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APPLICATION OF JAPP-KLINGEMANN REACTION IN THE SYNTHESIS OF AZACARBAZOLE DERIVATIVES: SYNTHESIS OF 1,8-DISUBSTITUTED-2,3-DIHYDRO-1*H*-PYRIDO[3,2-b]INDOL-4-(5*H*)-ONES FROM ARYL AMINES

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ABSTRACT

Application of the Japp-Klingemann reaction on N-substituted-(3-hydroxymethylidine)-piperidin-4-one **2(a-d)** and aryldiazonium chloride **1(a-d)** yielded 3-aryl hydrazones of N-substituted piperidin-4-ones **3(a-g).** Fischer indolization of these hydrazones with Kent's reagent (4:1 mixture of acetic acid : HCl) afforded 1,8-disubstituted-2,3-dihydro-1H-pyrido[3,2-b]-indol-4-(5H)-ones **4(a-g)** in moderate to good yield. Azacarbazole derivatives **4(a-g)** were characterized by microanalysis, IR, ^{1}H NMR and MS spectral data.

Key words: Carbazoles, Azacarbazole, Japp-Klingemann reaction, Fischer indole synthesis.

INTRODUCTION

Azacarbazoles elicit a variety of important beneficial and untoward biological responses. The interest in azacarbazoles has stemmed ever since these nuclei have exhibited promising activity as antioxidants[1] but their major practical applications have emerged in the medicinal field where their derivatives showed such widely differing activities as bacteriostatic[2], anti-inflammatory[3], anti-viral[4], anti-cancer[5], antihistaminic[6], antitumor and psychopharmacological[7] properties. A recent demonstration that these compounds can be used as potential anti-HIV agents has stimulated further interest in these molecules from yet another perspective[8].

Synthetic approaches[9] to azacarbazoles have been of special interest and of contemporary importance on account of a large variety of azacarbazole derivatives showing

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cytotoxic properties[10,11]. For many azacarbazoles, the cytotoxocity can be related to DNA dependent topoisomerase and telomerase enzyme inhibition. Due to their polycyclic and planar structure for intercalation with DNA, the azacarbazoles remain one of the main targets in synthesis for the study of their cytotoxic properties. This unique property of azacarbazole derivatives has triggered the development of a variety of methods for their synthesis. We report in this communication the synthesis of 1, 8-disubstituted derivatives of 2, 3-dihydro-1*H*-pyrido [3, 2-b] indol-4(5*H*)-ones from aryl amines and N-substituted 4-piperidones. Diazotized aryl amines have been known to undergo Japp-Klingemann reaction[12-14] with 2-hydroxymethylidine cyclohexanones (which can be generated on treatment of cyclohexanone with ethyl formate in presence of EtONa) and give the carbazole derivative on Fischer indolization. This strategy when applied on 3-hydroxymethylidine-4-piperidones **3(a-g)** afforded the azacarbazole derivatives **4(a-g)** in moderate to good yield.

EXPERIMENTAL

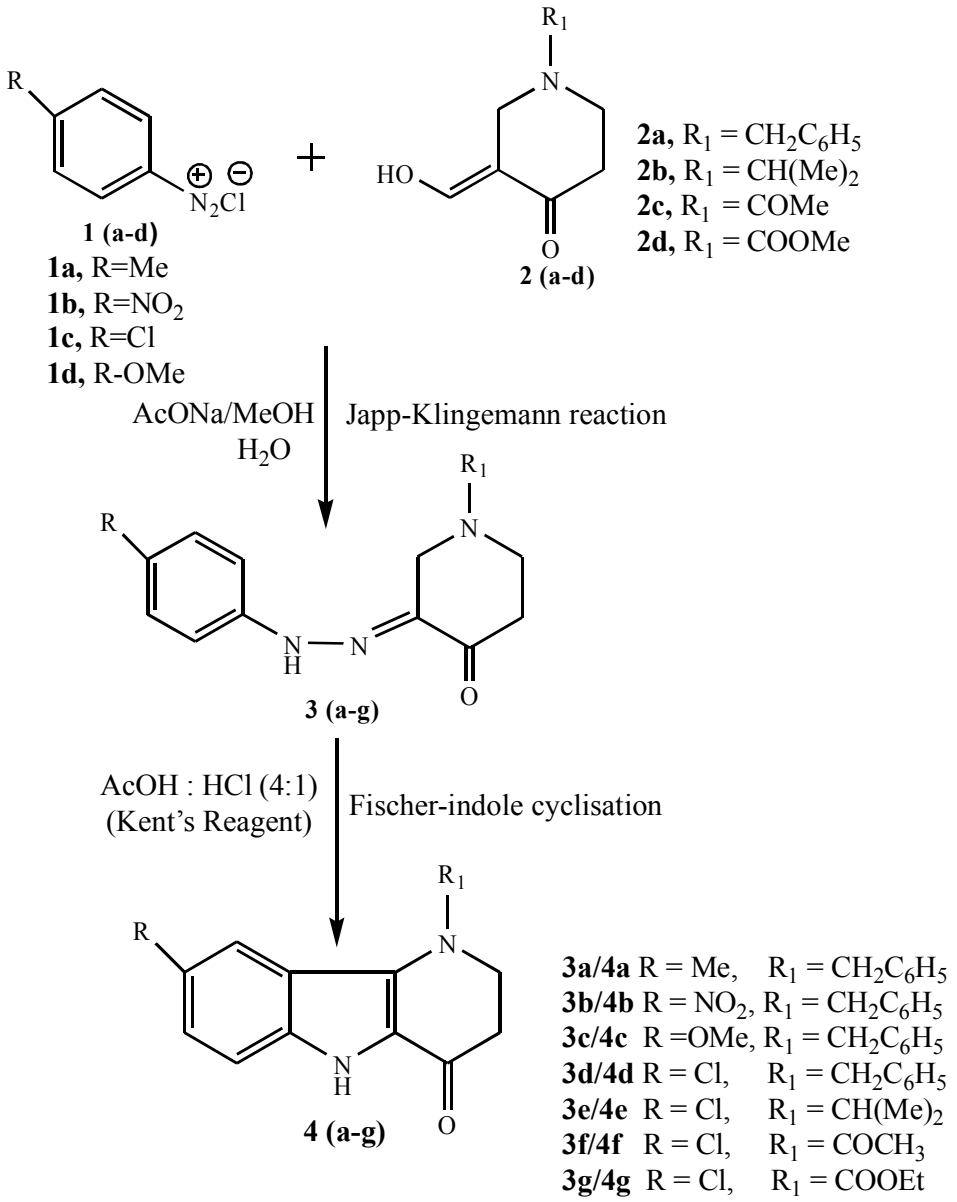
General method for the preparation of 4(a-g)

Preparation of hydrazone (3a)

A solution of *p*-toluidine **1(a)** (0.8 g, 0.01 mol) in aqueous HCl (2.0 mL conc. HCl in 4.0 mL water) was treated with a cold saturated solution of sodium nitrite (0.8 g in 2 mL water) while the temperature was kept at 0 to 5ºC. The solution was kept aside for 10 min. It was then added portion wise to an ice cooled mixture containing 1-benzyl-3-(hydroxymethylidine)-piperidin-4-one **2(a)** (1 mL), sodium acetate trihydrate (2.0 g), methanol (10.0 mL) and water (6 mL) over a period of 0.5 hrs. with stirring. The contents were allowed to stand for further 0.5 hrs and the resulting solid **3(a)** was filtered, washed with water, dried and recrystallized from ethanol. The compounds **3(b-g)** were prepared by adopting the same procedure.

Cyclization of hydrazone (3a)

A solution of hydrazone **3(a)** (0.4 g, 0.01 mole) in a mixture of acetic acid (4.0 mL) and HCl (1.0 mL) was refluxed on an oil bath preheated to 125-130ºC for 0.5 hrs. The contents were then cooled and poured into cold water with stirring. The separated brown solid **4(a)** was purified by passing through a column of silica gel using 50% benzene in pet ether. The compounds **4(b-g)** were prepared in a similar way.



Scheme - 1

RESULTS AND DISSCUSION

The procedure developed by Japp-Klingemann for the preparation of the hydrazones from aryl amines and the carbonyl compounds containing an adjacent methylene group was

adopted in the present work for the preparation of **3(a-g)** from **1(a-d) (Scheme 1).** The intermediates **2(a-d)** were obtained by the base catalyzed condensation of N-substituted-4-piperidones with ethyl formate. Compounds **3(a-g)** underwent a facile acid catalyzed cyclocondensation with Kent's reagent (a 4:1 mixture of acetic acid and hydrochloric acid) under Fischer indolization to furnish the desired azacarbazole derivatives **4(a-g)** in good yield. The nitrogen analysis and spectral data of all the compounds (Tables 1 and 2) were found to be in good agreement to the assigned structures. The most diagnostic evidence for the incorporation of N-substituted-4-piperidone skeleton in the indole framework was provided by the appearance of NH proton of indole in the ^{1}H NMR spectrum in the region of δ 10.0 in all the compounds.

Physical and spectral data of all the compounds are given in Tables 1 and 2, respectively.

Table 1: Physical data of compounds 4(a-g)

Compd.	Molecular formula	M. P (°C)	Yield (%)	N Analysis (%) (Cald./Found)
4a	$C_{19}H_{18}ON_2$	135-137	65	10.00/9.65
4b	$C_{18}H_{15}O_3N_3$	140-142	58	13.08/13.28
4c	$C_{19}H_{18}O_2N_2$	130-132	60	9.13/9.42
4d	$C_{18}H_{15}ON_2Cl$	145-147	69	10.75/10.46
4e	$C_{14}H_{15}ON_2Cl$	135-137	70	10.74/10.66
4f	$C_{13}H_{11}O_2N_2Cl$	140-142	58	9.67/9.46
4g	$C_{14}H_{13}O_3N_2Cl$	150-152	61	9.24/9.04

Table 2: Spectral data of compounds 4 (a-g)

Compd.	IR (KBr) cm^{-1}	^{1}H NMR (δ ppm)	MS: m/z
4a	3200, 1612, 1465, 1334, 1095	10.1 (1H, s, NH); 6.9-7.14 (8H, m, ArH); 2.63-3.39 (4H, t, $(CH_2)_2$); 4.32 (2H, s, CH_2); 2.35 (3H, s, CH_3)	290.14 (100.0%) 291.14 (20.5%)

Cont…

Compd.	IR (KBr) cm^{-1}	^1H NMR (δ ppm)	MS: m/z
4b	3093, 1643, 1450, 1388, 1072,	10.2 (1H, s, NH); 7.07-7.14 (8H, m, ArH); 4.32 (2H, s, CH_2); 2.63-3.39 (4H,t, $(CH_2)_2$)	321.11 (100.0%) 322.0 (19.5%)
4c	3016, 1689, 1465, 1496, 1249	10.0 (1H,s, NH); 6.6-7.14 (8H, m, ArH); 4.32 (2H,s, CH_2); 2.63-3.39 (4H,t, $(CH_2)_2$); 3.73 (3H,s, CH_3)	306.13 (100.0%) 307.14 (20.5%)
4d	3090, 1650, 1452, 1286	10.2 (1H,s, NH); 7.1-7.14 (8H,m, ArH); 4.32 (2H,s, CH_2); 4.32 (2H,s, CH_2); 2.63-3.39 (4H,t, $(CH_2)_2$)	310.08 (100.0%) 312.08 (32.0%)
4e	3055, 1690, 1471, 1263	9.8 (1H, s, NH); 7.1-7.6 (3H, m, ArH); 2.55-3.71 (4H, t, $(CH_2)_2$); 2.02 (3H,s, CH_3)	262.08 (100.0%) 264.08 (32.0%)
4f	3170, 1620, 1496, 1280	9.9 (1H,s, NH); 7.1-7.6 (3H, m, ArH); 2.97 (1H,m, CH); 2.63-3.39 (4H,t,$(CH_2)_2$); 1.05(6H,d,$(CH_3)_2$)	262.05 (100.0%) 264.04 (32.0%)
4g	3093, 1643, 1450, 1296	10.1 (1H,s, NH); 7.1-7.6 (3H, m, ArH), 4.12 (3H,q, CH_3); 2.66-3.29 (4H, t, $(CH_2)_2$); 1.30 (2H, t, CH_2)	292.08 (100.0%) 294.08 (32.0%)

CONCLUSION

Two noteworthy features of the reactions employed in the preparation of 4-oxo azacarbazole derivatives are apparent from our study. Firstly, it establishes that the Fisher indolization of the 3-aryl hydrazones of piperidin-4-ones provides a very convenient synthetic entry to the difficultly accessible azacarbazole derivatives. Secondly, it establishes further the versatility of Japp-Klingemann reaction to provide a one pot synthetic approach to the preparation of the aryl hydrazones on the adjacent methylene carbon in a cyclic nitrogen containing carbonyl species.

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