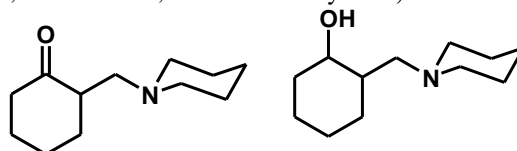


STUDY OF 2-(PIPERIDINOMETHYL) CYCLOHEXANONE REDUCTION**ZAHRA ABDI PIRALGHAR^{a1}, MOHAMMAD RAOUF DARVISH^b**^aMSc of Organic Chemistry, Shahr-e Rey Branch, Islamic Azad University, Tehran, Iran^bDepartment of Chemistry, Shahr-e Rey Branch, Islamic Azad University, Tehran, Iran

Abstract: Amino alcohols are of great significance in synthesis of organic compounds. The most important application of these compounds is in drug chemistry. Amino alcohols are found in a variety of drug compositions including aminoglycosides, cephalosporins and anti-fungal drugs. These agent groups are important intermediates in organic chemistry as they are applied in biosynthetic, agricultural and pharmaceutical processes and industrial dye works due to their diverse pharmaceutical and biological properties. Due to this efficiency, synthesis of (2) amino alcohol from (1) carbonyl composition was taken into account. The initial substance was derived from reaction of paraformaldehyde and piperidine with cyclohexanone. In the next step, reclamation of carbonyl compound with sodium borohydride reagent was carried out for synthesis of amino alcohol and then in another technique, the carbonyl compound was reacted with lithium aluminum hydride as a result of which the relevant amino alcohol was prepared. Results of these reactions were examined with IR, Mass and NMR spectra.

KEYWORDS: Amino Alcohol, Reclamation, Sodium Borohydride,



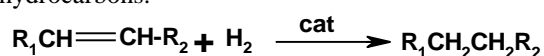
1. APPLICATION OF AMINO ALCOHOLS

Emersion of organic chemistry with its synthetic agents and bidirectional, profound relationship with pharmacology led to a new evolution in synthetic methods used in industries such as drug and dye manufacturing as well as agriculture. Since amines and amino alcohols are among the most abundant chemical structure, many have focused their research on this type of substances while Mannich bases are considered among the important tools for synthesis of new compounds. The most significant application of amino alcohols is in drug chemistry. Amino alcohols are found in a variety of pharmaceutical compositions. Some of these drugs include: aminoglycosides, tetracyclines, narcotic pain relievers, cytotoxics, anti-fungal drugs, ethambutol hydrochloride and aryethanolamines.

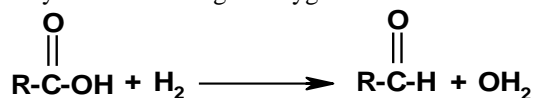
2. RECLAMATION AND ITS METHODS

If hydrogen is added to an organic compound or oxygen is removed from its molecule or in case both hydrogen addition and oxygen removal procedures are carried out simultaneously, then reclamation has taken place. Therefore, reclamation takes place in one of the three following forms:

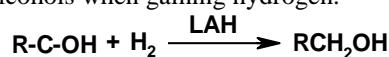
a) Ethylene hydrocarbons easily attract hydrogen and transform into saturated hydrocarbons.



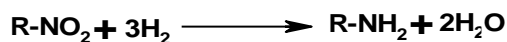
b) Organic acids turn into relevant aldehydes when losing an oxygen atom.



Also, carboxylic acids transform into type-one alcohols when gaining hydrogen.



c) Reclamation of nitrate derivatives involves oxygen loss and hydrogen gain with the nitrate derivatives finally turning into amines.



3. EXPERIMENTAL OBSERVATION

3-1. APPLIED DEVICES

IR spectrum with device Thermo Nicolet Nexus 870-FT-IR

HNMR spectrum and melting point spectrometer C NMR with device AVAVCE DRX 500M

Melting point apparatus Bamsetead Electro Thermal

Rotary operator device Heidolph WB Eco-Laborata 4000 Efficient

Mass spectrum with device Finigan mat 70ev EI

Iodine vapor was used to detect T.L.C.

3-2- PREPARATION OF 2-(PIPERIDINOMETHYL)-CYCLOHEXANONE:

Two methods were applied for preparation of 2-(piperidinomethyl)-cyclohexanone.

First Method:

Droplets of 10% HCL were added to 8.5 g (100 mmol) piperidine stirred within a 250 ml two-neck flask with adapter joint in order to yield piperidine hydrochloride salt. (Neutralization was controlled by pH meter paper). Then, 9.8 g (100 mmol) cyclohexanone, 37% formaldehyde 16/21 (150 mmol), 50 cc ethanol and a few droplets of HCL were added to the flask only to be refluxed for 6 hours. The contents were then transferred into the rotary operator flask. As the solvent evaporated, a yellow viscous substance was derived. The solution was then alkalized with sodium hydroxide while being cooled off with ice. Next, this substance was extracted for three times, each time using 400 cc diethyl ether. Na₂SO₄ was then added for dewatering and then filtered through a cone with cotton plugged in its neck as the evaporation of solvent yielded 3.8 g of product. Reaction efficiency is 21%.

Second Method:

A 250 ml two-neck flask with adapter joint was filled with 17.67g cyclohexanone (180 mmol), 10.94g piperidinium hydrochloride (90 mmol) and 2.7g paraformaldehyde (90 mmol) along with 20 cc of acetic acid. As this mixture was stirred with magnetic stirrer, it was treated with heat up to 95 °C until a transparent solution was yielded. The derived solution was then transferred into the rotary operator flask and the acetic acid was removed at 90 °C.

The derived sediment was refluxed with acetone for 10 minutes. Then the sediment was filtered and cleansed with acetone. As a result, a pure sediment substance was derived. The sediment was then placed in vacuum oven to be completely dried. Thus, a white sediment substance with melting point of 229-230 °C was derived. The reaction efficiency is 82% considering the amount of piperidine hydrochloride used.

The sediment was first dissolved in the water and then 30% NaOH was added to it as it was being continuously stirred and cooled off with ice, and then it was alkalized up to pH12 as it was being controlled by a pH meter paper.

The solution was then cleansed for three times, each time with 400 cc of ether. Na₂SO₄ was added to the etheric matter for dewatering and left there for 1 hour only to be sometimes stirred with glass stirrer.

The etheric matter was passed through a cotton plugged cone into the rotary operator flask in order to be evaporated at 20°C.

As a result 11.4g 2-(piperidinomethyl)-cyclohexanone was yielded with 65% reaction efficiency.

The IR spectrum consists of the following data (Spectrum 1-A):

2773-2934 cm^{-1} related to stretching vibration of CH Alkanes

1709 cm^{-1} related to carbonyl

1447 cm^{-1} related to bending vibration of CH_2

¹H NMR spectrum from CDCl_3 solvent (spectrum B-1):

2 protons in 2.42-2.68 ppm (multiple) related to CH_2 protons between two cyclohexanone and piperidine rings

7 protons in 2.18-2.29 (multiple) related to CH_2 protons attached to N in piperidine ring and the CH and CH_2 protons attached to carbonyl group

12 protons in 1.2-2.11 ppm (multiple) related to other alkane protons in both rings

¹³C NMR spectrum in CDCl_3 solvent (Spectrum C-1):

212.9 ppm related to carbonyl group

58.5 ppm related carbon attached to two piperidine-cyclohexanone rings

55.2 ppm related to carbon attached to N in piperidine ring

48.9 ppm related to carbon, CH of cyclohexanone ring

24.6, 24.9, 26.3, 28.4, 33.3 and 42.3 ppm related to the remaining CH_2 carbons within the cyclohexanone-piperidine ring

3-3. 2-(PIPERIDINOMETHYL)-CYCLOHEXANONE REDUCTION WITH SODIUM BOROHYDRIDE:

17.35g (0.089 mol) 2-(piperidinomethyl)-cyclohexanone was dissolved in 100 ml ethanol and approximately 3.4g (0.039 mol) sodium borohydride was gradually added to it so that it would be stirred at room temperature and then the methanol was evaporated by rotary flask followed by addition of water 2 times the volume of remaining substance.

Then, extraction was performed using ether and 6.2g of substance i.e. 2-

(piperidinomethyl)-cyclohexanone was derived following the evaporation of solvent due to sodium sulfate drying.

3-4. 2-(PIPERIDINOMETHYL)-CYCLOHEXANONE REDUCTION WITH LITHIUM ALUMINUM HYDRIDE:

In this method, 2-(piperidinomethyl)-cyclohexanone is reclaimed under reflux conditions within a dewatered etheric solvent in presence of lithium aluminum hydride and then water is gradually added to the system subsequent to completion of reaction so that no more hydrogen gas would be emitted which is a sign of lithium aluminum hydride decomposition.

Then the conventional extraction methods are carried out that lead to 2-(piperidinomethyl)-cyclohexanone.

3-5. PURIFICATION OF 2-(PIPERIDINOMETHYL)-CYCLOHEXANONE:

Purification was carried out using column chromatography with constant aluminum oxide with 75% hexane solvent and 25% diethyl ether which resulted in 0.75 substance with 34% efficiency.

Spectral Data

IR spectrum consists of the following data (spectrum 2-A):

3255 cm^{-1} related to OH peak

Removal of 1790 cm^{-1} in carbonyl group

¹H NMR spectrum from CDCl_3 solvent (spectrum 2-B):

A single peak at 2.8 ppm related to OH

¹³C NMR spectrum from CDCl_3 solvent (spectrum C-2):

72.7 ppm related to carbon attached to OH

61.003 ppm related to carbon attached to

N

24.48, 24.55, 25.98, 26.21, 29.21, 32.03, 34.77 and 40.30 ppm related to carbons attached to cyclohexanone-piperidine ring

Mass spectrum also includes the following data (Spectrum D)

197 (7.5), 180 (51.1), 179 (7.2), 98 (8.2), 84 (63.2), 42 (100)

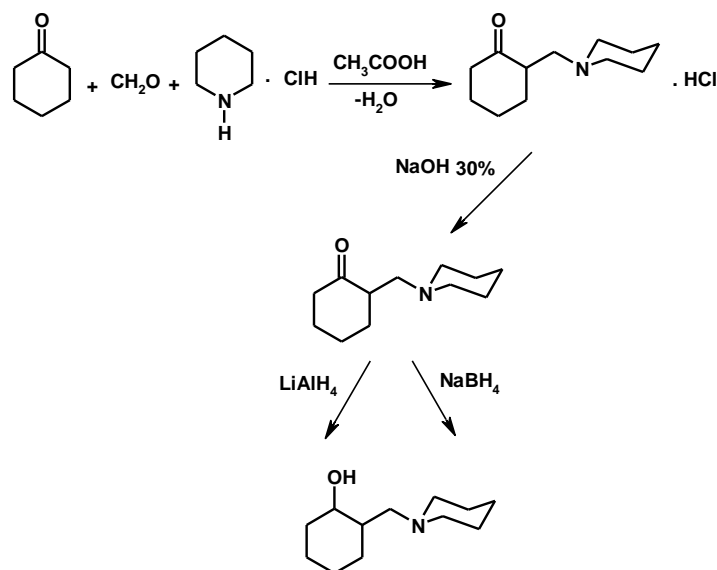
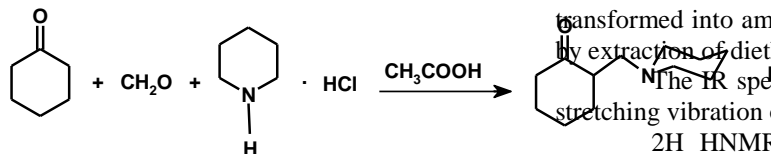


Figure 1. Schematic illustration of reactions

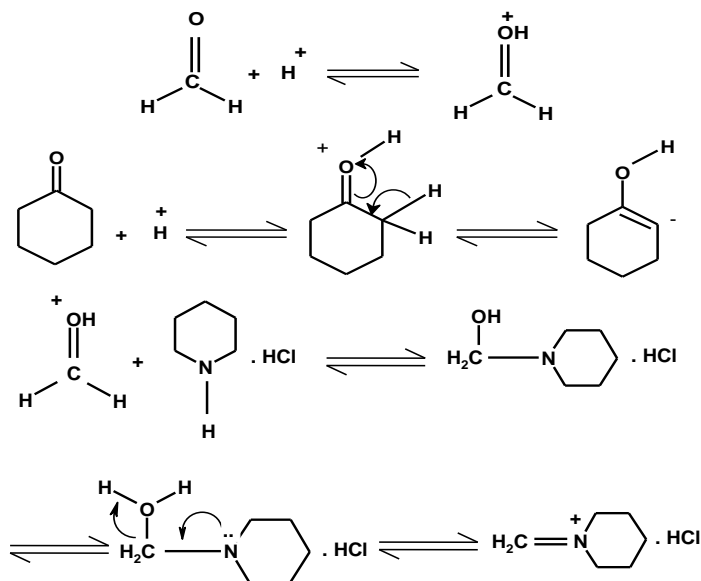
4. CONCLUSIONS AND DISCUSSION

4-1. PREPARING 2-(PIPERIDINOMETHYL)-CYCLOHEXANONE:

A yellow greasy liquid is derived from reaction of piperidinium hydrochloride with formaldehyde and cyclohexanone in presence of acetic acid.



In this reaction also known as Mannich, carbocation is derived from formaldehyde in acidic medium while carbanion is derived from cyclohexanone. Carbocation derived from formaldehyde reacts with non-bonded electrons of piperidine and then new carbocation is derived Mechanism of reaction:



subsequent to dewatering which reacts with the enol from cyclohexanone as a result of which 2-(piperidinomethyl)-cyclohexanone hydrochloride salt is yielded. The efficiency of this reaction is 82%.

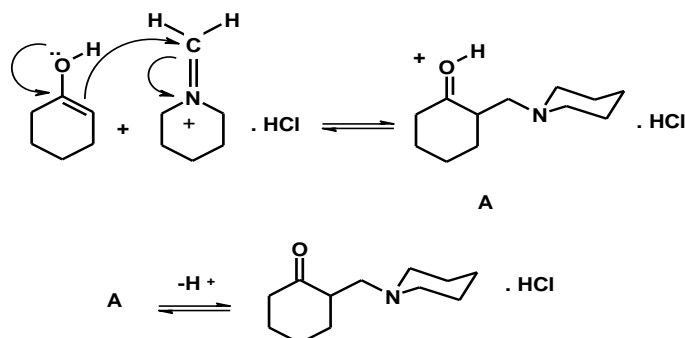
The resulting salt is refluxed with acetone for 10 minutes and thus the purification take place.

The salt is then dissolved in the water and transformed into amines with 30% NaOH followed by extraction of diethyl ether.

The IR spectrum of this compound shows stretching vibration of carbonyl at 1709 cm^{-1} .

^2H HNMR spectrum at 2.64-2.68 ppm (quadruple) related to CH_2 protons between two piperidine and cyclohexanone rings and shows multiple peaks within 1.2-2.21 (19H) range related to the two rings.

^{13}C NMR spectrum at 212.9 ppm shows carbonyl group.



4-2. REDUCTION OF 2-PIPERIDINOMETHYL CYCLOHEXANONE:

In the next stage, 2-(piperidinomethyl) cyclohexanone is reclaimed with sodium borohydride and amino alcohol 2-(piperidinomethyl) cyclohexanone is derived.

In the other technique used, 2-(piperidinomethyl) cyclohexanone was reclaimed with lithium aluminum hydride which yielded the same 2-(piperidinomethyl) cyclohexanone.

The following conclusion may be made as a result of comparison of these two methods:

The method applying sodium borohydride is easier in terms of safety and simplicity since the other method with lithium aluminum hydride required a completely dry medium as it is highly flammable and explosive in presence water and humidity.

In terms of efficiency, the reaction with sodium borohydride has higher efficiency while it is also more cost-effective.

The following variations were found in the study of IR spectrum of 2-(piperidinomethyl) cyclohexanone substance compared to the spectrum of initial composition which confirms the formation of substance:

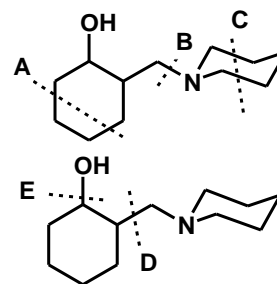
Removal of carbonyl from 1709 cm⁻¹ zone

Emergence of OH peak in 3255 cm⁻¹ zone

The most important variation in HMNR spectrum of substance compared to the initial substance is the single OH peak within 2.8 ppm zone.

72.7 ppm peak emerging in CNMR spectrum is related to carbon attached to OH.

Mass spectrum includes the following prominent fractions:



Product M = 197 $\frac{gr}{mol}$

Fraction A related to = 42 m/e

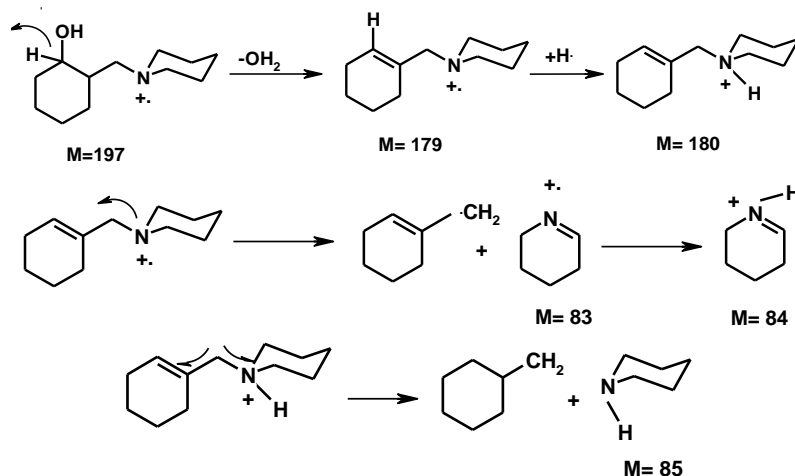
Fraction B related to = 84 m/e

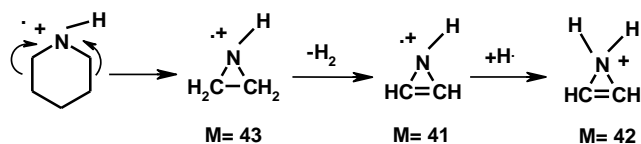
Fraction C related to = 42 m/e

Fraction D related to = 98 m/e

Fraction E related to = 180 m/e

Losing a water molecule it transforms into = 197 m/e





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