AN INVESTIGATION OF SOME NUCLEOPHILIC SUBSTITUTIONS IN THE BENZENE NUCLEUS

AN INVESTIGATION OF SOME NUCLEOPHILIC SUBSTITUTIONS IN THE BENZENE NUCLEUS

By

EVERETT BELL FISHER
Bachelor of Arts
Wittenberg College
Springfield, Ohio
1949

Submitted to the Department of Chemistry
Oklahoma Agricultural and Mechanical College
In Partial Fulfillment of the Requirements
For the Degree of
MASTER OF SCIENCE
1950

APPROVED BY:

Ernest M. Hodnett
Chairman, Thesis Committee

Henry P. Johnston
Member of the Thesis Committee

O C Dermer
Head of the Department

D.C. McIntosh
Dean of the Graduate School

ACKNOWLEDGMENT

The author wishes to express his sincere gratitude to Dr. E. M. Hodnett, under whose direction and guidance this work has been done.

At the same time, he acknowledges the financial aid rendered by the Oklahoma A. and M. College in the form of a graduate fellowship in the Chemistry Department.

TABLE OF CONTENTS

INTRODUCTION

This work was undertaken in an attempt to clarify, in part, the existing theories of nucleophilic substitution in the benzene nucleus.

The present day theories of resonance state that a nucleophilic reagent such as the hydroxide ion, the cyanide ion, or the amide ion should enter the benzene nucleus in an <u>ortho</u> or <u>para</u> position to an electrophilic substituent such as the nitro group, the carboxyl group, the carbonyl group, the cyano group, or the sulfone group.

No record could be found in the literature of a systematic study of this type of reaction, so it was deemed feasible to carry out a series of investigations in the hope that optimum conditions for nucleophilic substitution could be found.

HISTORICAL DISCUSSION

As stated previously, no systematic study has been made of nucleophilic substitutions, although there are isolated reports in the literature of this type reaction. Wohl (17) found that o- and traces of p-nitrophenol are formed when nitrobenzene reacts with dry powdered potassium hydroxide. Druker (6) has done further work on this reaction. Tschitschibabin (14) obtained 2-pyridone by passing pyridine vapors over dry potassium hydroxide at 300-320°. Barth and Schreder (2) obtained phloroglucinol by the fusion of phenol or resorcinol with potassium hydroxide. Baeyer and Caro (1) reported the formation of 1, 2-dihydroxyanthraquinone by fusing 1- or 2-hydroxyanthraquinone with potassium hydroxide.

Leffler (11) discusses the preparation of amino derivatives which are made by a nucleophilic type substitution. Among the reactions discussed are the production of 2-aminopyridine from pyridine, 2- and 4-aminoquinoline from quinoline, 4-amino-2, 6-dimethylpyridine from 2, 6-dimethylpyridine. In each of the reactions sodium or potassium amide is fused with the heterocyclic base with the production of the corresponding amino derivative. Sachs (13) reported the formation of 1-naphthylamine and 1, 5-diaminonaphthalene from the reaction of naphthalene and sodium or potassium amide in a like manner. De Bruy and van Geuns (5) obtained 2-nitro-6-ethoxybenzonitrile by the reaction of m-dinitrobenzene with potassium cyanide in alcohol.

PRELIMINARY DISCUSSION

In order to give the greatest impetus to a possible nucleophilic substitution, compounds containing two or more electrophilic groups were chosen for use in the various investigations. These compounds were 3-nitrobenzoic acid, 3,5-dinitrobenzoic acid, 3-nitroacetophenone, 3-nitrobenzonitrile, and 3-nitrodiphenylsulfone. Of the above compounds, the nitro acids were readily available while the remainder had to be synthesized. The greatest emphasis in this series of investigations was upon hydroxylation, however, some runs were made to determine if amination or cyanation by nucleophilic substitution was possible. Variations made in experimental conditions included dry fusion and change of solvent among water, benzene, diethylene glycol, and liquid ammonia. Oxidizing agents in the form of hydrogen peroxide and atmospheric oxygen were introduced into some of the reaction mixtures in the hope that they would promote nucleophilic substitutions.

EXPERIMENTAL

Preparation of Intermediates

I. Preparation of 3-Nitroacetophenone

First run: The procedure of Corson and Hazen (4) was used for the preparation of 3-nitroacetophenone. One hundred fifty milliliters of concentrated sulfuric acid was put into a 1-liter three-necked flask equipped with a mechanical stirrer, a small dropping funnel, and a thermometer reaching almost to the bottom of the flask. The flask was immersed in a large crock containing a salt-ice mixture. The sulfuric acid was stirred and when the temperature fell to -2°, 60 g. of pure acetophenone was slowly dropped into the acid at such a rate that the temperature did not exceed 5°. The reaction mixture was allowed to cool to -7° and the cooled (15°) nitrating mixture which consisted of 40 ml. of nitric acid (sp. gr. 1.42) and 60 ml. of concentrated sulfuric acid was slowly added. Corson and Hazen (9) state that during the addition of the mixed acids the temperature should not be allowed to rise above 0°. It was found, that when using readily available apparatus, the temperature could not be held at this low value, and that it rose as high as 20° on three occasions during the addition of the nitrating mixture. The run was continued in the hope that the desired product could be obtained. The stirring was continued for ten minutes after the addition of the mixed acids and the contents of the reaction flask were poured, with vigorous stirring, into a mixture of 750 g. of cracked ice and 1.5 l. of water. The product should have separated as a yellow flocculent solid; instead a dark brown tarry residue was obtained. The preparation was discontinued at this point.

Second run: The procedure in the first run was modified by the use of dry ice as a cooling agent. Small pieces of dry ice were introduced directly into the reaction flask during the entire course of the reaction. The temperature at all times was maintained below -10° and the mixed acids could be added in about one-third the time required in the first run.

When the reaction mixture was poured into the ice-water mixture the reported yellow flocculent solid separated out. The product was washed with water, ice-cold ethyl alcohol and finally recrystallized from hot ethyl alcohol. The product, melting at 76.5° uncorr. was 60% of the theoretical yield.

II. Preparation of 3-Nitrobenzonitrile

The method of Bogert and Beans (3) was used for the preparation of 3-nitrobenzonitrile without modification. One hundred ten grams of pulverized potassium nitrate was thoroughly mixed with 300 ml. of concentrated sulfuric acid and cooled to 10°. This mixture was placed in a 1-liter three-necked flask equipped with a mechanical stirrer, a dropping funnel, a thermometer, and then the flask was immersed in an ice bath. One hundred grams of benzonitrile was added over a period of three hours while the temperature was maintained at less than 20°. The reaction mixture was allowed to stand in the ice bath for an additional hour, after which it was added to 2 l. of an ice-water mixture with stirring. A yellow solid settled out. It was suction-filtered and washed several times with cold water. The solid material was placed in a large evaporating dish and thoroughly mixed with a 6N solution of ammonium hydroxide, filtered, and washed with water. The process was repeated, eight times, until the ammoniacal filtrate had only a slight yellow tint. The product was recrystallized from a 50% ethanol-water mixture. A 90% yield of product, melting at 117° uncorr., was obtained.

III. Preparation of 3-Nitrobenzenesulfonyl chloride.

3-Nitrobenzenesulfonyl chloride was prepared according to the method of Hodgson and Whitehurst (10). One hundred twenty-three grams of dry nitrobenzene and 350 g. of chlorosulfonic acid were thoroughly mixed at room temperature. The temperature was gradually raised to 100°, held there for two hours, then maintained at 110-120° for six hours. The reaction was brought to completion by a final heating at 125-130° for two hours. After cooling, the solution was poured into a mixture of 1 kg. of ice and 1 l. of water. The white precipitate which settled out was washed with water and air-dried. The crude product was dissolved in 500 ml. of glacial acetic acid, filtered, cooled below 15°, and added cautiously to 200 ml. of water with stirring. The purified product then separated out, was washed with 50% acetic acid and air-dried. The product, melting at 61° uncorr., was 50% of the theoretical yield.

IV. Preparation of 3-Nitrodiphenylsulfone.

The method of Olivier (12) was attempted for the preparation of 3-nitrodiphenylsulfone, but the yield of the crude product was low and difficult to purify. In view of this, the procedure given in the following paragraph was employed.

Twenty grams of the carefully dried 3-nitrobenzenesulfonyl chloride previously prepared was dissolved in 50 ml. of benzene, and the solution heated under reflux. While the solution was refluxing gently 12.1 g. of anhydrous aluminum chloride was added in small portions over a time interval of two hours. Steam distillation was utilized to remove the excess benzene, and the crude product was recovered from the aqueous residue by filtration. It was washed with water, and recrystallized from hot ethyl alcohol after treatment with charcoal. A total yield of 20 g. of product which melted at 80-81° resulted from two runs.

Attempted Nucleophilic Reactions

I. By Fusion.

A. Reaction attempted with 3, 5-dinitrobenzoic acid.

Twenty grams of 3, 5-dinitrobenzoic acid and 4 g. of potassium hydroxide were heated together in an iron pot at the full capacity of a R. H. type electric hot plate. A very vigorous decomposition occurred after 15 minutes heating, and large quantities of black smoke were evolved. Only carbonaceous matter remained from which no products could be isolated.

B. Reactions attempted with 3-nitrobenzoic acid.

First run: Four grams of sodium hydroxide and 8 grams of 3-nitrobenzoic acid were mixed in an iron pot to which a condenser was attached. A previously calibrated thermocouple was placed in the pot so that the reaction mixture covered the glass tube containing the thermocouple. The reaction vessel was heated for 13 hours over a temperature range of 100-135°. When the reaction vessel was opened a minute amount of white needle-like crystals were observed on the sides of the vessel. The entire reaction mixture was dissolved in about 50 ml. of water, and concentrated hydrochloric acid added until the solution was strongly acid. A light tan solid which settled out was filtered off and dried. It gave a melting point of 138-140°. A mixed melting point with pure 3-nitrobenzoic acid gave a value of 139-140°.

Second run: The first run was repeated with a heating time of 48 hours, at 100-135° in an attempt to obtain a larger amount of the white crystals noted above. 3-Nitrobenzoic acid was again recovered unchanged as the only product. The acidified filtrate was boiled twice with charcoal and yielded a pale yellow solution. It was extracted with four 15-ml. portions of ether. The combined extracts were dried over anhydrous potassium carbonate and filtered. No residue was obtained upon evaporation of the ether.

C. Reactions attempted using 3-Nitroacetophenone.

First run: One-half gram of potassium hydroxide was heated with 1.5 g. of 3-nitroacetophenone in an open beaker for one-half hour at approximately 150°. The ketone melted and formed a dark brown viscous solution. The cooled reaction mixture was suspended in 50 ml. of water and upon acidification with dilute sulfuric acid a brown solid settled out. The product, upon treatment with charcoal and recrystallization from ethanol, melted at 79°. A mixed melting point determination made with the original ketone gave no depression. Both the aqueous reaction filtrate and the alcoholic recrystallization filtrate gave a negative test for a phenolic hydroxyl group when tested with ferric chloride solution. This method of isolation and purification was utilized throughout the balance of the runs in which 3-nitroacetophenone and 3-nitrodiphenylsulfone was used as the electrophilic reagents, and will be referred to as the standard procedure for purification.

Second run: One-half gram of 3-nitroacetophenone was mixed with 0.5 g. of sodium cyanide and heated in an open beaker. The reaction was discontinued due to copious evolution of hydrogen cyanide.

D. Attempted reactions using 3-Nitrodiphenylsulfone.

First run: One gram of the sulfone was mixed with 1 g. of potassium hydroxide and maintained at steam-bath temperature for three hours. Purification was carried out using the standard procedure. The 3-nitrodiphenylsulfone was recovered unchanged with no evidence of any hydroxylated material.

Second run: A thoroughly dried mixture consisting of 4 g. of potassium hydroxide and 4 g. of 3-nitrodiphenylsulfone was placed in a specially constructed ball mill, which could be maintained at 100°, kept air tight, and still be rotated. The mixture was kept at 100° while being rotated for four hours. The reaction mixture when purified by the standard method resulted in the recovery of the unchanged 3-nitrodiphenylsulfone. No evidence of any formation of hydroxylated product could be detected.

II. Aqueous Solvent.

A. Attempted reactions with 3-nitroacetophenone.

First run: One-half gram of potassium hydroxide was dissolved in the minimum amount of water and 1.5 g. of 3-nitroacetophenone was added. After the reaction mixture was boiled gently for one-half hour a dark brown viscous solution was obtained. Subsequent treatment of this residue gave only unchanged 3-nitroacetophenone.

Second run: One gram each of sodium hydroxide and 3-nitroacetophenone were added to 20 ml. of water contained in a 50-ml. three-neck flask equipped with a gas dispersion tube and an extra long reflux condenser. When the top of the condenser was attached to an aspirator, air could be pulled through the mixture in the flask. The mixture was refluxed gently for four hours. The mixture was treated by the standard method and gave only unchanged 3-nitroacetophenone.

Third run: The first run above (II-A) was repeated with the same results except for the following exceptions. Sodium cyanide was used instead of sodium hydroxide, 10 ml. of water was used as solvent, and precautions were exercised during acidification.

Fourth run: The second run above (II-A) was repeated with the same results except for the following exceptions. Sodium cyanide was used instead of sodium hydroxide, and the reflux time was reduced to three hours.

B. Attempted reactions with 3-nitrodiphenylsulfone.

First run: Two milliliters of a saturated alcoholic solution of potassium hydroxide was added to 30 ml. of benzene in which 1 g. of 3-nitroacetophenone had been dissolved and the mixture refluxed for two hours. The benzene was removed by steam distillation and the residue treated by the standard method. The ketone was recovered unchanged and no traces of hydroxylated materials could be detected.

Second run: One-half gram of 3-nitroacetophenone was added to 1 g. of sodium cyanide suspended in 25 ml. of benzene and the mixture was refluxed for two hours. The cyanide did not go into solution and was filtered from the reaction mixture at the end of the reflux period. The benzene was removed by steam distillation and the residue was purified by the standard procedure. The unchanged 3-nitroacetophenone was the only product.

Third run: One-half gram of 3-nitroacetophenone and 1.5 g. of sodium cyanide were added to 25 ml. of benzene, and air was pulled through the reaction mixture while it refluxed for seven hours. The cyanide, which did not go into solution, was filtered off and the benzene was removed by steam distillation. The residue was purified according to the standard method and only unchanged 3-nitroacetophenone was recovered from the reaction mixture.

B. Reactions attempted using 3-nitrodiphenylsulfone.

First run: One gram each of potassium hydroxide and 3-nitrodiphenylsulfone were added to 25 ml. of benzene and the mixture refluxed for three hours. The benzene was removed from the reaction mixture by steam distillation and the residue treated by the standard method. The only product recovered was unchanged 3-nitrodiphenylsulfone.

Second run: One gram each of 3-nitrodiphenylsulfone and potassium hydroxide were added to 25 ml. of benzene and the mixture was refluxed for five hours while air was pulled through it. The benzene was removed by steam distillation and the residue treated according to the standard procedure. Unchanged 3-nitrodiphenylsulfone was the only product recovered.

IV. High-Boiling Solvent.

A. Reaction attempted with 3-nitrobenzoic acid.

First run: Six grams of sodium hydroxide and 8 g. of 3-nitrobenzoic acid were mixed in a three-necked flask equipped with a reflux condenser, a mechanical stirrer, and a thermometer. One hundred milliliters of diethylene glycol was added as a solvent and gentle heat was applied. As the temperature increased, two effects were noted; (a) the sodium hydroxide became increasingly more soluble, and (b) the solution deepened in color. At the reflux temperature (180°) the sodium hydroxide was completely dissolved and the solution had turned extremely dark brown. The reaction mixture was refluxed for two hours and then allowed to cool. The cooled reaction mixture consisted of an extremely dark brown viscous solution with a black solid mass in the bottom of the flask. The solution was decanted and a 10-ml. portion was acidified with dilute hydrochloric acid and extracted with ether. When the ether had air-evaporated an orange oil remained. It was recrystallized from hot ethanol and a small amount of yellow-orange crystals were obtained. These crystals melted above 320°, left no residue upon ignition, and showed acidic properties by being soluble in dilute base but insoluble in dilute acid. The small quantity of product was consumed in making these preliminary characterizations and could not be obtained again.

The solid residue from the original reaction mixture was dissolved in dilute sodium hydroxide and the solution filtered. The filtrate, upon acidification with dilute hydrochloric acid, yielded a brownish-gray waxy solid. An attempt was made to purify this substance, but it met with no success.

The remainder of the original decanted solution was treated as the 10-ml. portion except that the ether was distilled off.

A black tarry substance, soluble in dilute base, remained. The basic solution was neutralized and a substance very similar in appearance to that obtained from the original solid residue remained. Again, the substance could not be purified or crystallized.

Second run: Eight and four-tenths grams of potassium hydroxide was added to 150 ml. of diethylene glycol and the mixture placed in a three-neck flask equipped as in the first run. When the mixture had been heated to 150°, the potassium hydroxide had completely dissolved and the resulting solution was orange.

Eight grams of 3-nitrobenzoic acid was dissolved in the minimum amount of diethylene glycol (55 ml.) and the solution slowly poured down the reflux condenser into the hot solution of diethylene glycol and potassium hydroxide. The reaction mixture darkened at once and in a very short time became dark brown. After the solution had refluxed for two hours it was set aside to cool. The cooled reaction mixture resembled that produced in the first run. The same method of isolation and purification of products was attempted, but it met with no success.

V. Aqueous solvent with oxidizing agent present.

A. Attempted reaction using 3-nitroacetophenone.

Seven-tenths grams of potassium metal was added to approximately 30 ml. of liquid ammonia contained in a Dewar flask surrounded by an acetone-dry ice bath. Nickel oxide and ferric nitrate were added in minute amounts to catalyze the formation of potassium amide. The solution turned deep blue upon the addition of the potassium.

The blue color disappeared slowly and was replaced with a light brown precipitate. One gram of 3-nitroacetophenone was added to this mixture. It turned red for a short time, but quickly deepened to dark brown. The liquid ammonia was allowed to evaporate over a period of six hours. A black metallic residue remained in the reaction vessel. It was extracted with acetone several times and dried. As the solid residue showed very little change upon strong ignition it was assumed to consist of the catalysts previously introduced into the reaction mixture.

The acetone extract was a reddish brown in color. No products could be isolated from it.

DISCUSSION OF RESULTS

The results of this investigation gave no evidence of nucleophilic substitution in the benzene nucleus under the conditions imposed.

In only two instances were any new substances isolated. The white needlelike crystals obtained from the fusion of sodium hydroxide and 3-nitrobenzoic acid, and the colored crystals obtained from the reaction of sodium hydroxide and 3-nitrobenzoic acid using diethylene glycol as a solvent. In both cases, the yields were too small to permit complete characterization of these substances. Additional runs were made in an attempt to isolate these products in larger yields, but they met with no success.

In general, the balance of the runs gave two results. Either complete decomposition, as typified by the fusion of 3, 5-dinitrobenzoic acid with sodium hydroxide, and the attempted reaction of 3-nitroacetophenone with potassium amide in liquid ammonia; or recovery of the unchanged electrophilic reagent in substantially the starting quantity, as typified by any of the attempted reactions between 3-nitroacetophenone and sodium or potassium hydroxide.

The experimental conditions were varied in an attempt to effect nucleophilic substitutions. In addition to dry fusion various types of solvents were used including aqueous, inert (benzene), high boiling (diethylene glycol), and liquid ammonia. Among the nucleophilic reagents used were sodium and potassium hydroxide, sodium cyanide, and potassium amide. Oxygen was introduced into some of the reaction mixtures in the hope that it would promote a nucleophilic substitution by combining with any hydride ion formed (15) and thus shift the equilibrium in favor of the nucleophilic reaction. Oxygen was supplied by two methods. Hydrogen peroxide was used as a solvent, and air was pulled through the reaction mixture by use of a gas dispersion tube and an aspirator. None of the variations in the experimental procedure had any apparent effect in promoting nucleophilic substitution.

Because of limited time and previous results, 3-nitrobenzonitrile was not used in this series of investigations.

The negative results obtained in this series of investigations lead to one of two conclusions. Either the theories of resonance and aromatic substitution as expressed and understood today are incorrect, or the correct experimental conditions for nucleophilic substitution have yet to be determined. Fieser (8), Pauling (9) and Wheland (16) each state, in effect, that electrophilic groups decrease the electron density in the ortho and para positions of the benzene nucleus. Thus electrophilic substitutions should take place at the meta position with difficulty. This has been proven (7) by numerous experiments. It is further reasoned that nucleophilic substitutions should take place at the ortho and para positions with relative ease. Only a few isolated references could be found to substantiate this last statement.

It is believed by this author that, while this research was rewarded with only negative results, the basic concepts leading to the theory of nucleophilic substitution are correct and that further work will establish the experimental conditions necessary for nucleophilic substitutions.

BIBLIOGRAPHY

1. Baeyer and Caro, Ber., 7, 968 (1874).

2. Barth and Scheder, Ber., 12, 417 (1879).

3. Bogert and Beans, J. Am. Chem. Soc., 26, 468 (1904).

4. Blatt, "Organic Synthesis," Collective Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 434-8.

5. de Bruyn and van Geuns, Rec. trav. chim., 23, 26 (1904).

6. Druker, "The Conversion of Aromatic Nitro Compounds to Nitrophenols by Alkalies," Thesis, Oklahoma A. and M. College, 1942.

7. Gilman, "Organic Chemistry," 2nd ed., Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 204.

8. Ibid, p. 211.

9. Ibid., Vol. II, pp. 1977-8.

10. Hodgson and Whitehurst, J. Chem. Soc., 482 (1944).

11. Adams, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1942, Chapter 4.

12. Olivier, Rec. trav. chim., 35, 110 (1915), via C. A., 10, 1635 (1916).

13. Sachs, Ber., 39, 3006 (1906).

14. Tschitschibabin, Ber., 56, 1879 (1923).

15. Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 256.

16. Ibid., p. 262.

17. Wohl, Ber., 32, 3486 (1899).

BIOGRAPHY

Everett Bell Fisher was born in Chicago, Illinois, on October 6, 1922. He attended the Public School Systems of Bellefontaine and Springfield, Ohio, and was graduated from Springfield Senior High School in June, 1940. In September of the same year, he enrolled in Wittenberg College, Springfield, Ohio.

He enlisted in the United States Army Air Force on May 4, 1942, as a private. Upon graduation from the Army Air Force Officer's Candidate School in Miami Beach, Florida, he was commissioned as a Second Lieutenant on December 9, 1942. On February 16, 1946, he was released from active duty as a Captain after having served as a Supply Officer in both the United States and Italy.

He reentered Wittenberg College in June 1946 and completed the requirements for the Bachelor of Arts degree in August 1948. His degree was conferred in June 1949.

On January 31, 1947, he was married to Muriel Jeanne Michener and a daughter, Patricia Jeanne, was born on February 12, 1948.

In September 1948 he entered the Graduate School of Oklahoma A. and M. College where he has been employed as a graduate fellow in the Department of Chemistry until the present time.

Typed by:

Mrs. J. O. Richardson