Oligomerisation Of Lysergol

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Abstract- *Homocoupling/oligomerization of lysergolwasattempted using two importantmethods.In the first method, lysergol was reacted with potassium hexacyano ferrate {$K_4[Fe(CN)_6]$} in presence of $Pd(OAc)_2$ and $Cu(OAc)_2$ in DMSO. Another oligomerization of lysergol was attempted using bifunctional alkyl halidein the presence of potassium hydroxide as base in DMSO,at indolic nitrogen through alkylation.*

Keywords- Homocoupling/oligomerization, lysergol, {$K_4[Fe(CN)_6]$}, $Pd(OAc)_2$, $Cu(OAc)_2$,DMSO and alkylation.

I. INTRODUCTION

Indole is a heterocyclic organic compound found in many natural products, biopharmaceuticals and agrochemicals [1-5]. Several natural compounds such as tryptophan, serotonin, and melatonin etc. with many important physiological activities contain indole moiety [12-14].Indole derivatives like diindolyl methane play a very important role in the synthesis of several compounds with pharmacological activity[12-14]. Severalnaturally occurring alkaloids containingdimericindoleframework can be synthetically prepared from bis(indolyl) compounds.These bis(indolyl) compounds have been found to exhibit a wide range of pharmacological activities, including antibiotic, antitumor, antidepressant, antiviral, diuretic, and anticancer action [6-11]. In view of their diverse biological properties, structural modification of the indole nucleus has attracted the attention of many synthetic organic chemists in recent years.

Thus, the synthesis of indole derivatives using different catalysts has been developed [15-21]. It was reported that under acidic conditions, indole itself polymerizes to polyindole (dimer or trimer) (Scheme 1) [22-23]. Geller [24] reported the first acid-catalyzed self-addition product of indole as a trimer, which was further studied by Smith [25] and it was found to have the structure of indole- 3,3′-trimer **(1)**. Later, the Ishii group reported a new indole- 2,3′-trimer **(2)** formed by the self-addition of indole in the presence of p-toluenesulfonic acid (p-TSA) in benzene at reflux [26]. When indole was treated with 98% formic acid, indoletrimer**(2)** and dimer **(4)** were obtained in 30 and 32% yields, respectively [27]. A mixture of indoletrimers**(2)** and **(3)** and dimer **(4)**and was obtained by the reaction of 3-bromoindole and indole in the presence of trifluoroacetic acid (TFA) in dichloromethane at room temperature [28]. These reactions were catalyzed by Brønsted acids and required a stoichiometric amount of catalyst. Pal et al. reported $InCl_3$-mediated oligomerization of indole in which indole 3,3′-trimer **(1)** was obtained in 46% yield along with unexpected 3-acetylindole [29]. Thus, indoleoligomerization [29-30] is sensitive to the substituent on the indole ring, acid concentration, temperature, and the nature of both the solvent and the acid [5].

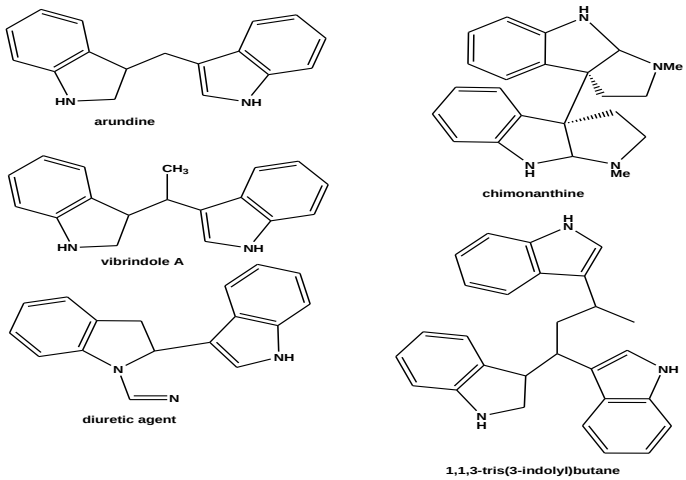
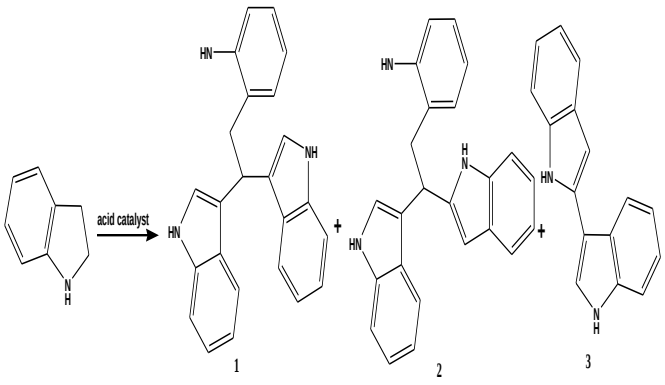


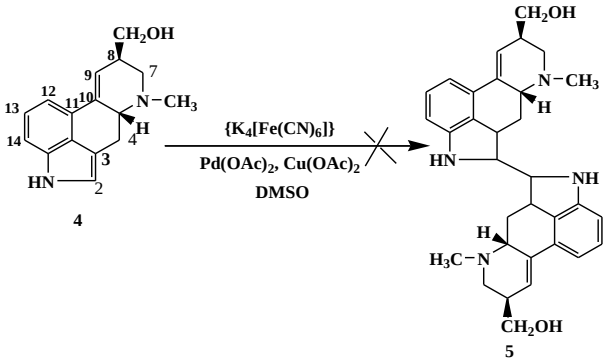
Figure 1 Structures of some bioactive indole dimers and trimers.



CF_3CO_2H/CH_2Cl_2	8%	2%	6%
p-TSA		39%	
HCH_2Cl_2H	30%	-	32%
$InCl_3$	46%	-	-

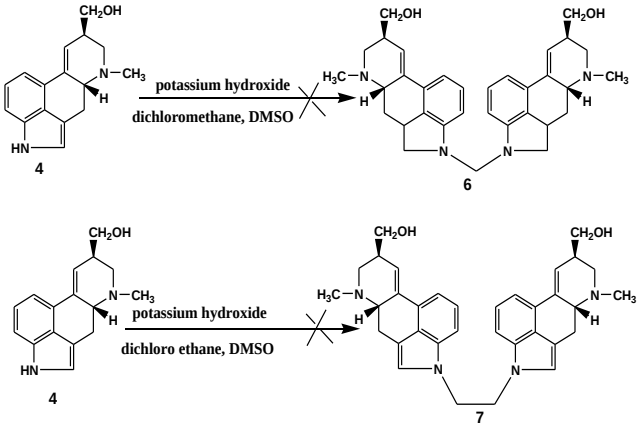
Scheme 1 Acid-catalyzedoligomerization of indole [22-23].

II. RESULTS AND DISCUSSION



Scheme 2: Attemptedhomocoupling of lysergol**(4)** to give lysergol dimer**(5).**

Homocoupling of indoles has been reported by Wang et al using palladium acetate and potassium hexacyanoferrate (III) [31]. As reported in literature, we attempted homocoupling of lysergol under similar conditions. Lysergol**(4)**was reacted with potassium hexacyano ferrate $\{K_4[Fe(CN)_6]\}$ in presence of $Pd(OAc)_2$ and $Cu(OAc)_2$ in DMSO. But, this reaction did not lead to the lysergol dimer **(5)**, rather there was decomposition of the aromatic indole ring of lysergol.



Scheme 3: Attemptedoligomerisation of lysergol

It is documented that clustered alkaloids have substantially higher affinity towards the respective receptor than single molecules [32]. Therefore, the oligomerization of lysergol**(4)** was attempted using potassium hydroxide in DMSO method at indolic nitrogen through alkylation. In this process bifunctional alkyl halide e.g. dichloromethane and 1,2-dibromoethane were used for the alkylation in the presence of potassium hydroxide as base (Compounds **6** and **7**). But, instead of oligomerization the spectral data showed the starting compound lysergol**(4)**.

III. CONCLUSION

Two processes were attempted for Homocoupling/oligomerization of lysergol. It was found that lysergol did not behave similar to indole during oligomerisation. The non reactivity of lysergol towards oligomerisation may be due to the conjugation of indole ring double bond with the double bond between C_9-C_{10}. The reason seems to be that the electrons of double bond at C_2-C_3 position are not available as freely as in an unsubstitutedindole.

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 tetramethylsilane as an internal standard (δ= 0 ppm) for ^1H NMR and DMSO-d_6 (δ= 39.50ppm) for ^{13}C NMR spectra.

Attempted preparation of lysergol oligomer (5): Palladium acetate (10 mol%, 0.011 g, 0.045mmol), copper acetate (3 equiv., 0.245 g, 1.45 mmol) and lysergol (0.5g, 1.96 mmol) were dissolved in DMSO (5 mL). The reaction mixture was heated at 130° C for 5 h. After 5h DMSO was evaporated under vacuum. The residue was dissolved in water (15 mL), extracted with ethyl acetate (3 × 15 mL). The organic layer was dried over sodium sulphate and evaporated under vacuum to give orange solid (0.055 g).

TLC, ^1H NMR and^{13}CNMR spectrum of the residue showed the presence of starting material only.

Attempted preparation of N,N'- Methylene dilysergol (6): Finely powdered KOH (0.55 g, 0.0132 mmol) was stirred with DMSO (4 mL) for 10 min. Lysergol was added and the stirring was continued for another 30 min. The mixture was cooled to 10-15º C and dichloromethane (0.042 g, 0.492 mmol) was added in portions. The reaction mass was stirred at room temperature for 16 h. After reaction completion the contents were was poured into water (35 mL). The precipitates formed were filtered and recrystallized from methanol to give dark brown crystals.

^1H NMR and ^{13}CNMR spectrum of the residue showed only lysergol.

Attempted preparation of N,N'-Ethylene dilysergol (7): Finely powdered potassium hydroxide (0.728 g, 0.0132 mmol) was stirred with DMSO (2 mL) for 10 min. Lysergol was added and the stirring was continued for another 30 min. The mixture was cooled to 10-15° C and 1, 2-dibromoethane (0.092 g, 0.492 mmol) was added in portions. The reaction mass was stirred at room temperature for 7.5 h. After reaction completion the contents were poured into water (30 mL). The precipitates formed were filtered and recrystallized from methanol to give dark brown crystals (0.130 g).

TLC, ^{1}H NMR and ^{13}CNMR spectrum of the residue showed only lysergol.

V. ACKNOWLEDGEMENT

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