Preparation of Secondary Alcohols from 1-N-benzyl 9,10- dihydrolysergol

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Abstract- *The Swern oxidation of 1-N-benzyl 9,10-dihydrolysergol using TFAA, DMSO, and TEA afforded 1-N-benzyl- 9,10- dihyrolysergal. The aldehyde moiety so produced was used for introduction of various substituents by employing Grignard reaction to yield new ergoline derivatives.*

Keywords- 9,10- Dihydrolysergal, TFAA, DMSO, TEA, Grignard reagent, ergoline.

I. INTRODUCTION

Ergot alkaloids are secondary metabolites produced by filamentous fungi such as Claviceps purpurea. These are pharmacologically important indole alkaloids. For example, ergot alkaloid such as pergolide is used as antiprolactin and anti-Parkinson's disease drugs [1-5]. Another ergot alkaloid Cabergoline is found to be a potent long-lasting prolactin inhibitor [6,7].

The broad physiological effects of ergot alkaloids are based mostly on their interactions with neurotransmitter receptors on the cells. The presence of "hidden structures'' resembling some important neurohumoral mediators (e.g. nor adrenaline, serotonin, dopamine) in the molecules of ergot alkaloids could explain their interactions with these receptors [8,9].

Ergot alkaloids also affect other organisms including bacteria, nematodes, and insects [10-15]. The mechanism behind the activities of ergolines is very less understood. Due to the pharmacological importance as well as structural appeal, ergot alkaloids have attracted considerable interest from the synthetic community.

Therefore, in the present work, syntheses of new ergot alkaloid derivatives were carried out by introducing secondary alcohol group at C-17 position. These derivatives were prepared from 1-N benzyl 9,10 -dihydrolysergal by using classically known Grignard's reaction. For the Grignard's reaction aldehyde functionality was required which was obtained by oxidation of 1-N benzyl 9,10 -dihydrolysergol.

II. RESULTS AND DISCUSSION

The Swern oxidation of 1-N-benzyl 9,10 -dihydrolysergol (1) [16] using triflouroacetic anhydride (TFAA), dimethylsulfoxide (DMSO) and triethyl amine (TEA) afforded 1-N-Benzyl- 9,10-dihyrolysergal (2) (Scheme 1). In this reaction, TFAA acts as activating agent for DMSO whereas TEA acts as base. The reaction was carried out essentially at low temperature because the intermediates formed during this reaction were unstable above -60o. As the reaction was light and moisture sensitive, it was carried out under nitrogen atmosphere in dark conditions. The procedure afforded dark brown solid as 1-N-benzyl 9,10 -dihydrolysergal (2), m.p. 138℃ in 67% yield.

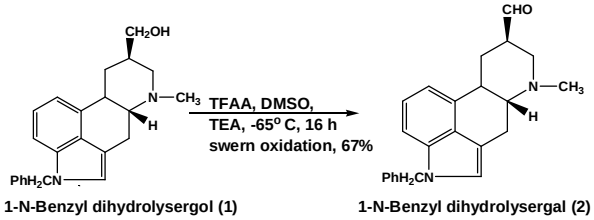

Figure 1.

Scheme 1: Preparation of 1-N-benzyl 9,10- dihydrolysergal (2) from 1-N-benzyl 9,10- dihydrolysergol (1).

The IR spectrum showed absorption at 1692 cm^{-1} for carbonyl carbon of the aldehyde group. The ^1H NMR spectrum of 1-N-benzyl 9,10- dihydrolysergal (2), showed aldehydic proton at δ 9.76 ppm. 13C NMR spectrum showed aldehydic carbon at δ 202 ppm.

The aldehyde moiety so produced was used for introduction of various substituents by employing Grignard reaction to yield new ergoline derivatives. For this various Grignard reagents were prepared in dry THF [17,18]. The reaction conditions required were strictly moisture free as the Grignard reagents are highly moisture sensitive and could lead to side product formation.

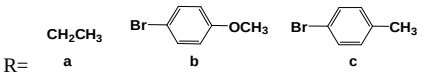

Figure 2.

Scheme 2: Synthesis of Grigrard's reagents of various alkyl halides.

The Grignard's reagents were prepared in situ and used for further reaction with 1-N-benzyl- 9,10- dihydrolysergal. After the syntheses of Grignard reagents (Scheme 2), various C-17 derivatives (secondary alcohols) were prepared from 1-N-benzyl 9,10- dihydrolysergal (2) using above prepared Grignard reagents (Scheme 3) [19]. The synthesized secondary alcohols were purified using flash column chromatography and characterized by 1H NMR, ^{13}CNMR and IR spectroscopy.

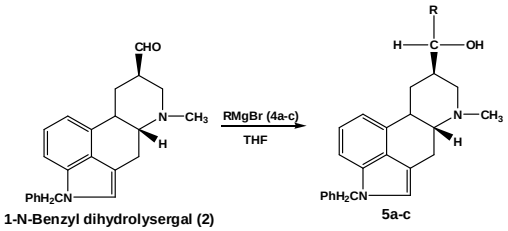

Figure 3.

Scheme 3: Preparation of various secondary alcohols of 1-N-benzyl dihydrolysergal (2).

The Grignard reaction of ethyl magnesium bromide (4a) with 1-N benzyl 9,10- dihydrolysergal (2) afforded 1-N-Benzyl-17- ethyl 9,10- dihydrolysergol (5a). The IR spectrum of product (5a) showed absorption at 3254 cm^{-1} for hydroxyl group of secondary alcohol and the peak for carbonyl group of aldehyde of 1-N-benzyl 9,10- dihydrolysergal (2) at 1692 cm^{-1} disappeared. The ^{1}H NMR spectrum of the product showed multiplet at δ 4.01 ppm for H-17 and at δ 1.18 ppm for ethyl group. The ^{13}C NMR spectrum of the product showed peaks at δ 22 ppm for –CH_3 and at δ 22 ppm for –CH^2 of ethyl group.

The Grignard reaction of 4- methoxy phenyl magnesium bromide (4b) with 1-N benzyl 9,10- dihydrolysergal (2) afforded 1-N-Benzyl- 17- (4-methoxy phenyl) 9,10- dihydrolysergol (5b). The IR spectrum of hydroxyl group showed absorption at 3225 cm^{-1} for hydroxyl group of secondary alcohol and the peak for carbonyl group of aldehyde of 9,10- dihydrolysergal (2) at 1692 cm^{-1} disappeared. The ^{1}H NMR spectrum of the product showed a multiplet at 3.99 ppm for H-17 and a singlet at δ 3.75 ppm for methoxy group present at para position. The ^{13}C NMR spectrum of the product showed peaks at δ 131, 132, 136, 199 ppm which were assigned to the meta, ortho, para and ipso carbons of tolyl group of product (5b).

Table 1. Data for secondary alcohols derived from lysergol.

Entry	Appearance	m.p (℃)	% yield
5a	Dark brown	170 (dec.)	43
5b	Black	186	52
5c	Black	182	57

The Grignard reaction of 4- methyl phenyl magnesium bromide (4c) with 1-N-benzyl 9,10- dihydrolysergal afforded 1-N-Benzyl-17-tolyl 9,10- dihydrolysergol (5c). The IR spectrum of hydroxyl group showed absorption at 3355 cm^{-1} for hydroxyl group of secondary alcohol and the peak for carbonyl group of aldehyde of 9,10- dihydrolysergal at 1692 cm^{-1} disappeared. The ^{1}H NMR spectrum of the product showed a doublet at δ 4.01 (J= 8 Hz) for H-17 and a singlet at δ 1.17 ppm for methyl group present at para position. The ^{13}C NMR spectrum of the product showed peaks at δ 128, 130, 132, 137 ppm which were assigned to the meta, ortho, para and ipso carbons of tolyl group of product. The data for these derivatives is given in Table 1.

III. CONCLUSIONS

In the present work various secondary alcohols were synthesized by oxidizing 1-N-benzyl 9,10– dihydrolysergol to 1-N-benzyl 9,10– dihydrolysergal. The aldehyde group was used for the synthesis of various aliphatic as well as aromatic secondary alcohols by employing Grignard reaction. The alcohols were produced in 40-60% yield.

IV. EXPERIMENTAL

General: Melting points (°C) (m.p) were taken in open capillaries are uncorrected. Infrared spectra (IR) were recorded using Perkin Elmer Model 1430 spectrophotometer with potassium bromide (KBr) palette. Only principle absorption bands of interest are reported and expressed in cm-1. NMR spectra were recorded using BRUKER AVANCE II 400(400MHz). Chemical shifts are given in ppm relative to tetramethyl silane as an internal standard (δ= 0 ppm) for 1H NMR and DMSO-d6 (δ= 39.50ppm) for 13C NMR spectra.

1- N-Benzyl-9,10- Dihydrolysergal[16] (2): Triflouroacetic anhydride (0.4 mL, 2.761 mmol) in dichloromethane (1 mL) was added drop wise to a solution of dichloromethane (1ml) and DMSO (0.26 mL, 3.43 mmol) under nitrogen atmosphere at -78o C and a solution of 1-N Benzyldihyrolysergol (0.200 g, 0.602 mmol) in the mixture of dichloromethane (2 mL) and DMSO (0.7 mL) was added drop wise. The mixture was

stirred for another 30 min at -78o C and triethyl amine (1 mL, 7.69 mmol). The mixture was stirred for 10 min and allowed to warm up to r. t. and stirred in dark under nitrogen for 26 h. After reaction completion the reaction mass was diluted with brine (35 mL). The aqeous layer was dichloromethane extracted with dichloromethane (3 × 20 mL). The combined organic layer was washed with saturated sodium bicarbonate solution (2 × 20 mL). The organic layer was dried over sodium sulphate and evaporated to give sticky material (0.380 g). The residue was purified using flash column chromatography to give brown solid, m.p. 138o C (0.182 g, 91%).

IR (KBr, cm^{-1}): 3430, 2959, 2926, 2854, 1718, 1599, 1579, 1438, 1395, 1339, 1287, 1122, 1073, 1039, 964, 743, 704, 650, 718.

1H NMR (CDCl3, 400MHz , δppm) : 1.43 (d, 1H, H-9a), 2.31 (m, 1H, H-5), 2.56 (s, 3H, N-CH3), 2.78 (m, 1H, H-4a), 2.90 (m, 1H, H-9e), 2.99 (m, 1H, H-8), 3.47 (m, 1H, H-4e), 3.08 (m, 1H, H-10) , 3.36 (m, 1H, H-7), 3.42 (m, 1H, H-9e), 5.25 (s, 2H, CH2Ph), 6.80 (m, 1H, H-2), 7.08 (m, 1H, H-12), 7.15 (m, 3H, H-13, H-ortho, H-para), 7.28 (m, 2H, H-meta), 9.76 (CHO).

^{13}CNMR ($CDCl_3$, 100 MHz, δppm): 26.56 (C-4), 27.71 (C-8), 43.52 (N-CH3), 50.22 (CH2), 50.24 (CH2Ph), 56.31 (C-7), 67.05 (C-5), 107.68 (C-14), 107.69 (C-3), 112.98 (C-12), 121.82 (C-2), 122.11 (C-13), 126.96 (C-16, ortho), 127.63 (para), 128.72 (C- meta), 134.10 (C-15), 137.80 (C-ipso).

Ethyl magnesium bromide (4a): To a flame dried three necked flask magnesium (0.010 g, 0.454 mmol), dry THF (0.5 ml) and a small crystal of iodine were added. To this 4- bromo toluene (0.080 g, 4.6 mmol) was added drop wise through syringe. The reaction mixture was stirred for 30 min under nitrogen.

1-N–benzyl-17-ethyl-9,10- dihydrolysergol (5a): To the ethyl magnesium bromide (0.080 g, 0.320 mmol) was added drop wise solution of 1-N-benzyl 9,10 –dihydrolysergol (0.100 g, 0.303 mmol) in THF (15 mL) under nitrogen. The reaction mass was stirred overnight at room temperature. After reaction completion solution of ammonium chloride (5 mL) was added. The reaction mass was extracted with chloroform (3 × 20 mL). The combined organic layer was washed with brine (15 mL), dried over sodium sulphate and evaporated to give black solid (0.046 g, 43%).

IR (KBr, cm-1, neat): 3428, 3254, 2959, 2922, 2858, 2354, 2118, 1651, 1432, 1258, 1048, 1024, 997, 825, 763, 628.

^{1}H-NMR (300MHz, DMSO-d6, δppm): 0.92 (m, 1H, H-7a), 1.18 (m, 5H, ethyl), 1.98 (s, 3H, N-CH3), 2.76 (m, 1H, H-8), 3.72 (m, 1H, H-4e), 4.03 (m, 1H, CHOH), 5.03 (s, 2H, CH2Ph), 6.81 (m, 1H, H-9), 7.20 (m, 9H, H-aromatic).

^{13}C-NMR (100 MHz, DMSO-d6, δppm): 21.95 (-CH3 ethyl), 22.28 (-CH2 ethyl), 23.89 (C-4), 38.66 (C-8), 40.05 (N-CH3), 48.79 (C-7), 49.78 (CH2Ph), 59.04 (C-5), 70.93 (C-17), 122.01 (C-9), 126.21 (C-18), 126.67 (C- ortho), 126.91 (C-para), 127.09 (C- meta), 128.17 (C-11), 126.28 (C-10), 129.26 (C-15), 138.98 (C- ipso).

4-Methoxy phenyl magnesium bromide (4b): To a flame dried three necked flask magnesium (0.010 g , 0.24 mmol) , dry THF (15 ml) and a small crystal of iodine were added . To this 4- bromo anisole (0.044 g, 0.24 mmol) was added drop wise through syringe. The reaction mixture was stirred for 30 min under nitrogen.

1-N–benzyl-17-(4-methoxy) phenyl-9,10-dihydrolysergol (5b): To the 4-methoxy phenyl magnesium bromide (0.080 g, 0.348 mmol) was added drop wise solution of 1-N-benzyl 9,10 –dihydrolysergol (0.100 g , 0.303 mmol) in THF (15 mL) under nitrogen. The reaction mass was stirred overnight at room temperature. After reaction completion solution of ammonium chloride (5 mL) was added. The reaction mass was extracted with chloroform (3 × 20 mL). The combined organic layer was washed with brine (15 mL), dried over sodium sulphate and evaporated to give black solid (0.068 g, 52%)

IR (KBr, cm-1, neat): 3394, 3225, 3070, 2924, 2856, 2597, 2361, 2258, 2125, 1885, 1690, 1616, 1509, 1458, 1244, 1133, 1025, 820, 761, 735, 698, 576.

1H-NMR (300 MHz,DMSO-d_6, δppm) : 1.17 (m, 1H, H-7a), 1.92 (s, 3H, N-CH3), 2.18(m, 1H, H-8), 3.75 (s, 3H, OCH3), 3.85 (m, 2H, H-9), 3.99 (m, 1H, CHOH), 4.75 (m, 2H, CH2Ph), 6.65-7.82 (m, 13H, H-aromatic).

13C-NMR (100 MHz, DMSO-d_6,δppm) : 25.58 (C- 4), 29.07 (C- 9), 34.11 (C- 5), 38.42 (C-8), 40.32 (N-CH3), 54.86 (CH2), 62.77 (C-5), 67.77 (C-17), 113.23 (C-14), 113.88 (C-12), 115.58 (C-2), 122.27 (C-13), 126.40 (C-16), 126.59 (C-ortho), 127.07 (para), 128.19 (C-meta), 128.71(C-11), 131.39 (C- meta-methoxy), 132.24 (C- ortho-methoxy), 134.97 (C-15), 147.87 (C- ipso phenyl), 198.47 (C- ipso methoxy).

4-Methyl phenyl magnesium bromide (4c): To a flame dried three necked flask magnesium (0.010 g ,0.454mmol) , dry THF (0.5 ml) and a small crystal of iodine were added . To this 4- bromo toluene (0.080 g, 0.472 mmol) was added drop

wise through syringe. The reaction mixture was stirred for 30 min under nitrogen.

1-N–benzyl-17-tolyl-9,10- dihydrolysergol (5c): To the 4-methyl phenyl magnesium bromide (0.088 g, 0.454 mmol) was added drop wise solution of 1-N-benzyl 9,10 – dihydrolysergol (0.100 g , 0.303 mmol) in THF (15 mL) under nitrogen. The reaction mass was stirred overnight at room temperature. After reaction completion solution of ammonium chloride (5 mL) was added. The reaction mass was extracted with chloroform (3 × 20 mL). The combined organic layer was washed with brine (15 mL), dried over sodium sulphate and evaporated to give black solid (0.061 g, 57%).

IR (KBr, cm-1): 3355, 3026, 2923, 1681, 1607, 1497, 1452, 1304 (N-H), 1071, 817, 743, 700, 644, 577, 553.

1H-NMR(DMSO-d_6,300 MHz, δppm):1.17 (s, 3H, p-CH3) , 1.56 (m, 1H, H-9a), 1.95 (m, 1H, H-7a) , 2.24 (s, 3H, N-CH3), 2.31 (m, 2H, H-7a, 4a), 2.67 (m, 2H, H-8, H-10), 3.55 (m, 2H, H-7e, H-4e), 4.01 (d, J= 6.68 Hz, 1H, H-17), 5.01 (s, 2H, CH2), 7.12 (m, 13H, aromatic).

^{13}C-NMR (DMSO-d_6 , 100 MHz, δppm): 20.62 (p-CH3), 26.67 (C-4), 30.68 (C-9), 34.12 (C-5), 35.24 (N-CH3) , 61.08 (C-7), 61.62 (C-5), 124.72 (C-2), 125.40 (C-13), 125.79 (C-2), 126.59 (C-16), 127.22 (C- ortho phenyl), 127.81 (para phenyl), 128.04 (meta phenyl), 128.24 (C- meta tolyl), 129.95 (C-ortho tolyl), 132.24 (C- para tolyl), 135.68 (C-11), 135.92 (C-15), 137.25 (C- ipso phenyl), 140.75 (C- ipso tolyl).

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