STUDY OF THE SYNTHESIS OF DIHYDROCINNOLINES USING HYDRAZINE AND SUBSTITUTED AND UNSUBSTITUTED CARBONYL COMPOUNDS

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ABSTRACT

The preparation of 1,4-dihydrocinnoline by a general method in which phenylhydrazine and α-halo carbonyl compounds condense to form phenylhydrazones which then undergo intramolecular Friedel-Crafts alkylation to give 1,4-dihydrocinnoline derivative. An alternative method was applied to further proof of the structure of 1,4-dihydrocinnolines.

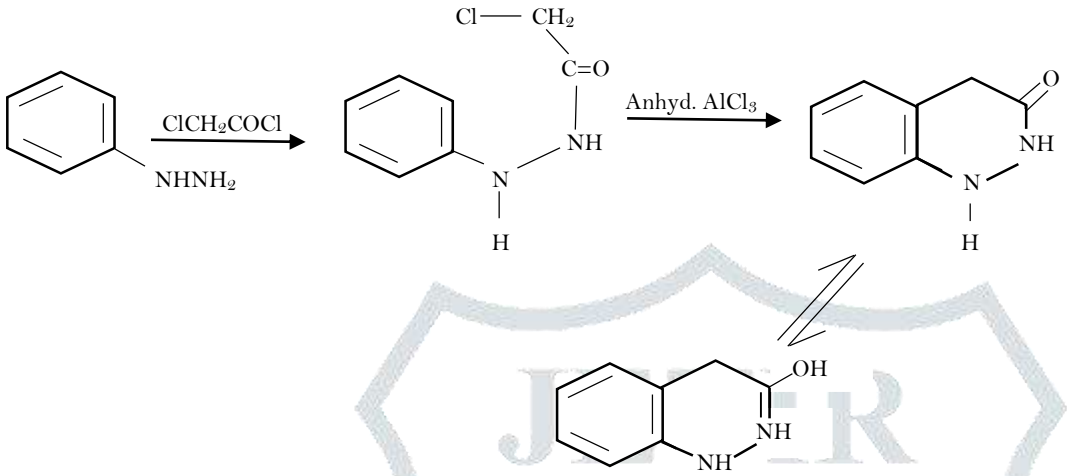
KEY WORDS : Phenylhydrazine, α-halo carbonyl compound, 1,4-dihydrocinnoline

INTRODUCTION :

Cinnoline is a pale yellow solid of germanium like odour which is soluble in water. It crystallizes from ether with one molecule of solvent and then melts at 24-25°C. The solvent free base melts at 39°C. Cinnolines are pharmaceutically and biologically important structure with anticancer, antimicrobial, antinflammatory, antiparasitic, activities. The synthesis of nitrogen containing heterocyclic compounds from carbonyl compounds and hydrazine is a field of great interest.

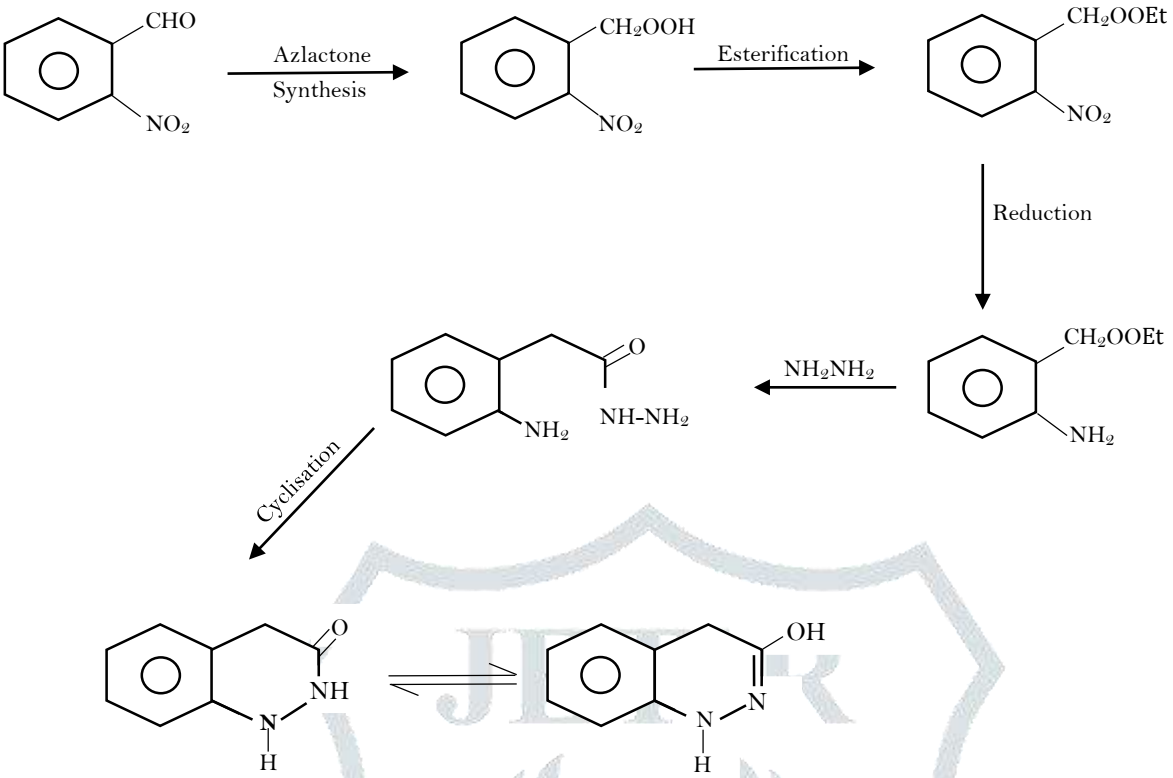
Synthesis of 1,4-dihydrocinnoline was carried by choosen phenylhydrazine and chloroacetyl chloride. Formation of phenylhydrazine is from easily available aromatic amines. Accordingly phenylhydrazine was condensed with chloroacetyl chloride using standard method in ethanol solution under reflux in water bath and the product was recrystalised in ethanol. Friedel-Crafts intramolecular rearrangement reaction was then carried out in carbon-disulphide

solution of ordinary temperature. A steady evolution of hydrogen chloride in the reaction showed the progress of reaction and time to time t.l.c examination as also carried out. A pure crystalline product was correctly analysed for the structure of dihydrocinnoline.



An alternative method was applied to further proof of the structure of 1,4-dihydrocinnoline. In the following method, o-nitrobenzaldehyde was converted into o-nitrophenylacetic acid by Azlactone synthesis and then esterified into ethyl ester. Reduction of this ester leads to the formation of ethyl-o-amino-phenylacetate. Ethyl ester of o-aminophenylacetic acid is treated with hydrazine to give 0-aminophenylacetylhydrazide. This was heated under forcing conditions to boil about its cyclisation to 3-hydroxy-1,4-dihydrocinnoline. The cyclisation was effected by heating them with hydrogen chloride gas, perchloric acid, phosphorus pentoxide in carbon tetrachloride as well as heating directly i.e. alone for several times (four to ten hours). The progress of the reaction was checked by t.l.c examination from time to time. The cyclisation product in all cases was of good yield, since acidic reagents are found to be more effective in bringing about such cyclisations. Ammonia gas is evolved in the reaction.

The product from this reaction was identical with that obtained earlier as shown by t.l.c examination, melting point and the complete identity of their I.R. spectra. Thus, the compound obtained was 1,4-dihydrocinnoline.



EXPERIMENTAL :

Preparation of p-nitrophenylhydrazine

For the preparation of p-nitrophenylhydrazine, standard method of Vogel was followed. A solution of p-nitro aniline (20 ml) in concentrated hydrochloric acid (30ml) and water (50ml) was diazotized using sodium nitrite solution with constant stirring. The diazotized solution was added to an ice cold solution of sodium sulphate (80g) in water (200ml) containing sodium hydroxide (8g). It was then acidified by adding concentrated hydrochloric acid (150ml) with stirring, till the yellowish white solid is separated out from the reaction mixture. The reaction mixture was left over night at room temperature and then the precipitated solid was removed by filtration. The solid was heated with concentrated hydrochloric acid (40ml)on water bath and the resulting solution was then cooled. The p-nitrophenylhydrazine hydrochloride and sodium salt was filtered off, dissolved in water and the solution then treated with concentrated solution of sodium

acetate. This cause the precipitation of almost pure p-nitrophenylhydrazine (12.7g) was obtained by recrystalising from ether

Preparation of N-chloroacetyl-p-nitrophenylhydrazide

According to the standard procedure of Vogel, a mixture of chloroacetylchloride (20ml) in chloroform (35ml) and 10g of

p-nitrophenylhydrazine was treated under reflux for two hours, till a homogeneous mixture was obtained. The reaction started with the evolution of hydrogen chloride gas and progress of the reaction was monitored by t.l.c examination time to time.The solution was then cooled,which resulted in separation of yellowish brown solid, which was collected by filtration. Recrystallization from carbon tetrachloride to furnish yellowish brown crystals of n-chloro-p-nitrophenylhydrazine (11.5g), m.p. 251°C.

Preparation of 3-hydroxy-6-nitro-1,4-dihydrocinnoline

(The above prepared n-chloroacetyl-p-nitrophenylhydrazide undergo Friedel-Crafts Cyclisation)

Anhydrous aluminium chloride (0.6g) and carbondisulphide (10ml) were placed in a small flask fitted with stirrer, a dropping funnel and a condenser. The flask was cooled at about 10°C by immersing it in cold water. A solution of above prepared compound (1.5g) in carbon disulphide (10ml) was then added drop-wise with stirring. The flask being cooled externally with ice. Stirring was continued till the evolution of hydrogen chloride gas slackened. The reaction mixture was allowed to stand at room temperature for two hours and then poured it into a mixture of ice (20g) and concentrated hydrochloric acid (1ml). The solution was then extracted with ether and ethereal extract washed with water and dried over calcium chloride. Removal of ether and carbon disulphide by distillation left a gummy residue which crystallized on trituration from benzene and light petroleum. Recrystallisation from benzene gave the pure crystals of 3-hydroxy-6-nitro-1,4-dihydrocinnoline, m.p. 154°C.

Analysis

Found … N…..21.60%

Calculated N for formula $C_8H_3N_3O_3$ …. …..21.75%

I.R. Streching frequencies

KBr 1580 cm^{-1} for C=N stretching frequencies

γ_{max} 1605 cm^{-1} for substituted benzene ring

3250 cm^{-1} for -NH- stretching frequencies

1415 cm^{-1} for -C(=O)-OH (grouping)

The N.M.R. spectrum of the compound had adsorption for three sets of protons. The three aromatic protons had resonance at δ5.4, a singlet corresponding to two protons at δ2.7 due to the benzylic group and a singlet for one proton at δ4.3 for the -NH- group as well as a singlet for one proton at δ8.2 for -C(=O)-OH group.

RESULT & DISCUSSION :

The structure of the proposed compound obtained above was further proved by alternative method of synthesis. The cyclised products in both cases were compared by means of melting point and mixed melting point, elemental analysis as well as matching spectral datas of IR & UV spectra. The progess of the reaction was checked time to time in each and every steps of the reaction by thin layer chromatography (T.L.C).

The above proposed organic research work is a field of interest due to its biological action, as it contains two nitrogen atoms and lead to the formation of nitrogen containing heterocyclic ring system. Thus it is essential to explore the synthesis covering simpler method of preparation with high yield too.

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