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A New Method For N- β -Hydroxyethylation of Aromatic Amines

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A New Method For N- β -Hydroxyethylation of Aromatic Amines

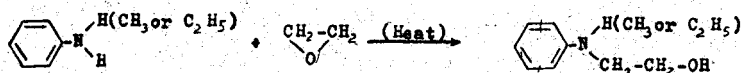
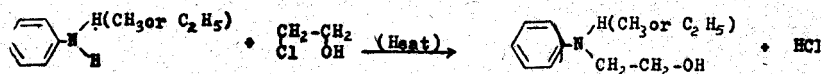
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In this article, a new method for N- β -hydroxyethylation of aromatic amines has been described. Aniline, N-methylaniline and N-ethylaniline were converted to their halomagnesium salts with a proper Grignard reagent, then these salts reacted with ethylene oxide and so formed complexes hydrolyzed with aqueous ammonium chloride.

INTRODUCTION

In order to N- β -hydroxyethylate aniline, N-methylaniline and N-ethyl-aniline, β -hydroxyethanol or ethylene oxide have widely been used. The general equations of these reactions are:



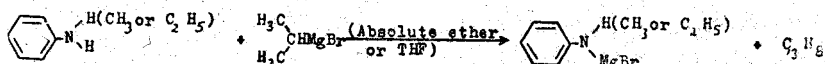
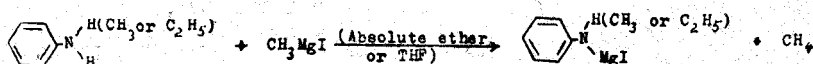
A number of authors have investigated these reactions: Otto [1] heated aniline with β -chloroethanol, Rindfus and Harnack [2] heated these two compounds in presence of small amount of sodium carbonate, Dashen and Brewster [3] refluxed these two compounds, Yamamoto and Ikegam [4] heated at 90–100°C for 4–6 hours, all obtained N- β -hydroxyethylaniline. Laun [5] heated N-methylaniline with β -chloroethanol, Wilson [6] heated these compounds

35 hours at 100°C; Teplov, Godovikov and Kabachnik [7] heated these two compounds and obtained the same compound, N-methyl-N- β -hydroxyethylaniline. Laun [5] also heated N-ethylaniline with β -chloroethanol in a sealed tube, Latters and Verdier [8] heated these two compounds and N-ethyl-N- β -hydroxyethylaniline was formed. Demole [9] and Gabel [10] heated aniline with ethylene oxide in a sealed tube, Hughes and Hush [11] heated the same compounds at 90°C for 12 hours, Petrov and Tal'ovskii [12] heated the same compounds 6 hours and all they obtained N- β -hydroxyethyl-aniline. Gabel [1] also heated N-dimethylaniline with ethylene oxide with or without water and N-methyl-N- β -hydroxyethylaniline was formed in about the same but low yield. Bent et al. [13] heated these two compounds in a sealed tube and they get the same compound in a good yield. Horyna and Virac [14] heated N-ethylaniline, N, N-diethylaniline and ethylene oxide (or β -chloroethanol) in an autoclave and obtained N-ethyl-N- β -hydroxyethyl-aniline in good yield.

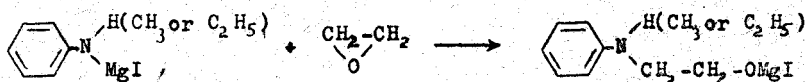
Besides of these hydroxyethylation reactions there were some unusual or indirect methods of hydroxyethylation of aniline, N-methylaniline or N-ethylaniline in the literature: Gault [15] reacted aniline with ethyl- β -chloroacetate and obtained N- β -carbethoxyethylaniline, reduction of this compound by means of sodium and ethanol gave N- β -hydroxyethylaniline. Adams and Segur [16] heated aniline with β -chloroethylchlorocarbonate in benzene as solvent and N- β -chloroethylaniline was formed. Hydrolysis of this compound with aqueous NaOH or KOH gave N- β -hydroxyethylaniline. Butler and Renfrew [17] heated aniline with β -benzoyloxyethyl-p-toluene sulfonate, hydrolysis of so formed compound with dilute HCl gave the same compound in 50 per cent yield. Carlson [18] heated aniline with ethylenecarbonate and the same compound was formed in 51 per cent yield. Gulbins and Hamann [19] heated the same compounds but in presence of small amount of lithium chloride under nitrogen atmosphere and both obtained N- β -hydroxyethylaniline. Gault [15] also reacted N-ethylaniline with ethyl- β -chloroacetate and N-ethyl-N- β -carbethoxyethylaniline was formed, reduction of this compound gave N-ethyl-N- β -hydroxyethylaniline. Braun and Kirschbaum [20] reacted N-methylaniline with 1-chloro-2-bromoethane and obtained

N-methyl-N-β-chloroethylaniline. Reaction of this compound with sodium benzoate gave N-methyl-N-β-benzoyloxyethylaniline.

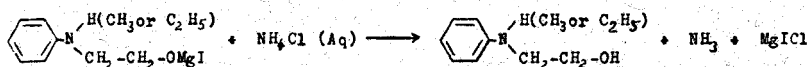
In this work, ethylene oxide has been used as hydroxyethylation agent but in completely different way. First aniline, N-methylaniline or N-ethylaniline were converted to their halomagnesium salts by means of a Grignard reagent (either methylmagnesium iodide or isopropylmagnesium bromide was used):



Ethylene oxide was passed in the ethereal or tetrahydrofurane suspension of this complex at room temperature, and nucleophilic addition of nitrogen atom on ethylene oxide took place:



Hydrolysis of this adduct salt by means of aqueous ammonium chloride gave the corresponding N-β-hydroxyethylaniline:



Since this new method is a room temperature reaction, it eliminates prolonged heating of the reaction components in a sealed tube or in an autoclave which are tedious work in organic chemistry laboratory and also reaction times is shorter than the other methods

EXPERIMENTAL

N-β-Hydroxyethylaniline

In a 250 ml three neck round bottom flask which was set on a magnetic stirrer and equipped with a reflux condenser dropping

funnel and a gas inlet tubing put a small magnetic bar and 1.2 g (50 miliatomgrams) of magnesium turnings. Inside of the apparatus was swept out with dry nitrogen. 10 ml of Absolute ether was introduced into the flask and a solution of 7.1 g (50 mmoles) of methyl iodide (or 6.2 g of isopropyl-bromide) in 20 ml of absolute ether was introduced into the dropping funnel. Magnetic stirrer was started and a "Grignard reagent" was prepared as known manner. Into this solution 4.6 g (50 mmoles) of aniline (freshly distilled) in 20 ml of absolute ether was added dropwise. In the course of the reaction temperature was kept at 0–5°C and copious of gas evolution was observed and a white precipitate formed. Ethylene oxide which was generated from 2-chloroethanol and soda lime, passed into the suspension in a moderate rate for (two hours while stirring. White precipitate turned to grey and became voluminous. In order to decompose so formed complex, a solution of 6 g of ammonium chloride in 25 ml of water was added into the reaction mixture and stirred until to get clear solutions, then ether layer was separated, aqueous layer extracted once with 20 ml of ether, ether layers combined and dried over anhydrous sodium sulfate for one hour. Ether solution was filtered into the flask of sodium sulfate for one hour. Ether solution was filtered into the flask of a vaccum distilling apparatus, ether distilled first, traces of it was removed by means of a water pompe. Remaining dark colored liquid was distilled under diminished pressure provided by an oil pompe. Unchanged aniline was distilled first at 45–50°C/1 mm Hg., then N- β -hydroxyethylaniline collected at 110–111°C/1 mm Hg. as a viscous and pale oil (Reported b.p. 134–5°/5 mm Hg.), 3.1 g (23 mmoles, 44 %). Picrate derivative crystallized from ethanol, melted at 122–24°C (Reported 124°C). No depression was observed in melting point with a mixture of an authentic sample.

Instead of ether, tetrahydrofurane (THF) was used as solvent and slightly lover yiled was obtained.

N-Methyl-N- β -hydroxyethylaniline

In this experiment the same apparatus was used. A Grignard reagent was prepared from 1.2 g (50 miliatomgrams) of magnesium and 7.1 g (50 mmoles) of methyl iodide or 6.2 g (50 mmoles) of

isopropylbromide. Into this solution 5.4 g (50 mmoles) of methylaniline (redistilled) in 20 ml of absolute ether was added dropwise while stirring. Temperature of the reaction mixture was kept at 0–5°C. Gas evolution was observed and a white precipitate formed. Ethylene oxide was bubbled in the suspension in a moderate rate for three hours while stirring vigorously. Precipitate became voluminous at the end of the reaction. In order to decompose so formed complex, a solution of 6 g of ammonium chloride in 25 ml in 25 ml of water was added into the reaction mixture and stirred until to get clear solutions. Ether layer was separated, aqueous layer extracted once with 20 ml of ether, ether layers combined and dried over anhydrous sodium sulfate for one hour. Ether solution filtered into a vacuum distilling apparatus flask, ether removed first (traces of it removed by means of a water pumpe). Remaning dark liquid was distilled under diminished pressure provided by means of an oil pumpe. Unchanged methylaniline distilled first at 47–51°C/1 mm Hg., then N-methyl-N- β -hydroxyethylamine was collected at 112–4°C/1 mm Hg. (Reported b.p. 148–50°/13 mm Hg.) as viscous and pale oil, 2.9 g (19 mmoles, 38 %). This compound did not give a picrate derivative, but acetylated with acetanhydride to give N-methyl-N- β -acetoxyethylamine which gave a picrate, crystallized from ethanol and melted at 152–3°C (Reported 153°C [21]).

N-Ethyl-N- β -hydroxyethylamine

The same apparatus was used. 50 mmoles of Grignard reagent (either methylmagnesium iodide or isopropylmagnesium bromide) was prepared first. Into this solution 6.1 g (50 mmoles) of N-ethylamine (redistilled) in 20 ml of absolute ether was added dropwise and worked up as above. N-Ethyl-N- β -hydroxyethylamine was distilled at 124–5°C/1 mm Hg. as viscous and pale oil, 3.0 g (17 mmoles, 34 %). This compound also did not give a picrate derivative like N-methyl analogous. It was treated with POCl₃ and heated to convert chloride derivative, N-ethyl-N- β -chloroethylamine, this gave picrate, which was chrystallized from ethanol, melted at 107–9°C (Reported, 108–109.5°C [6]).

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Ö Z E T

Bu çalışmada aromatik aminleri N- -hidroksietillemek için yeni bir metod verilmiştir. Bu metodda anilin, N-metilanilin ve N-etilanilin, uygun bir Grignard reaktifiyle N-halomagnezyum tuzlarına çevrilmiş bu tuzlar etilen oksidile reaksiyona sokularak meydana gelen kompleks tuzlar sulu amonyum klorür çözeltisiyle hidrolizlenerek kendilerine tekabül eden N- -hidroksietillenmiş anilinler elde edilmiştir.

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