



SYNTHESIS AND CHARACTERIZATION OF SUBSTITUTED AND UNSUBSTITUTED HETEROCYCLIC DIHYDROCINNOLINES

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ABSTRACT

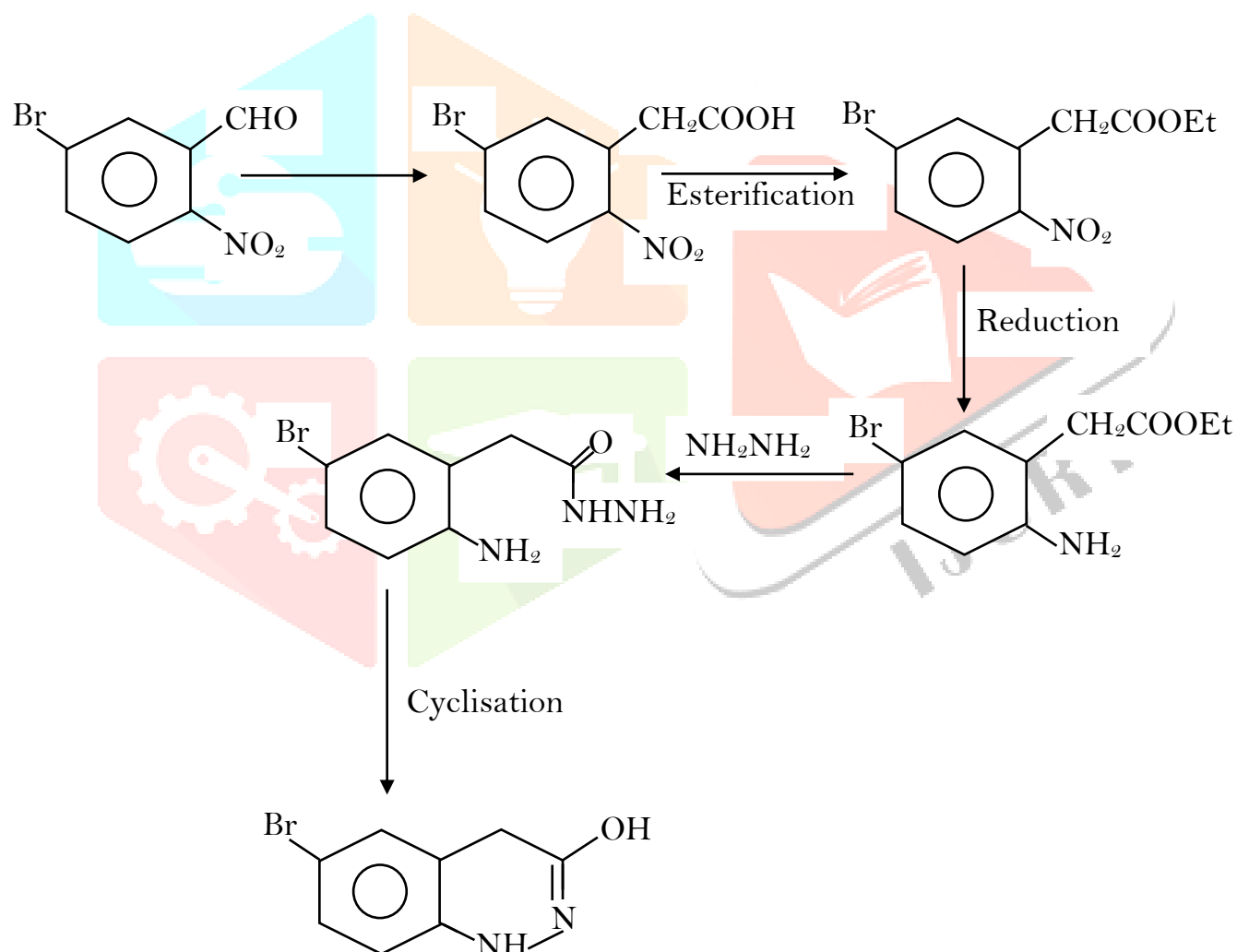
The condensation of carbonyl compounds with suitable hydrazines and phenylhydrazines, substituted and unsubstituted phenylhydrazones were obtained. Hydrazones so obtained may react further undergo ring closure reaction resulting in the formation of six membered heterocyclic ring compounds dihydrocinnolines. All the results were characterised and finally conformed by the alternative method of synthesis.

KEY WORDS : Carbonyl compounds, phenyl hydrazine, dihydrocinnolines.

INTRODUCTION :

Hydrazines and aryl hydrazines are easily available and have replaceable H-atom ; various works have been done in national and international level. Hydrazones obtained from condensing hydrazine with carbonyl compounds are usually crystalline compounds with well defined melting points. These are frequently employed for identification of carbonyl compounds. The hydrazone may cyclise resulting in the formation of heterocyclic compounds.

Literature survey of such series of heterocyclic compounds say that they are having numerous physiological activities and may be used for the beneficial service to humanity. This prompted to explore the possibility of cyclising aryl hydrazones as well as acid hydrazides by closing the ring and result would be a dihydrocinnolines derivatives. It has been found that these series of compounds have antimalarial activity and may be drug precursors. Thus it is essential to explore the synthesis covering intramolecular cyclisation method of preparation with high yield too. The cyclised product further identified by elemental analysis, spectral analysis i.e. IR, UV, & NMR Spectra.



EXPERIMENTAL :

The reaction sequences which were expected to yield dihydrocinnoline compounds could involve the following steps 5-bromo-2-nitrobenzaldehyde was converted into 5-bromo-2-nitrophenylacetic acid by Azlactone synthesis and then esterified into ethyl ester. Reduction of this ester leads to the formation of ethyl 2-amino-5-bromophenylacetate. Ethyl ester of 2-amino-5-bromophenylacetic acid is treated with hydrazine to give 5-bromo-2-aminophenylhydrazide. This was heated under forcing conditions to boil about its cyclisation to 6-bromo-3-hydroxy-1,4-dihydrocinnoline. The progress of the reaction was checked by t.l.c examination from time to time. Accordingly, various substituted benzaldehyde were used to prepare different substituted 1,4-dihydrocinnoline. 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 during the reaction.

The product from this reaction was identical with that obtained by the alternative method of synthesis as shown by t.l.c. examination, melting point and the complete identity of their I.R. spectra.

Preparation of 5-bromo-2-nitrophenylacetic acid from 5-bromo-2-nitrobenzaldehyde

A mixture of 5-bromo-2-nitrobenzaldehyde (15.4ml), hippuric acid (12g), acetic anhydride (13ml) and anhydrous sodium acetate (6g) were heated under reflux till when the mixture become homogenous in about half an hour. The resulting solution was boiled for a further one hour, cooled and then left for a further one hour, cooled and then left in an ice chest overnight. The precipitated yellow solid was removed by filtration, washed several time with cold water and then with boiling water.

The azlactone obtained above was heated under reflux with a solution of sodium hydroxide (25g in 100ml) for one hour. The reaction mixture was then cooled diluted with water (150ml) and then saturated with sulphur dioxide. The reaction mixture was then filtered. The filtrate was heated on a steambath in an open disc with concentrated hydrochloric acid (75ml) and then cooled.

The precipitate 5-bromo-2-nitrophenylpyruvic acid was collected and crystallised from benzene. The crystals were collected by filtration and heated under reflux in a round bottom flask with excess of hydrogen peroxide. The reaction mixture was cooled and the separated solid was collected by filtration. It was washed with cold water and recrystallised from hot water to have crystals of 5-bromo-2-nitro-phenylacetic acid (12.5g), m.p. 209°C.

Preparation of ethyl-5-bromo-2-nitrophenylacetate

A mixture of 5-bromo-2-nitrophenylacetic acid (12g), absolute ethanol (20ml) and concentrated sulphuric acid (1ml) were heated under reflux on water bath for two hours and then left at room temperature overnight. The excess of ethanol was then removed by distillation and the residual liquid washed with water, aqueous sodium bicarbonate solution (10%) and again with water several times. The liquid was dried over magnesium sulphate and cooled in ice-chest over night to give ethyl-5-bromo-2-nitrophenylacetate as a colourless solid (11.5g), m.p. 142°C.

Preparation of ethyl-2-amino-5-bromophenylacetate

According to the method of Blatt, a solution of (0.1 mole) of ethyl-5-bromo-2-nitrophenylacetate in (150 ml) of 95% alcohol is placed in the reaction bottle of the catalytic reduction apparatus and (0.2g) of platinum oxide catalyst was added. The mixture is shaken well with hydrogen until three molecular equivalent have been absorbed. The platinum was filtered off and the alcohol was removed from the filtrate by distillation. The resulted amino compound was recrystallised from about 40ml of ether with 80-85% yield.

Preparation of 2-amino-5-bromo-phenylacetic hydrazide

Following the method of Vogel, ethyl-2-amino-5-bromophenylacetate (11g) in ethanol (30ml) was heated with hydrazine hydrate (5ml -90%) under reflux for three hours till when homogeneous mixture was obtained. The volume of the solution was reduced to half. On cooling this solution, yellowish white solid was separated which was collected by filtration. Recrystallization of the solid from methanol furnished pure, 2-amino-5-bromo-phenylacetic hydrazide (9g) as a yellowish white crystal, m.p. 254°C.

Analysis

Found	... N	...17.10%
Calculated N for formula $C_8H_{10}ON_3Br$17.21%

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

(The condensation was done under a variety of conditions)

(A) Direct on heating :

2-amino-5-bromo-phenylacetic hydrazide (0.5g) in methanol (5ml) was heated under reflux for ten hours and then set aside at room temperature overnight. The yellowish brown solid separating from the reaction mixture was triturated with dilute HCl washed with then sodium bicarbonate solution and water and then recrystallised from ethanol to furnish the pure 3-hydroxy-6-bromo-1,4-dihydrocinnoline (0.5g), m.p. 182°C.

(B) With dry hydrogen chloride gas :

2-amino-5-bromo-phenylacetic hydrazide (0.5g) and methanol (5ml) were heated on a water bath. A steady current of dry hydrochloric acid was passed for nearly three hours when reaction was shown to be complete by t.l.c. examination.

The reaction mixture was left at room temperature over night. Next day the separated solid was triturated with benzene and ethanol and then 6-bromo-1,4-dihydrocinnoline (0.86g), m.p. 182°C.

(C) With perchloric acid :

A mixture of 2-amino-5-bromo-phenylacetic hydrazide (0.5g), perchloric acid (1ml) and methanol (5ml) was heated under bath under reflux for six hours and then set aside at room temperature over night. The yellowish brown solid separating from the reaction mixture was triturated with aqueous sodium bicarbonate solution, washed with cold water and then recrystallised from ethanol to furnish the pure 6-bromo-3-hydroxy-1,4-dihydrocinnoline, m.p. 182°C (0.82g).

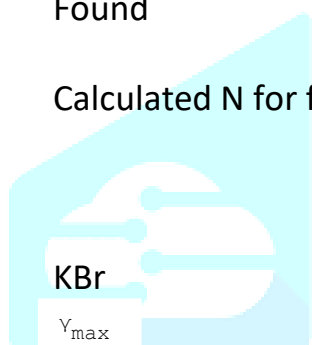
(D) With phosphorus pentoxide :

2-Amino-5-bromo-phenylacetic hydrazide (0.5g), methanol (5ml) and phosphorus pentoxide (0.02 ml) in carbon tetrachloride were heated on a water bath for nearly six hours till when the reaction show to be completed by t.l.c. examination. The reaction mixture was left at room temperature over night. The separated solid was triturated with benzene and methanol and then recrystallised from ethanol to furnish the pure 6-bromo-3-hydroxy-1,4-dihydrocinnoline (0.9g), m.p. 182°C.

Analysis

Found N12.50%

Calculated N for formula $C_8H_7N_2OBr$ 12.35%

**I.R. Stretching frequencies**

1600 cm^{-1} for C=N stretching frequencies

1610 cm^{-1} for substituted benzene ring

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

1415 cm^{-1} for -C-OH (grouping)
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RESULT AND DISCUSSION :

The structure of the proposed compound obtained above was further proven by alternative method of synthesis. The cyclised products in both the cases was now compared by means of melting point, elemental analysis as well as IR & UV spectra.

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