DEVELOPMENT OF CLEMMENSEN REDUCTION

A M.Sc. Dissertation report by:

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DEVELOPMENT OF CLEMMENSEN REDUCTION

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The Degree Of M.Sc (Organic Chemistry)

By

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DECLARATION

I declare that the literature review titled "**Development Of Clemmensen Reduction"** has been carried out by me in the Chemistry Department, School Of Chemical Sciences, Goa University, The information derived from the literature has been duly acknowledged in the text and a list of references is provided.

Sadanand C. Harmalkar

CERTIFICATE

This is to certify that the literature review entitled:"**Development Of Clemmensen Reduction"** submitted by the student is the record of research work carried out by the candidate during the academic year 2021-2022 under my supervision in the partial fulfillment of the requirements for the degree of Master of Science in Chemistry.

Dr. Kashinath Dhumaskar **Prof.Vidhyadatta Verenkar**

(Project Guide) (Dean of SCS GoaUniversity)

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ABSTRACT

Clemmensen Reduction is of the important organic chemical reaction is used for the reduction from carbonyl to ch2 group.In traditional clemmensen reduction uses very harsh conditions.Efforts have been made to give some evidence for the complex pathway single electron transfer.This review focuses on making the reader aware of this development towards clemmensen reduction.

INTRODUCTION

Clemmensen reduction is a chemical reaction described as a reduction of ketones (or aldehydes) to alkanes using zinc amalgam and concentrated hydrochloric acid. This reaction is named after Erik Christian Clemmensen, a Danish chemist.

The original Clemmensen reduction conditions are particularly effective at reducing aryl-alkyl ketones, such as those formed in a Friedel-Crafts acylation. The two-step sequence of Friedel-Crafts acylation followed by Clemmensen reduction constitutes a classical strategy for the primary alkylation of arenes. With aliphatic or cyclic ketones, modified Clemmensen conditions using activated zinc dust in an anhydrous solution of hydrogen chloride in diethyl ether or acetic anhydride is much more effective.[1]

The substrate must be tolerant of the strongly acidic conditions of the Clemmensen reduction (37% HCl). Several alternatives are available. Acid-sensitive substrates that are stable to strong base can be reduced using the Wolff-Kishner reduction; a further, milder method for substrates stable to hydrogenolysis in the presence of Raney nickel is the two-step Mozingo reduction.[1]

In spite of the antiquity of this reaction, the mechanism of the Clemmensen reduction remains obscure. Due to the heterogeneous

nature of the reaction, mechanistic studies are difficult, and only a handful of studies have been disclosed.[7] Mechanistic proposals generally invoke organozinc intermediates, sometimes including zinc carbenoids, either as discrete species or as organic fragments bound to the zinc metal surface. However, the corresponding alcohol is believed not to be an intermediate, since subjection of the alcohol to Clemmensen conditions generally does not afford the alkane product.

Erik Christian Clemmensen (August 12, 1876 – May 21, 1941) was a Danish-American chemist. He is most commonly associated with the Clemmensen reduction, a method for converting a carbonyl group into a methylene group.

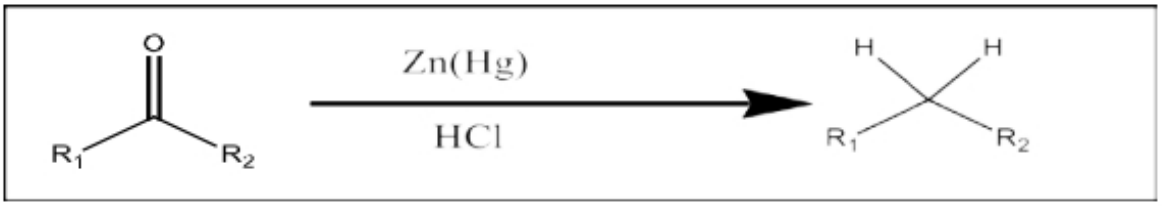
He is best known for the reaction that he developed while at Parke, Davis & Co. This reaction involves the reduction of ketones using a zinc amalgam and HCl. It has been employed in the preparation of polycyclic aromatics and aromatics containing linear hydrocarbon side chains, the latter not being obtainable from a Friedel-Crafts alkylation

The Clemmensen reduction reaction and Wolff Kishner reduction reaction differ in a few conditions. In Clemmensen Reaction, the conversion of ketones or aldehydes into alkanes takes place, whereas, in the case of Wolff-Kishner Reaction, the conversion of carbonyl groups into methylene groups takes place. These conversions are processed by reducing functional groups. Both the reactions require specific reaction conditions and the catalyst for the successful progression of the reaction.

Alkane from alkenyl chloride (halide) can be prepared from any organic compound which can be transformed into alkenyl halide.

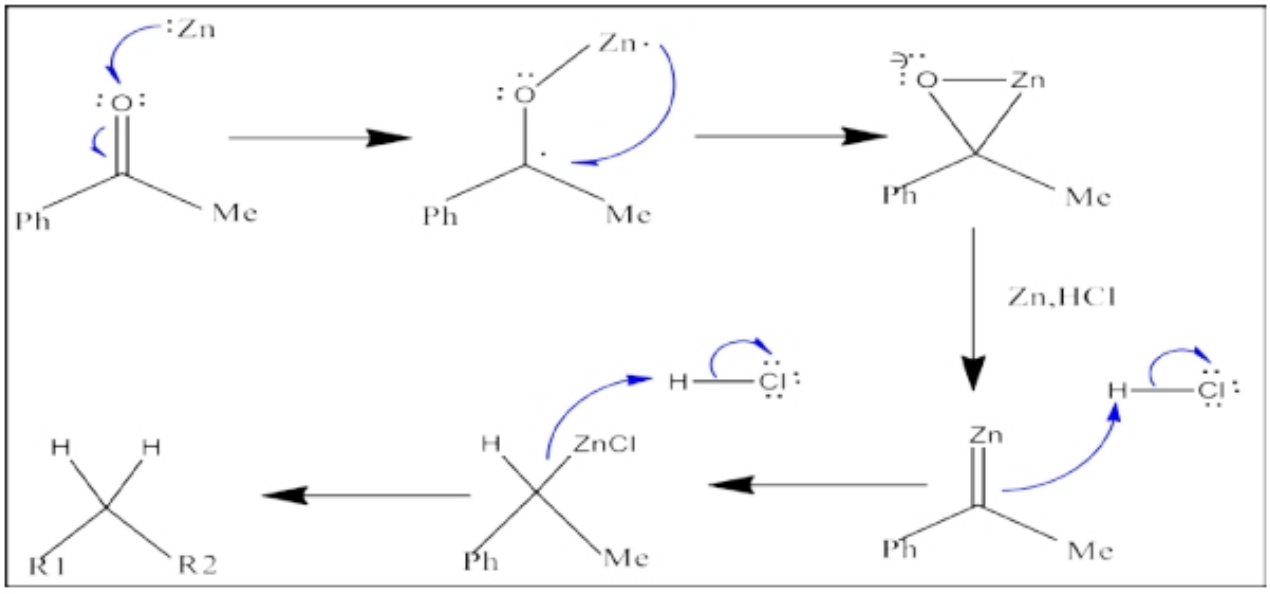
The reaction is widely used to convert the carbonyl group into a methyl group. Preparation of polycyclic aromatics and aromatics containing unbranched side hydrocarbon chain.The reaction helps to reduce the aliphatic and mixed aliphatic-aromatic carbonyl compounds. The reduction of Clemmensen is most widely used to transform acyl benzene (from acylation by Friedel-Crafts) to alkylbenzene.

The General Reaction:



Scheme 1: general clemmensen reduction

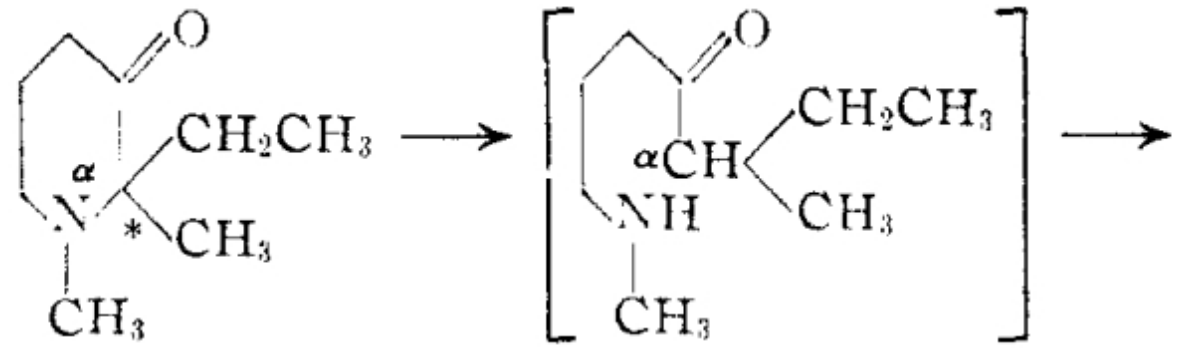
Mechanism:

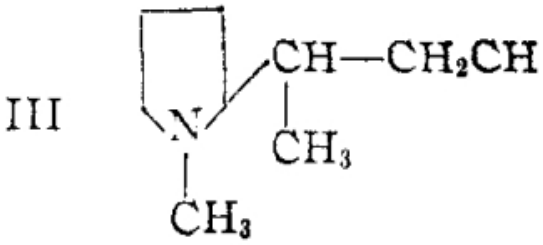


Scheme 2: Mechanism of clemmensen reduction

Literature Review

Rearrangement of a-Aminoketones during Clemmensen Reduction. The Fate of Asymmetry at the a-Carbon2





Scheme 3:rearrangements of a-aminoketones

The resolution of 1,2-dimethyl-2-ethyl-3-piperidone has been effected, and the optically active ketone has been subjected to Clemmensen reduction. The loss of optical activity and, hence, of asymmetry at the a-carbon atom during the Clemmensen reduction-rearrangement of this a-aminoketone is consistent with the concept of initial cleavage of the Cor -N bond.[2]

a study of the effect of ring size on the rearrangement of monocyclic aaminoketones' supports this hypothesis. Like wise a study of the electrolytic reduction of aaminoketones6 has indicated clearly that the

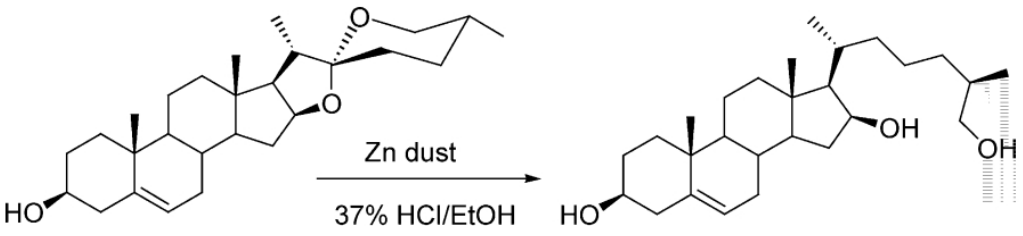
nature of the products obtained required initial Ca-N cleavage of the a-aminoketone, followed by such further reduction of the resulting intermediate as will occur at the particular cathode employed. The present investigation was undertaken to determine the fate of asymmetry at the a-carbon atom of an a-aminoketone undergoing Clemmensen reduction, since loss of optical activity during the process would be consistent with initial cleavage of the Ca-N bond.

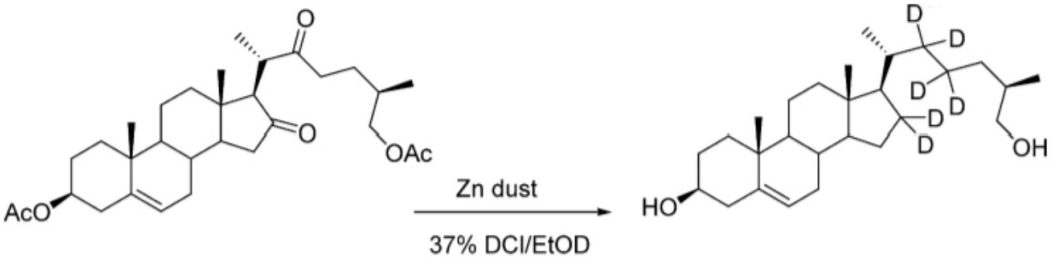
It was necessary to select an a-aminoketone which would not be racemized by hydrochloric acid alone. It was also necessary to ascertain the course of the Clemmensen reduction of the corresponding racemic a -aminoketone before proceeding with the optically active form. The compound 1,2-dimethyl-2-ethyl-3-piperidone (I) satisfied these conditions, since it has no enolizable hydrogen on the 2-carbon and since the racemic form of 1,2-dimethyl-2-ethyl-3-piperidone has been shown to give 1-methyl-2-s-butylpyrrolidine (111) on Clemmensen red~ction.~

The synthesis of ruc-l,2-dimethyl-2-ethyl-3-piperidone (I)7 was improved, and resolution of the aminoketone was accomplished through the use of dibenzoyl-D-tartaric acid. The less soluble form (in SO% ethanol) of the optically active salt of I was recrystallized to nearly constant, maximum rotation and melting point, and was then decomposed to give the free base. It was not established that the (+)-1,2-dimethyl-Z-ethy1-3-piperidone thus obtained was the optically pure dextrorotatory enantiomorph, but the liquid exhibited sufficient optical activity (a = 0.79' in a 1-dm. tube) to validate conclusions based upon observed loss or retention of activity during its reduction. The identity of the resolved

aminoketone I was checked by elemental analysis and by the infrared absorption maximum at 1712 em.-', indicative of the presence of the ketone carbonyl. The Clemmensen reduction of (+)T1,2-dimethyl-2-ethyl -3-piperidone yielded 1-methyl-2-s-butylpyrrolidine (III), as indicated by microanalysis and by the absence of infrared absorption in the 3 and 6 p regions. The product was devoid of measurable optical activity, and it was converted in quantitative yield to a picrate which was identical with that of the inactive 1- methyl-2-s-butylpyrrolidine obtained from Clemmensen reduction of ruc-1,2-dimethyl-2-ethyl-3- piperidine.~ The complete loss of optical activity during the process is consistent with the occurrence of Ca-N bond scission in I to yield as an intermediate the 2°-aminoketone I1 (or protonated), since such a s-butyl ketone, even if asymmetric as initially formed would be racemized extremely rapidly in the refluxing hydrochloric acid.

Clemmensen reduction of diosgenin and kryptogenin: synthesis of [16,16,22,22,23,23-2H6]-(25R)-26-hydroxycholesterol



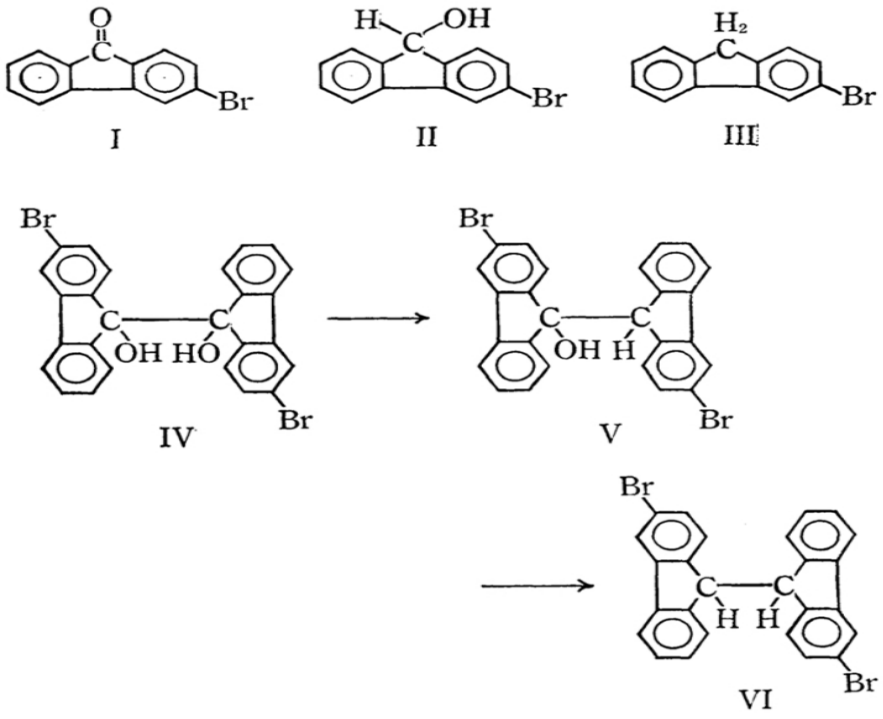


A mixture of diosgenin (2) (0.10 g; 0.24 mmol), Zn dust (2.25 g, 34.4 mmol) and ethanol (15.0 ml) was refluxed for 15 min and then 37% HCl (7.0 ml) was added during a period of 15 min.[3] At the end of the addition, the reaction, monitored by TCL (CH2Cl2/MeOH, 97:3, v/v), was cooled to room temperature and filtered to remove Zn dust.[4] CH2Cl2 (20.0 ml) was then added to the solution and the organic layer was washed with water, aqueous saturated NaHCO3 and water.[5] The organic phase was dried with Na2SO4 and the solvent evaporated at reduced pressure. The residue was purified by flash chromatography (CH2Cl2/MeOH, 99:1, v/v) to give the product 4 as a white solid (0.050 g, 50%).[6]

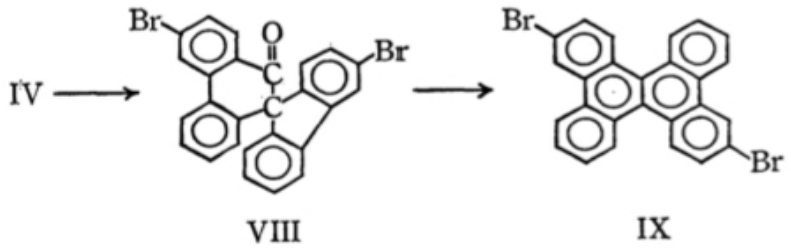
Kryptogenin diacetate (5) was prepared by an overnight reaction from kryptogenin (3) (0.2 g, 0.46 mmol), acetic anhydride (0.4 ml) and pyridine (0.8 ml) in 82% yield (0.206 g).[7] To a solution of kryptogenin diacetate (5) (0.1 g, 0.18 mmol) in EtOH (14.0 ml), Zn dust (1.64 g, 25.0 mmol) was added and the mixture stirred and refluxed for 15 min. Then 37% HCl (3.0 ml) was added dropwise during a period of 15 min and the reaction, monitored by TLC (petroleum ether/AcOEt, 70:30, v/v), was slowly cooled to room temperature. After filtration of Zn dust, CH2Cl2 (20.0 ml) was added and the organic layer was washed with water, aqueous saturated NaHCO3 and water.[8] The organic solution was dried with Na2SO4 and the solvent evaporated at reduced pressure.[9] The residue was purified by flash chromatography (petroleum ether/AcOEt, 80:20, v/v) to give the product 1 as a white solid (0.055 g, 76%).[10] Mp 169–170 ◦C

In order to obtain the deuterated derivatives of compound 4, we performed the Clemmensen reduction under our conditions using deuterated reagents.[11] NMR spectra of the product could only suggest that labeling was located in the side chain and the integration of the complex signals between 0.90 and 2.30 ppm indicated involvement of positions going from C21 to C24. Analysis of mass spectra shows that a variable number of deuterium atoms were randomly incorporated into the structure.[12] Table 1 reports the fragmentation pattern of unlabeled and labeled (25R)-cholest-5-en-3,16,26-triol (4) derivatized as trimethylsilyl ether (mol. wt. 634).[13] The most intense peak in the non-deuterated compound is at m/z 454 representing the [M-(Me3SiOH)2] ion that becomes m/z 456 in deuterated 4 corresponding to an enrichment of two deuterium atoms and is accompanied by close ions at m/z 457, 458, 459 of variable intensities

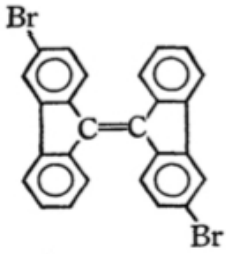
The Clemmensen Reduction of 3-Bromofluorenone



Scheme 4:reduction of 3-bromofluronone



VIII IX



X

Chart 2

Scheme 4

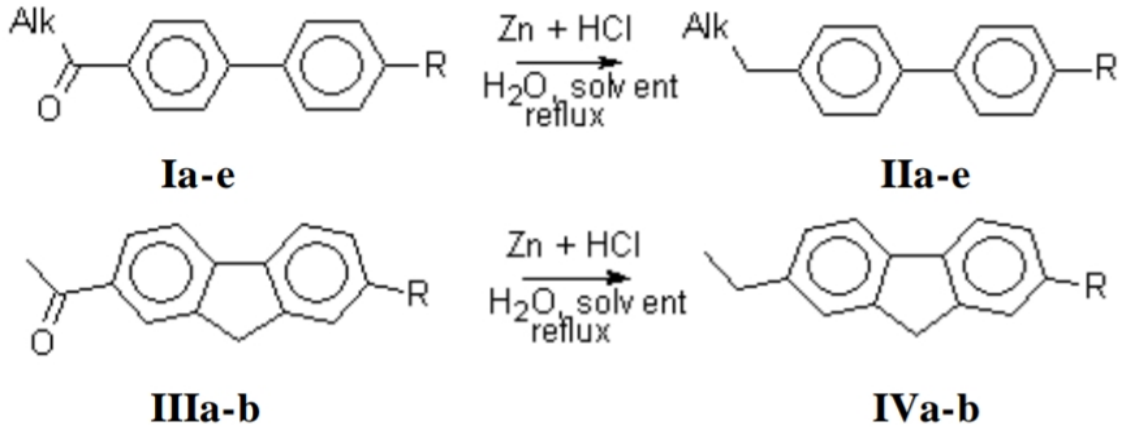
In this synthesis, a small amount of a compound (mp 267-268•Ž) was isolated during the course of the deamination process. From the infrared spectrum (1705 cm-1 (C=0), 1510, 1340 cm-1 (NO2)) and the analytical results (C, 51.25; H, 1.95%), this compound was identified as the 2-nitro-6-bromofluorenone (mp 267-268•Ž) reported by M. V. Bhatt

duced by the procedure employed with fluorenone and 2-bromofluorenone, using toluene as the solvent. From the reaction products, 3-bromofluorenol (II),4J 3-bromofluorene (III),4) 3, 3'-dibromo-9, 9'- dihydroxy-9, 9'-bifluorenyl (IV), 3, 3'-dibromo-9- hydroxy-9, 9'-bifluorenyl (V), 3, 3'-dibromo-9, 9'- bifluorenyl (VI),') and an unknown compound with a melting point of 225•Ž (VII) were isolated by means of a combination of recrystallization and column chromatography.[14].

The experimental results are summarized in Table 1. The formation of IV reached a maximum after 4-5 hr. reaction. The yields of compounds III

and VI4 gradually increased during this time. The IR spectra of IV and V were very similar to those of 2, 2'-dibromo-9, 9'-dihydroxy-9, 9'-bifluorenyl and 2, 2'-dibromo-9-hydroxy-9, 9'- bifluorenyl respectively. The reduction of IV (Run 7) also gave V, which was converted to a red 3, 3'-dibromo-9, 9'-bifluorenylidene (X) by alkali. Although VI and VII gave the same elementary analyses and very similar IR and NMR spectra, the structure of VII is not clear at present. When IV was heated with sulfuric acid in acetic acid, it afforded spiro[3-bromofluorene-9, 9'(10')- 3'-bromophenanthrene]-10'-one (VIII) by pinacol rearrangement; this was then reduced to 3, 3'dibromophenanthreno[9', 10' :9, 10]phenanthrene (IX), as is illustrated in Chart 2. The pinacol rearrangement of IV, however, did not occur during the reduction. The IR spectra of VIII and IX were very similar to those of the corresponding 2-bromo substituted compounds.

Modified Clemmensen reduction of some polycyclic alkylarylketones. Comparison of zinc dust and granulated zinc action.



Scheme 5

Unsubstituted arylalkylketones were reduced to correspondent alkylarenes with moderate yields. Reactions proceeds more slowly than for alkylphenylketones [1], probably, due to more hydrophobic character of compounds used.[15] Addition of solvent immiscible with water some increases yields, addition of solvents miscible with water increases yields significantly. Yields of hydroxy-substituted compounds were higher, than for non-phenolic compounds.[16] Addition of solvent miscible with water also increases the yield.

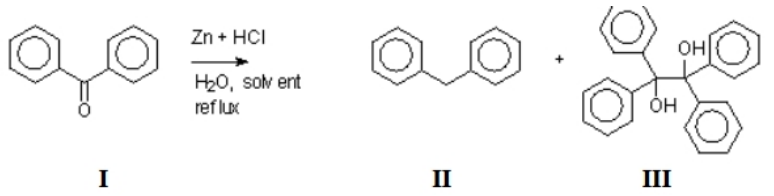
In most of runs we have used zinc dust. For comparison, we have used granulated zinc and zinc dust for reduction Ia to IIa. We have found that reduction with granulated zinc proceeds during longer time than with zinc dust, no other differences we have observed.[17]

To 0.1 mol of alkylarylketone and 0.3 mol of zinc dust 50 ml of water and 50 ml of concentrated hydrochloric acid were added. The reaction mixture was heated with reflux condenser at reflux during 24 hr. Each 6 hours 5 ml of concentrated hydrochloric acid was added. The reaction mixture was monitored with TLC.[18] After the end of reaction the reaction mixture was cooled and extracted with ethyl ether. After drying with sodium sulphate, filtration, and removing of solvent the residue purified by crystallisation.

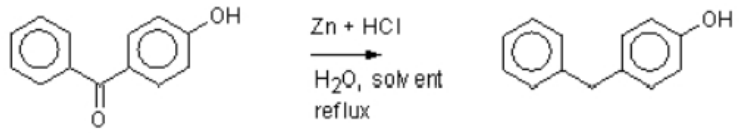
To 0.1 mol of alkylarylketone and 0.3 mol of zinc dust 50 ml of water, 50 ml of concentrated hydrochloric acid, and 50 ml of solvent were added. The reaction mixture was heated with reflux condenser at reflux during 24 hours. Each 6 hours 5 ml of concentrated hydrochloric acid was added. The reaction mixture was monitored with TLC. After the end of reaction the reaction mixture was cooled, water layer separated and

extracted with ethyl ether.[19] Combined organic solutions were dried with sodium sulphate, filtered, and solvents were removed at reduced pressure. The residue purified by crystallisation.[20]

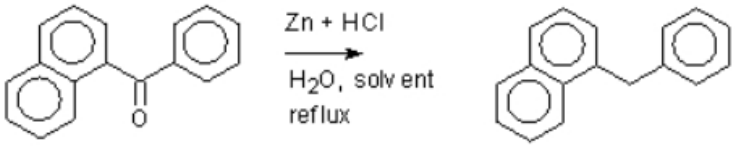
Modified Clemmensen reduction of some diaryl ketones with non-amalgamated zinc



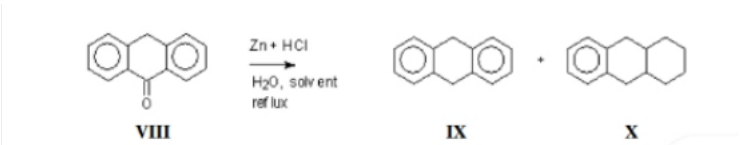
I II III



IV V



VI VII



VIII IX X

In course of our investigation directed to replace zinc amalgam for non-amalgamated zinc in Clemmensen reduction of carbonyl group to methylene group (preceeding poster [1]) we have investigated reduction of some diaryl ketones.

Unsubstituted benzophenone I was reduced with zinc dust without additional solvent to diphenylmethane II with low yield. Benzpinacone III was isolated as the main product. Reduction in ethanol-water medium proceeds with moderate yields of II and III.[21]

4-Hydroxybenzophenone IV was reduced to correspondent 4-hydroxydiphenylmethane V with zinc dust or with granulated zinc with high yield. Pinacone-type by-product was not detected.

1-Benzoylnaphthalene VI was reduced to 1-benzylnaphthalene VII with moderate yield. Addition of ethanol cosolvent did not improve yield significantly

Reduction of anthrone VIII was proceeds to dihydroanthracene IX and hexahydroanthracene X mixture. Addition of solvent miscible with water also increases the yield of IX.

Conclusion

Clemmensen reduction is an organic chemical reaction is used for the reduction from carbonyl to ch2 group although various methods have been reported the mechanism is still uncleared and some evidence for the complex pathway single electron transfer have been proposed.

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