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Hydroboration of Agroclavine and Lysergene

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Abstract

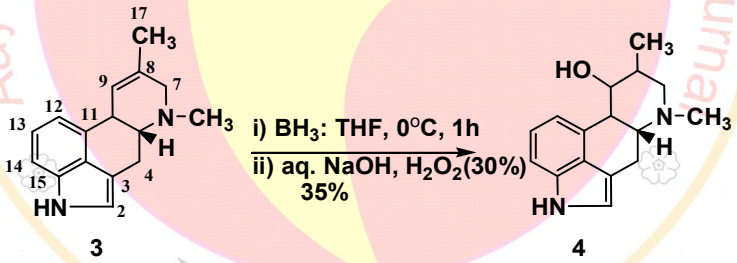
The hydroboration- oxidation reaction of lysergene and agroclavine has been carried out with diborane resulting in the formation of lysergol and 8-hydro-9-hydroxy agroclavine respectively in > 35% yield.

Keywords: Hydroboration, lysergene, agrocalvine, diborane, lysergol, 8-hydro-9-hydroxy agroclavine.

1. Introduction

Ergot alkaloids are pharmacologically important indole alkaloids produced by the fungus *Claviceps purpurea*, which grows parasitically on rye and other grains [1]. Ergot alkaloids have various potent biological activities therefore, they are used in the treatment of diseases like migraine, hypertension, acromegaly, postpartum bleeding, orthostatic circulatory disturbances, senile cerebral insufficiency, and Parkinsonism [2-11]. Due to striking physiological properties their synthesis and reactivity are subject of considerable interest. The present work aims towards the interconversion of ergot alkaloids using classically known hydroboration reaction.

Hydroboration-Oxidation is a two step reaction used to synthesize alcohols. The reaction proceeds in an anti-Markovnikov manner, where the hydrogen (from BH_3) bonded to the more substituted carbon and the boron is bonded to the least substituted carbon in the alkene bouble bond [12-14].



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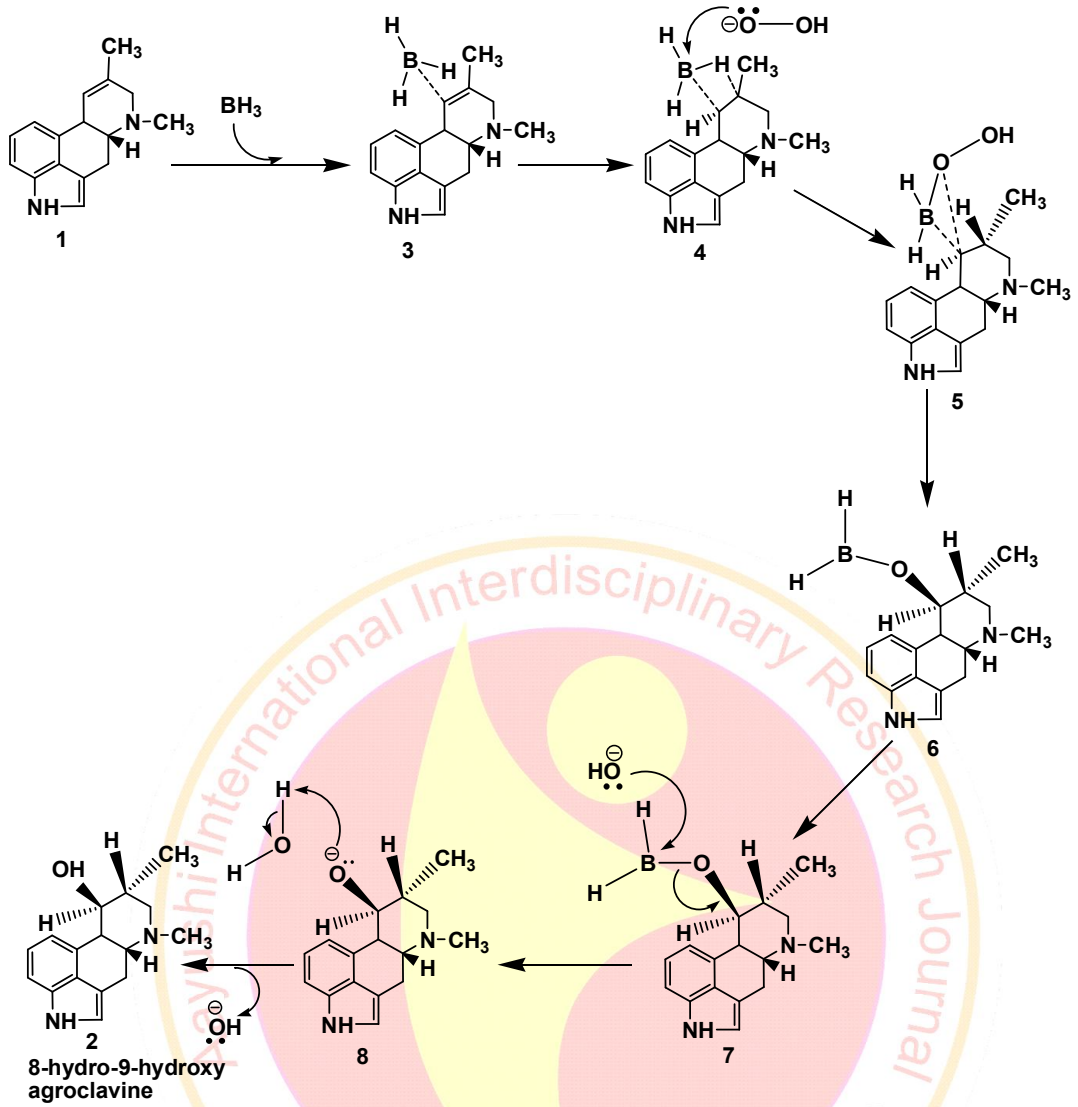
Scheme 1: Hydroboration of agroclavine (1) to give 8-hydro-9-hydroxy agroclavine (2).

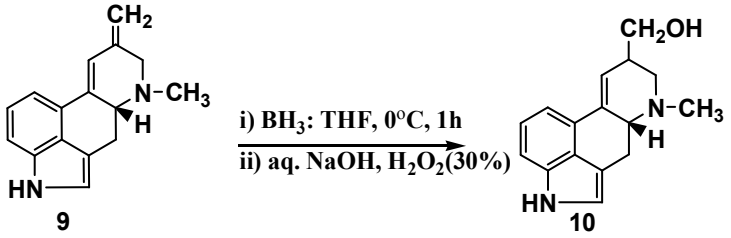
Hydroboration is an efficient method for the syn addition at the double bond of an alkene. Therefore, to see whether syn addition to the double bond of agroclavine takes place or not, it was reacted with diborane. The hydrobotarion treaction of agroclavine (1) was carried out with diborane to give 8-hydro-9-hydroxy agroclavine (2) in 41% yield



Scheme 2: Proposed mechanism for hydroboration of agroclavine (1) to give 8-hydro-9-hydroxy agroclavine (2).

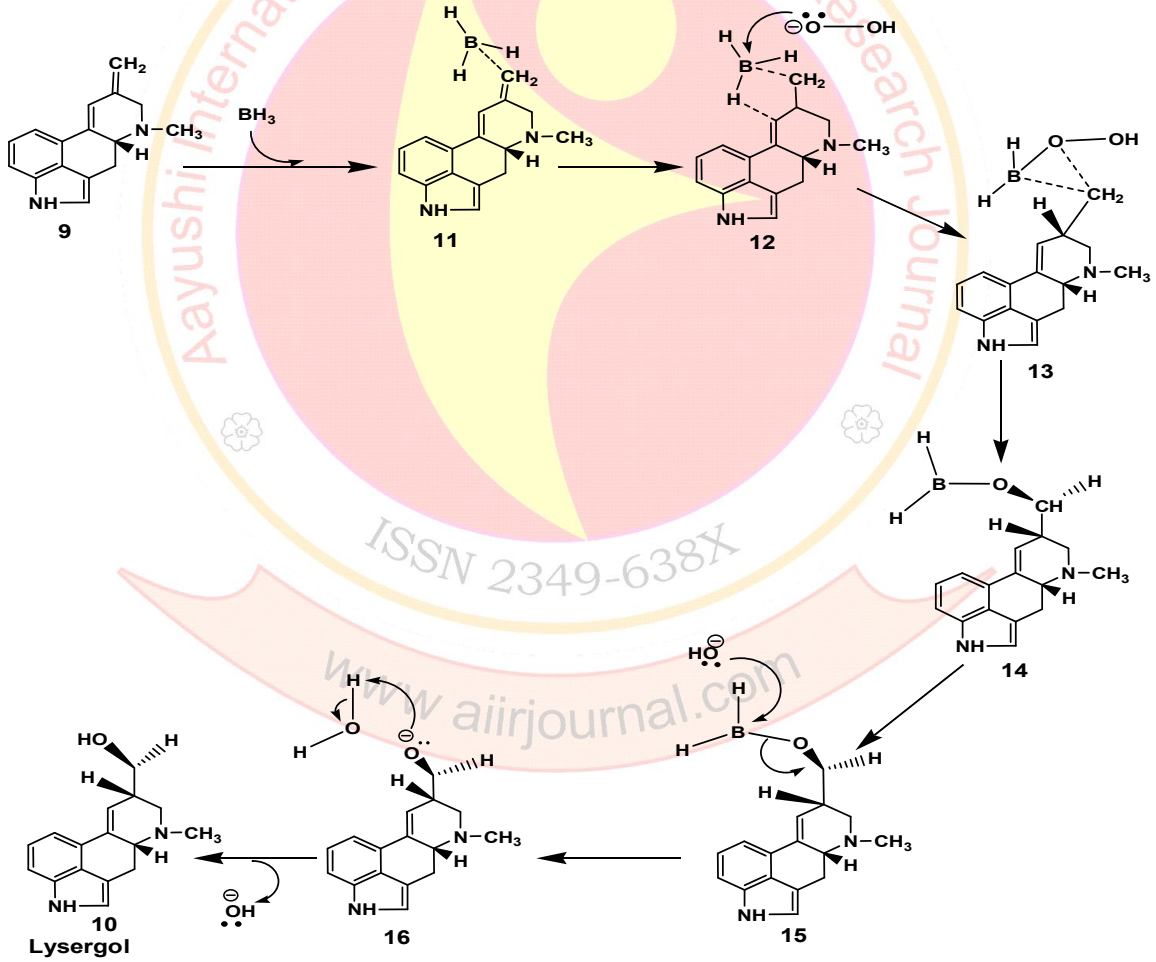
The proposed mechanism for the reaction is given in scheme 2. In agroclavine (1) when the hydroboration reaction is carried out, the boron atom gets bonded to C-9. When the filled Π- orbitals of C8-C9 of agroclavine adds to empty orbital of borane, it gives a stable intermediate (3). Hydroboration is a syn addition across double bond. As the addition of empty p- orbital of boron to less substituted C-9 occurs, a hydrogen atom from borane gets added with its electron pair to C-8. Thus C9-B bond and C8-H bond formation occurs simultaneously. Therefore, a four centered transition state is formed (4). Then oxidation occurs by nucleophilic attack of hydroperoxide ion to empty p- orbital of boron atom followed by rearrangement of C9-B bond to C9-O bond (5). The peroxide bond breaks and hydroxide ion leaves to give (6). Finally, hydroxide ion attacks boron to break B-O bond (7) and 8-hydro-9-hydroxy agroclavine (2) is formed.

Similarly, the hydroboration- oxidation of lysergene (9) was carried out using diborane to give lysergol (10) as the final product (scheme 3) in 35% yield. The proposed mechanism for the reaction is given in scheme 4.



Scheme 3: Hydroboration of lysergene (9) to give lysergol (10).

When lysergene (9) is subjected to hydroboration reaction, the boron atom gets bonded to C-17. When the filled Π- orbitals of C9-C17 of lysergene adds to empty orbital of borane it gives a stable intermediate (11). Hydroboration is a syn addition across double bond. As the addition of empty p- orbital of boron to less substituted C-17 occurs a hydrogen atom from borane gets added with its electron pair to C-9. Thus C17-Boron bond and C8-H bond formation occurs simultaneously. Therefore, a four centered transition state (12) is formed. Then oxidation occurs by nucleophilic attack of hydroperoxide ion to empty p- orbital of boron atom followed by rearrangement of C17-Boron bond to C17-O bond (13). The peroxide bond breaks and hydroxide ion leaves to give (14). Finally, hydroxide ion attacks boron to break B-O bond (15) and lysergol (10) is formed.



Scheme 4: Proposed mechanism for the hydroboration of lysergene (9) to give lysergol (10)

2. Experimental

2.1 General experimental

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 ^{1}H NMR and DMSO-d_6 (δ= 39.50ppm) for ^{13}C NMR spectra.

2.1.1. 8-hydro-9-hydroxy agroclavine (2): Agroclavine (0.100 g, 0.042 mmol) in dry THF (25 mL) at 0˚ C was added diborane in THF (0.33 mL, 7.5 eq.) drop wise under nitrogen atmosphere. The reaction mixture was stirred for 30 min and excess of diborane was destroyed with water (1.5 mL). Aqueous sodium hydroxide (0.1 mL, 3M) and hydrogen peroxide (0.1 mL, 30%) solution were added and stirring was continued for 2 h at room temperature. The progress of reaction was monitored on TLC. After reaction completion the solvent was evaporated under vacuum. The residue was dissolved in water (5 mL) and extracted with ether (3 × 15 mL). The combined ether layer was washed with brine (10 mL) dried over sodium sulphate and evaporated to give yellow oily residue (0.107 g). The residue obtained was purified using flash column chromatography to give yellow oil (0.044 g, 41%).

IR (Neat, cm^{-1}): 3417, 2997, 2914, 2359, 1996, 1653, 1576, 1435, 1341, 1312, 1202, 1026, 953, 897, 784, 703, 667, 507, 415.

^{1}HNMR (DMSO-d_6/ $CDCl_3$, 300MHz, δppm): 1.74 (s, 3H, CH_3), 2.57 (m, 3H, N-CH_3), 2.72 (m, 1H, H-4a), 2.76 (m, 1H, H-8), 3.35 (m, 1H, H-7), 3.81 (m, 1H, H-10), 6.21 (m, 1H, H-9), 6.99 (m, 4H, H-aromatic).

^{13}CNMR (DMSO-d_6/ $CDCl_3$, 75MHz, δppm): 18.95 (C-2), 27.77 (C-4), 39.00 (C-10), 61.76 (C-7), 64.13 (C-5), 107.68 (C-3), 110.19 (C-12), 110.74 (C-14), 118.18 (C-9), 120.45 (C-13), 126.82 (C-16), 128.56 (C-11), 132.00 (C-15).

2.1.2 Lysergol (1): Diborane: THF (0.22 mL, 5 equiv.) was added drop wise to a solution of lysergene (0.100 g, 0.042 mmol) in dry THF (7.5mL) at 0° C. The reaction mixture was stirred at room temperature for 30 min. The contents were quenched with water (1.5 mL), aq. NaOH (0.1 mL, 3M) and H_2O_2 (0.1mL, 30%). The reaction mass was stirred for 2 h at room temperature. The solvent was evaporated under vacuum and residue was dissolved in water (5 mL) and extracted with diethyl ether (2 × 15 mL). The combined ether layer was dried over sodium sulphate and evaporated to give yellow residue (0.317 g). Its purification by flash chromatography in $CHCl_3$: MeOH (8:2) gave lysergol (0.37g, 35%), Rf = 0.28, m.p. 250°-252°C [Lit. 253-255°C]. $[\alpha]_D^t$ = +53.33˚(c 0.3 in pyridine) [Lit. +54˚(c 0.3 in pyridine)] [15-16].

IR (KBr, cm^{-1}): 3426, 3105, 3071, 2995, 2946, 2875, 2808, 2767, 1888, 1826, 1763, 1653, 1606, 1559, 1546, 1500, 1458, 1446, 1414, 1372, 1342, 1317, 1342, 1317, 1293, 1241, 1220, 1163, 1143, 1125, 1099, 1078, 1054, 1037, 1000, 984, 945, 1923, 895, 883, 857, 844, 808.5, 781, 757, 746, 664, 634, 615.2, 575, 557, 494, 458.

^{1}HNMR ($CDCl_3$, 400MHz, δppm): 2.12 (m, 1H, H-7ax), 2.47 (s, 3H, N-CH_3), 2.52 (m, 1H, H-4α), 2.71 (s, 1H, H-8), 2.94 (m, 2H, H-5), 2.97(m, 1H, H-7β), 3.37 (m, 1H, H-4β), 4.81(t, J= 5.16 Hz, 1H, OH), 3.64 (m, 2H, H-17), 6.37 (s, 1H, H-9), 7.07 (m, 3H, H-12, H-13, H-14), 7.21(m, 2H, H-2).

^{13}CNMR ($CDCl_3$, 100MHz, δppm): 26.85 (C-4), 38.84 (N-CH_3), 43.72 (C-8), 56.87 (C-7), 63.15 (C-5), 63.62 (C-17), 109.13 (C-14), 109.46 (C-3), 110.88 (C-2), 119.07 (C-12), 122.18 (C-9), 125.84 (C-16), 127.81 (C-11), 133.80 (C-15), 134.91 (C-10).

3. Results and discussion

The hydroboration- oxidation of agroclavine (1) was carried out with a view to obtain 1,2 addition of water across C8- C9 double bond to give 8-hydro-9-hydroxy agroclavine (2) in 41% yield. The product obtained was purified by flash chromatography. It showed absorption at 3417 cm^{-1} for hydroxyl group. The ^{1}H

NMR of the product showed a singlet at δ 1.74 ppm for methyl protons at C- 17. A multiplet was shown at δ 2.76 ppm for H-8 and a doublet at δ 6.21 ppm for H-9. The ^{13}C NMR showed a signal at δ 118 ppm for C-9.

Similarly, the hydroboration- oxidation of lysergene (1) was carried out to give lysergol **(2)** as the final product. The IR spectrum of purified product showed absorption at 3426 cm^{-1} for hydroxyl group. The ^{1}H NMR of the product showed a multiplet was shown at δ 2.67 ppm for H- 8. A singlet was shown for -CH_2 protons at C-17 singlet at δ 2.91 ppm and a singlet at δ 6.32 ppm for H-9. The ^{13}C NMR showed a signal at δ 63.71 ppm for C-17, at 43.78 ppm for C-8 and at δ 122.27 ppm for C-9. All these data were in agreement to the reported data of lysergol.

4. Conclusions

In the present work classically known hydroboration reaction was used for inter conversion of ergot alkaloids. 8-hydro-9-hydroxy agroclavine was synthesized from agroclavine by addition of water across C8-C-9 double bond of ergoline ring system. Also, lysergol was synthesized from lysergene by addition of water across double bond present between C8- C-17 of ergoline ring system. Hydroboration oxidation was found to be an efficient method for the syn addition at the double bond. The hydroxy products obtained by hydroboration reaction of agroclavine and lysergene were obtained in >35% yield.

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