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Friedel-Crafts Cyclization of N,N-dibenzylethylenediamines

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FRIEDEL-CRAFTS CYCLIZATION OF N,N-DIBENZYLETHYLENEDIAMINES

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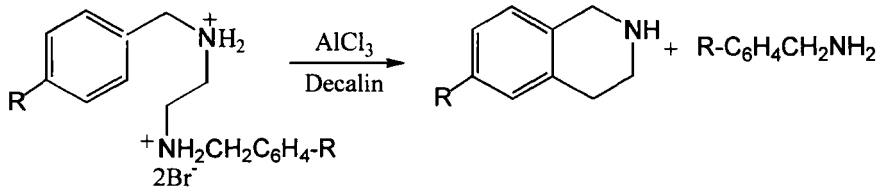
ABSTRACT: An efficient synthesis of substituted 1,2,3,4-tetrahydroisoquinolines is described. N,N-dibenzylethylenediamines smoothly under go Friedel-Crafts cyclization in the presence of anhydrous aluminum chloride in decalin to give 1,2,3,4-tetrahydroisoquinolines.

Tetrahydroisoquinoline and its derivatives are of considerable interest due to their biological activity and were found as naturally occurring alkaloids. Specifically, it was shown that chloro-substituted tetrahydroisoquinolines inhibit the enzyme phenylethanolamine N-methyltransferase (PNMT)[1]. In this paper, a smooth and efficient cyclization of various N,N-dibenzylethyleneamines is described which with aluminum chloride in decalin give good yields of corresponding 1,2,3,4-tetrahydroisoquinolines. 1,2,3,4-Tetrahydroisoquinolines have been traditionally prepared by the Bischler-Napieralski[2] Pictet-Gams, Pictet-Spengler[3-6] Pomeranz-Fritsch [7-11] reactions and various Friedel-Crafts cyclization procedures of N-(haloalkyl)aryl derivatives [12-19]. These reactions have often been used in the total synthesis of isoquinoline alkaloids [20-21].



1 **2**

a) R = H b) R = CH_3 c) R = Cl

Cyclization of the corresponding diaminehydrobromides, carried out in the presence of anhydrous aluminum chloride in decalin, led to decomposition at 180° to give higher yield of **2a** (78%), **2b** (87%) and **2c** (45%) with less tarry residue. The mechanistic concepts governing Friedel-Crafts reactions are treated in detail by Olah[22]. The dependence of the yield on electronic activation by the substituent is expected for a Friedel-Crafts electrophilic substitution as it parallels that found[12] in the cyclization of N-arylalkylbromides to tetrahydroisoquinolines. Since the starting compounds were easy to obtain, the present method was carried out on a large scale to afford clean products in high yields.

The intermediates N,N-dibenzylethylenediamine was commercially available from Aldrich but N,N-bis(p-chlorobenzylamino)ethane and N,N-bis(p-methylbenzyl-amino)ethane were prepared by condensation of the corresponding benzaldehydes with ethylenediamine to the Schiff base which was reduced without isolation with sodiumborohydride in ethanol to give good yields of products **1**.

EXPERIMENTAL:

Melting points were determined by Electrothermal apparatus and are reported uncorrected. N,N-dibenzylethylenediamine was obtained from Aldrich and used after distillation. All reagent and solvent were of commercial grade. All reactions were carried out under nitrogen atmosphere. Infrared spectra (KBr) were recorded by using Perkin-Elmer Model 580 spectrometer. Proton NMR spectra ($CDCl_3$ solvent) were obtained with Gemini 200 Variant instrument using tetramethylsilane (Me_4Si) as internal standard.

Typical Procedure for Preparation of N,N-bis (p-chlorobenzylamino)ethane 1c. To 14.00g (100mmol) of p-chlorobenzaldehyde partially dissolved in 150mL of absolute alcohol in a 500mL three neck flask, fitted with a reflux condenser and a dropping funnel, was added dropwise 7.5 mL of dry ethylenediamine. The mixture was heated with stirring under reflux for a period of 2hrs. Reflux was stopped and an additional 150 mL of ethanol added to the hot mixture. The solution was cooled to room temperature and sodium borohydride (5g) in 1M sodium hydroxide (50mL) was added dropwise with stirring, and the temperature was maintained below 20°. Stirring was continued for 1 hour after completion of addition and ethanol distilled off under reduced pressure. The mixture was extracted with dichloromethane (100 mL x 3). The organic extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To the brown oily residue was added about 40 mL of 48% hydrobromic acid and the

mixture refluxed for 1 hour. On cooling white crystalline solid, the dihydrobromide of the base was obtained. It was recrystallised from ethanol with a few drops of hydrobromic acid to give 20.3g (87%) of the **1c** mp 290-292°, lit[23] 290°. Dihydrobromide of **1c** was neutralized with sodium hydroxide and the free base obtained on treatment with acetic anhydride gave acetyl derivative, mp 137-139°, lit[23] 139-140°.

Similarly N,N-bis(p-methylbenzylamino)ethanedihydrobromide **1b** was obtained from 4-methylbenzaldehyde in 89% (mp. 294-295° lit[24] 296-297°).

1,2,3,4-Tetrahydroisoquinolines (2a-c). General Procedure. The dihydrobromide of dibenzylethylenediamine (40.20g,100mmol) was mixed with powdered anhydrous aluminum chloride (40.0g, 3mol.equiv.) in decalin (200mL) and the mixture heated with stirring at 180 ° (oil bath) for 2 hrs. The reaction mixture was cooled and decalin was decanted from the residue oil. Aluminum chloride was decomposed with ice and concentrated hydrochloric acid (pH 4). Any decalin left was removed by extraction with diethyl ether (100mL x 3). The aqueous mixture was basified with NaOH (pH 12). The brown oil obtained was extracted with diethyl ether (100 mL x 3) and dried over anhydrous magnesium sulfate. The magnesium sulfate was filtered off and the mixture was evaporated. The residue was distilled under reduced pressure bp 45° /2 mmHg, to give 11.5g (78%) of 1,2,3,4-tetrahydroisoquinoline, picrate (mp 194° .lit[25] 195°), hydrochloride (mp 191-193° , lit[25] 195-197°) and benzylamine, 5 %.

Similarly **2b** was obtained at bp 108-110° /11mm Hg, (87%), hydrochloride (mp. 194-196°, lit[25] 195-197° and picrate (mp. 201-204°, lit[25] 205°)

2c was obtained at bp 100° /5 mmHg, (45%), picrate (mp. 191-192° (ethanol) lit[13] 190-192°), hydrochloride (mp. 236-237° (ethanol) lit[13] 237-238°).

The tetrahydroisoquinolines prepared were further characterized by comparisons (ir and nmr) with authentic specimens.

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