 MHz) spectrophotometer. Chemical shifts are reported in δ scale (ppm) downfield from internal tetramethylsilane in $CDCl_3$/DMSO-d_6; data are presented as : chemical shift (multiplicity, number of protons, coupling constant in Hertz). Mass spectra were obtained at 70 eV. C, H and N analytical values for the nitrene adducts are found to be within the limits of experimental error. In general, the work-up procedure involved washing the organic phase with water, drying over $MgSO_4$, and removing the solvent under reduced pressure. The residue obtained was recrystallised from an appropriate solvent.

Addition of Phthalimidonitrene to Indoles and N-Phenylsulphonylindole

To a magnetically stirred solution of N-aminophthalimide (0.011 mole) and indoles/ N-phenylsulphonylindole (0.01 mole) in dichloromethane (30 ml) at 0°C, lead tetraacetate (0.012 mole) was added slowly and the product was worked up as usual and recyrstallised from petrol-ethyl acetate.

Addition of phthalimidonitrene to 1a, b, c, d or e (2.55 g/1.31 g/1.93 g/ 1.71 g/1.85 g) gave the aziridines 2a, b, c, d, and e (2.71 g, 65%/ 1.60 g, 55%/ 2.37 g, 70%/ 1.75 g, 53%/ 2.31 g, 67%) respectively.

2a; mp 167-168°C; IR 3100, 1750, 1720, 1600, 1400, 1180, 1120, 1100, 1080 cm^{-1}; ^{1}Hnmr 7.90-7.65 and 7.55-7.21 (m, 13H), 2.178 (d, 1H, 3), 2.046 (d, 1H, 3); MS m/z 417 (M^+).

2b; mp 138°C; IR 3350 (broad), 2970, 1780, 1720, 1610, 1380, 1240, 1040 cm^{-1}; ^{1}Hnmr 7.90 (broad, s, 1H), 7.52-7.22 (m, 8H), 2.211 (s, 1H), 1.584 (s, 3H); MS m/z 291 (M^+).

2c; mp 245°C; IR 3400 (broad), 1730, 1720, 1600, 1520, 1440, 1340, 1280, 1050 cm^{-1}; ^{1}Hnmr 8.2 (broad s, 1H) 7.80-7.11 (m, 13H), 2.205 (s, 1H); MS m/z 353 (M^+).

2d; mp 180°C (d); IR 3300, 2925, 1730, 1700, 1540, 1440, 1380, 1310, 1280, 1240, 1000 cm^{-1}; ^{1}Hnmr 7.82 (broad s, 1H) and 7.59-7.20 (m, 8H), 2.81 (t, 4H, 4), 2.28 (t, 4H, 4); MS m/z 331 (M^+)

2e; mp 145°C; IR 3425, 3025, 1780, 1740, 1660, 1380, 1040 cm^{-1}; ^{1}Hnmr 7.88 (broad s, 1H), 7.71-7.32 (m, 8H), 2.80 (t, 2H, 8), 2.52 (t, 2H, 8), 2.21 (q, 2H, 8); MS m/z 345 (M^{+}).

Reaction of the Aziridine (2b, c, d, e) with Dimsyl Anion

To a stirred suspension of sodium methylsulphinylmethanide prepared from sodium hydride (0.3 g, 0.015 mole) in dry dimethyl sulphoxide (15 ml) at 0°C under nitrogen atmosphere was added finely powdered aziridine (0.005 mole). The resulting solution was allowed to attain room temperature and stirred overnight. Dimethyl sulphoxide was then removed under reduced pressure and added HCl (6N, 5 ml) to the residue. The dark colored hydrochloride was separated by filtration. It was then dissolved in NaOH (6N) and extracted with ethyl acetate and worked up as usual. The products were purified by column chromatography with neutral alumina. Elution with petrol : ethyl acetate (1:3) gave quinazoline and with petrol : ethyl acetate (1:5) gave the indole derivative.

Reaction of the aziridine 2b, c, d or e (1.45 g/1.76 g/1.65 g/1.73 g) with dimsyl anion gave 2-methylquinazoline (0.216 g/30%), N-phthalimido-3-amino-2-methylindole (0.435 g/30%), 2-phenylquinazoline (0.71 g/70%), N-phthalimido-3-amino-2-phenylindole (0.18 g/10%), carbazole (0.72 g/85%), and 1-hydroxycarbazole (0.194 g/70%) respectively.

N-phthalimido-3-amino-2-methylindole; mp 120°C; IR 3550, 3450, 2900, 2850, 1730, 1560, 1380, 1100 cm^{-1}; ^{1}Hnmr 8.2 (broad, 1H), 7.4 (broad, 1H), 7.28-7.1 (m, 9H), 2.28 (s, 3H).

N-phthalimido-3-amino-2-phenylindole; mp 135°C, IR 3630, 3450, 2900, 1745, 1720, 1600, 1460, 1240, 1040 cm^{-1}; ^{1}Hnmr 8.5 (broad, 1H), 7.5 (broad 1H), 7.4-7.1 (m, 13H).

Reaction of the Aziridine 2a with Methanolic KOH

A solution of the N-phenylsulphonylaziridine (0.001 mole) in 10% methanolic KOH (20 ml) was stirred for 1 h. Methanol was evaporated and the residue was extracted with ethyl acetate and worked up as usual. Aziridine 2a (0.417 g) was treated with methanolic KOH to give indole (0.09 g/80%) and quinazoline (0.03 g, 20%).

Hydrazinolysis of the Aziridines 2a, b, c, d, and e

To a stirred suspension of the aziridine (0.001 mole) in ethanol (20 ml) a 98% solution of hydrazine (0.004 mole) in ethanol (10 ml) was added at 50°C during 10 min. The reaction mixture after stirring for 1 h was poured onto ice and worked up as usual.

Hydrazinolysis of 2a, b, c, d or e (0.417 g/0.291 g/0.353 g/0.331 g/0.345 g) afforded 1a, b, c, d, and e (0.23 g, 90%/0.13 g, 95%/0.16 g, 70%/0.38 g, 52%/ 0.12 g, 63%) respectively.

Low Temperature Hydrazinolysis of the Aziridine 2c

To a solution of the aziridine 2c (0.331 g) in ethanol (10 ml) at -10°C a solution of hydrazine hydrate (0.5 ml) in ethanol (2 ml) was added and stirred magnetically for 5 min. The reaction mixture was extracted immediately with dichloromethane and washed with ice water to remove hydrazine hydrate and dried (K_2CO_3) for a short period. A dark blue coloured solid was obtained after removing the solvent at low temperature (-10°C), mp 124°C; IR ($CHCl_3$) 3400, 3380, 3350, 3010, 2990, 1610, 1520, 1480, 1440 cm^{-1}.

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