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Final Report on Research Project NR 055-120

Contract No. N7onr-455 - Task Order II

with

Office of Naval Research

"Condensations by Acids and Bases (Condensations, Displacements,
Eliminations and Rearrangements)"

by

Charles R. Hauser, Professor of Chemistry
Duke University, Durham, N. C.

31 August 1954

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I. List of Publications and Uncompleted Problems.

The results obtained under this contract should ultimately yield the more than thirty articles listed below which includes some receiving only partial support from this source. The first nineteen of these articles, which are listed in chronological order, have been published, and reprints of them accompany this report. The twentieth and twenty-first are "in press". The latter, the chapter for "Organic Reactions", is listed here because one of the authors did a considerable amount of the literature survey and some of the writing while being supported by the Office of Naval Research. The twenty-second and twenty-third articles are practically ready for publication. The last nine titles listed (24-32) refer to problems in various stages of completion.

1. "Metalation and Carbonation of Benzohydrylamine and Derivatives Using Potassium Amide", by C. R. Hauser, Ina C. Flur and S. W. Kantor. J. Am. Chem. Soc., 71, 294 (1949).
2. "Boron Fluoride Catalyzed Addition of Aliphatic Anhydrides to Aldehydes", by E. H. Man, J. J. Sanderson and C. R. Hauser. J. Am. Chem. Soc., 72, 847 (1950).

3. *Reprint exhausted. Journal can be found in any chemical library.*
"Claisen Acylations and Carbethoxylations of Ketones and Esters by Means of Sodium Hydride", by F. W. Swamer and C. R. Hauser. J. Am. Chem. Soc., 72, 1352 (1950).
4. "Pentaphenylacetone and Tetraphenylacetone", by S. W. Kantor and C. R. Hauser. J. Am. Chem. Soc., 72, 3290 (1950).
5. "Formation of Symmetrical Ketones from Self-condensations of Anhydrides by Boron Fluoride", by E. H. Man and C. R. Hauser. J. Am. Chem. Soc., 72, 3294 (1950).
6. "Relative Ease of Cyclization of 2-, 3-, and 4-Aminopyridine Derivatives. Synthesis of Naphthyridines", by C. R. Hauser and G. A. Reynolds. J. Org. Chem., 15, 1224 (1950).
7. "Action of Basic Reagents on Benzonitrile to Form Triazines", by F. W. Swamer, G. A. Reynolds and C. R. Hauser. J. Org. Chem., 16, 43 (1951).
8. "Condensations of Nitriles Having alpha Hydrogen to Form beta-aminonitriles, Cyclic Trimers, and Substituted 2-Hydroxy-4-Aminopyridines", by G. A. Reynolds, W. J. Humphlett, F. W. Swamer, and C. R. Hauser. J. Org. Chem., 16, 165 (1951).
9. "The Claisen Acylation of Methyl Ketones with Branched Chain Aliphatic Esters", by E. H. Man, F. W. Swamer and C. R. Hauser. J. Am. Chem. Soc., 73, 901 (1951).
10. "Rearrangement of Benzyl Ethers to Carbinols by Potassium Amide. Mechanism of Isomerization of Carbanions Involving 1,2-Shifts", by C. R. Hauser and S. W. Kantor. J. Am. Chem. Soc., 73, 1437 (1951).
11. "Rearrangements of Benzyltrimethylammonium Ion and Related Quaternary Ammonium Ions by Sodium Amide Involving Migration into the Ring", by S. W. Kantor and C. R. Hauser. J. Am. Chem. Soc., 73, 4122 (1951).
12. "Cleavage of Benzyl-, Diphenylmethyl- and Triphenylmethyl-trimethylsilanes by Potassium Amide and Certain other Bases", by C. R. Hauser and C. R. Hance. J. Am. Chem. Soc., 73, 5846 (1951).
13. "Preparation and Reactions of alpha-Halo Derivatives of Certain Tetra-substituted Hydrocarbon Silanes. Grignard Syntheses of Some Silyl Compounds", by C. R. Hauser and C. R. Hance. J. Am. Chem. Soc., 74, 5091 (1952).
14. "Evidence for alpha- and beta-Elimination from Deutero Alkyl Halides with Potassium Amide", by D. G. Hill, W. A. Judge, P. S. Skell, S. W. Kantor and C. R. Hauser. J. Am. Chem. Soc., 74, 5599 (1952).

15. "Silico-alkylation of Sodio Esters with Trimethylchlorosilane to Form Silyl Esters", by C. R. Hance and C. R. Hauser. J. Am. Chem. Soc., 75, 994 (1953).
16. "A Rapid Method for the Resolution of *s*-Butyl Alcohol", by S. W. Kantor and C. R. Hauser. J. Am. Chem. Soc., 75, 1774 (1953).
17. "Rearrangement of Benzyl Sulfides to Mercaptans and of Sulfonium Ions to Sulfides Involving the Aromatic Ring by Alkali Amides", by C. R. Hauser, S. W. Kantor and W. R. Brasen. J. Am. Chem. Soc., 75, 2660 (1953).
18. "Rearrangement of Diphenyl to 9,10-Dihydro-9-Phenanthrol by Potassium Amide and Dehydration to Phenanthrene. Results with 1,8-Naphthalan, Phthalan, and 2,5-Dihydrofuran", by A. J. Weinheimer, S. W. Kantor and C. R. Hauser. J. Org. Chem., 18, 801 (1953).
19. "The Ortho Substitution Rearrangement versus beta-Elimination of Certain Quaternary Ammonium Ions with Sodium Amide. Extension of the Methods of Synthesis of Vicinal Alkyl Aromatic Derivatives", by C. R. Hauser and A. J. Weinheimer. J. Am. Chem. Soc., 76, 1264 (1954).
20. "Mechanisms of beta-Elimination with Alkyl Halides and Bases Using Deuterium as Tracer", J. Am. Chem. Soc., "In press".
21. "The Acylation of Ketones to Form beta-Diketone or beta Keto Aldehydes", Organic Reactions VIII, "In press".
22. "Synthesis and Reactions of alpha-Dialkylaminobenzyl *n*-Butyl Ethers. Condensations with Grignard Reagents to Form Tertiary Amines".
23. "Relative Extents of Rearrangement of Some Primary Amines of the Neopentyl Type with Nitrous Acid. Electronic versus Steric Factors".
24. "Controlled Acylation of Ketones with Acid Chlorides to Form beta-Diketones Using Sodium Amide".
25. "Some Methods of Synthesis of beta-Keto Esters of the Type $\text{RCOCH}_2\text{COOC}_2\text{H}_5$ ".
26. "Influence of Metallic Cation of Organic Metallic Compounds on Courses of Reactions".
27. "Theory of Formation of beta-Diketones from Anhydrides and Ketones by Boron Trifluoride".
28. "Stereochemistry of Rearrangement of Benzyl Secondary Butyl Ether by Potassium Amide".

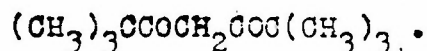
29. "Stereochemical Course of Rearrangement of bis-(alpha-Methylbenzyl)-ether".
30. "Beta-Elimination of Certain Ethers and Tertiary Amines with Potassium Amide".
31. "Exclusive beta-Elimination from Certain Deutero Alkyl Halides with Bases".
32. "Conversion of alpha Phenylalkyl Halides to Dimeric Olefins by Sodium Amide".

II. Summary of Results.

The results will be considered under the headings, (A) Condensations, (B) Rearrangements, and (C) Eliminations and Displacements. The numbers in parentheses refer to the above list of publications and uncompleted problems. The unpublished results will be treated more fully than the published ones, the abstracts and complete discussions of which can be found in the accompanying reprints.

A. Condensations.— (a) Acylation of Ketones to Form beta-Diketones.— The forthcoming chapter in Organic Reactions (21) presents a critical survey of this field employing both basic reagents and boron fluoride. Also other methods for preparing beta-diketones are considered.

The acylation of sodio methyl ketones (prepared by means of sodium amide) with branched chain esters was found to be effected much more satisfactorily with phenyl esters than with methyl or ethyl esters (9). The method has been especially useful for preparing beta-diketones having branching at both ends such as



Although phenyl esters generally produce good yields of beta-diketones, the yield of the unsaturated beta-diketone from phenyl cinnamate and acetophenone has been only 30% and the reaction follows another course (Michael reaction) with ethyl cinnamate (21).

A much better yield (70%) has now been obtained employing cinnamoyl chloride under controlled conditions (24). One equivalent of the acid chloride is added at 0° to the sodio ketone prepared from three equivalents each of the ketone and sodium amide.



It should be pointed out that, under the usual conditions, the acid chloride diacylates the ketone, that is, the beta-diketone (as its sodio derivative) is further acylated (21). The scope of the present method is being investigated.

Sodium hydride was shown to produce equally good yields as sodium amide and better yields than sodium ethoxide or sodium in various acylations of ketones with ethyl or methyl esters (3).

Boron trifluoride is especially appropriate for effecting certain acylations of ketones with aliphatic anhydrides (21), and the theory of the reaction is interesting. Evidence was obtained (27) that the boron trifluoride complex of the beta-diketone is first formed and that it loses hydrogen fluoride to give the boron difluoride complex of the beta-diketone from which the beta-diketone is subsequently liberated by means of hot sodium acetate solution. The evidence will be presented in a forthcoming paper together with more extensive results obtained under other sponsorship.

In connection with the acylations of ketones, a study was made of the self-condensation of aliphatic anhydrides by boron trifluoride which produces, after hydrolysis and decarboxylation of intermediates, good yields of certain symmetrical ketones (5).

In contrast to ketones, aldehydes having alpha-hydrogen fail to be acylated with acetic anhydride in the presence of boron trifluoride. Instead, addition occurs to form the diacetate (2).

(b) Other condensations Involving Carbonyl Compounds or Nitriles.

Sodium hydride was shown (3) to be a useful reagent for effecting the acylations of esters and the carbethoxylations of ketones and esters. It is particularly appropriate for certain mixed ester condensations (3).

Nitriles having alpha hydrogen were self condensed by basic reagents to form beta-amino nitriles (8). Certain mixed nitrile condensations were also effected (8).

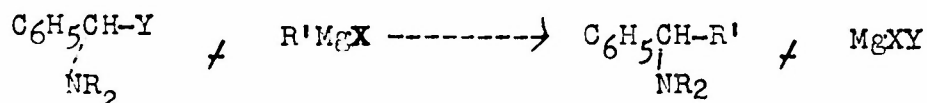
Potassium diphenylmethide, prepared from potassium amide and diphenylmethane, was acylated with triphenylacetyl and diphenylacetyl chlorides to form pentaphenylacetone and tetraphenylacetone respectively (4). The potassium derivative of benzohydrylamine, prepared from potassium amide and the amine, was carbonated to give the corresponding alpha-amino acid (1). Similar reactions were effected with certain derivatives of the amine (1).

Various condensation reactions leading to the formation of beta-keto esters of the type $\text{RCOCH}_2\text{COOC}_2\text{H}_5$ are being investigated (25). The work has not yet progressed sufficiently far to draw any conclusions as to the value of the several methods under consideration.

(c) Influence of Metallic Cation in Certain Condensations and Associated Reactions.-- When two courses of reaction are possible with a carbanion (or potential carbanion) the metallic cation may determine which course will predominate (26). Thus, whereas lithium phenyl and phenylmagnesium bromide add to the carbonyl groups of acetophenone and ethyl phenylacetate, sodium phenyl was found to ionize mainly the alpha-hydrogens of these carbonyl compounds to form the enolate anions which are the reactive intermediates in their self-condensations.

Similarly sodium phenyl ionized mainly the alpha-hydrogen of mesityl-acetonitrile whereas lithium phenyl adds largely to the nitrile group. However, like lithium phenyl, sodium phenyl underwent 1,2-addition with benzalacetophenone whereas phenylmagnesium bromide is known to exhibit exclusively 1,4-addition.

(d) Condensations of alpha-Dialkylaminobenzyl n-Butyl Ethers with Grignard Reagents to Form Tertiary Amines.- This type of condensation may be represented by the general equation in which Y stands for a relatively electronegative group.



The present reaction in which Y is OC_4H_9 produces much better yields than previous cases where Y is another group. The preparations of the alpha-dialkylaminobenzyl ethers are also of interest. The abstract of the paper soon to be submitted for publication is given below.

Abstract.- Methods have been developed for the synthesis of alpha-dialkylaminobenzyl n-butyl ethers and their p-methoxy and p-chloro derivatives from aromatic aldehydes, aliphatic secondary amines and butanol-1. The parent type of compound, $\text{C}_6\text{H}_5\text{CH}(\text{NR}_2)\text{OC}_4\text{H}_9$, $\text{R} = \text{CH}_3$, was shown to be readily interconvertable with the diamine, $\text{C}_6\text{H}_5\text{CH}(\text{NR}_2)_2$, but not with the acetal. A series of the amino ethers were condensed with Grignard reagents to form tertiary amines of the type, $\text{C}_6\text{H}_5\text{CH}(\text{NR}_2)\text{R}'$, certain of which are difficult to prepare by the more common methods. This substitution with Grignard reagents is freer of side reactions than that of amino nitriles, $\text{C}_6\text{H}_5\text{CH}(\text{NR}_2)\text{CN}$, with these reagents which has previously been employed for such tertiary amines.

An amino ether was reduced by ethylmagnesium chloride (involving the hydride ion) and by hydrogen in the presence of a catalyst. Certain aspects of the mechanisms of formation of the amino ethers and of their reactions with Grignard reagents are considered.

(e) Condensations to Form N-Heterocyclics.— The theory of the relative ease of aromatic cyclizations of 2-, 3-, and 4-aminopyridine derivatives was elucidated, and then used in the synthesis of new naphthyridines (6). Acyl derivatives of beta-imino nitriles (see b) were cyclized by sodium amide to form 2-hydroxy-4-aminopyridines (8). Benzonitrile was trimerized by basic reagents to form triazines (7).

(f) Condensations Involving Silicon Compounds.— The alpha-hydrogen of certain esters was metalated with sodium triphenylmethide and the resulting sodio esters then silico-alkylated with trimethylchlorosilane to form silyl esters (15). Grignard reagents prepared from alpha-halosilanes were condensed with acetic anhydride to form silyl ketones, with allyl bromide to form the silyl olefin, and with acetone and benzaldehyde to give silyl carbinols (13). Certain other condensation type of reactions were also effected with silyl compounds (13).

B. Rearrangements.— (a) The mechanism of the Stevens rearrangement involving the 1,2-shift of an alkyl group within a carbanion, was elucidated and then used in the extension of this type of rearrangement (10). In agreement with the mechanism, optically active benzyl secondary butyl ether was found to be rearranged by potassium amide with some retention of activity but further experiments are required before drawing conclusions (28). In connection with this work a rapid method for the resolution of s-butyl alcohol was devised (16).

The stereochemical course of the rearrangement of bis-(alpha-methyl-benzyl)-ether with potassium amide was investigated but further work is needed before definite conclusions can be drawn (22). Diphenan was rearranged to a phenanthrol and phenanthrene by potassium amide (18).

Quaternary ammonium ions having the benzyl group, which exhibit the Stevens 1,2-shift with most basic reagents, were shown to undergo rearrangement involving the benzene ring with sodium amide in liquid ammonia to form ortho substituted tertiary amines (11). The mechanism was elucidated and used in the extension of this remarkable type of rearrangement to form vicinal alkyl aromatic derivatives (11, 19). In contrast to benzyl ethers (10), benzyl sulfides were found to undergo this ortho substitution rearrangement (17).

(b) Rearrangements of Carbonium Ions.— A study was made of the factors governing the relative extents of rearrangement of certain primary amines of the neopentyl type with nitrous acid (23). These reactions involve presumably the intermediate formations of diazonium ions and unrearranged and rearranged carbonium ions. The present results illustrate the importance of both electronic and steric factors. The abstract of the paper soon to be submitted for publication is given below.

Abstract.— Four primary amines of the alpha-phenylneopentyl type have been prepared and their products of reaction with nitrous acid determined. Alpha-Phenylneopentylamine gave exclusively the corresponding unrearranged alcohol or its nitrite ester, whereas the amine having three ethyl groups on the beta-carbon atom and amines having a phenyl group and two methyl or ethyl groups on the beta-carbon atoms, formed rearranged products as well as the unrearranged alcohols.

The rearranged products consisted of two isomeric olefins and the rearranged alcohol. All of the rearranged and unrearranged alcohols, some of the olefins, and certain of the ketones produced on ozonization of the olefins were independently synthesized for comparison. In connection with the synthesis of two of the amines, the intermediate oximes were obtained more readily from the corresponding imines and hydroxylamine than from the corresponding ketones. The relative importance of electronic and steric factors in determining the extents of rearrangement have been considered.

C. Eliminations and Displacements.- (a) Beta-Eliminations versus alpha-Eliminations.- Appropriately substituted deuterio alkyl halides were employed to determine the mode of elimination of the halides with potassium amide in liquid ammonia. It was experimentally established that beta-elimination occurs exclusively or predominately with the halides studied but, when ether also was present, some alpha-elimination appeared to take place with n-octyl halide (14). However, further work has indicated that, in the absence of ether, even this halide exhibits exclusive beta-elimination (31). The problem is being thoroughly investigated.

In contrast to purely aliphatic alkyl halides having beta-hydrogen, alpha-phenylalkyl halides react with sodium amide in liquid ammonia to form dimeric olefins, and evidence was obtained that the reaction involves an alkylation mechanism and not alpha-elimination, accompanied by dimerization (32). Further work is in progress.

(b) Mechanisms of beta-Elimination.- By employing appropriately deuterated alkyl halides, evidence was obtained that the beta-elimination of the hydrogen halide from certain alkyl halides by potassium amide in liquid ammonia involves the simultaneous removal

of the proton and halide ion (14,20). However, the beta-elimination of methanol from certain beta-phenyl alkyl ethers by potassium amide evidently involves the intermediate formation of the corresponding carbanion, since, on adding deuterium oxide to the mixture before the completion of the reaction, some deuterium was found in the recovered ether (30).

(c) Displacements on Silicon and Carbon.- The benzyl, diphenylmethyl and triphenylmethyl groups in appropriately tetra-substituted hydrocarbon silanes were found to be displaced by potassium amide in liquid ammonia and by sodium ethoxide in refluxing ethanol, but not by certain other basic reagents (12). Weakly basic anions such as the acetate and cyanide ions attack the alpha-carbon displacing halide ion in certain alpha-halosilanes whereas the strongly basic amide ion attacks silicon displacing the halocarbon group (13). However, we believe that by employing an appropriate metallic cation along with the amide ion or other potentially strong base, it should be possible to effect displacements at the alpha-carbon of alpha-halosilanes without cleaving the silicon-carbon bond. We hope to study such reactions since they may lead to the synthesis of a number of new silicon compounds having functional groups.

Displacements on carbon were involved in certain of the reactions considered above. Thus, this type of reaction occurs in the alkylation mechanism for the conversion of alpha-phenylalkyl halides by sodium amide in liquid ammonia to dimeric olefins. This was considered above under C (a). Moreover, the reaction of alpha-dialkylaminobenzyl n-butyl ethers with Grignard reagents considered under A (d), appears to involve a particularly interesting type of displacement.

III. Contribution to Organic Chemistry

A complete evaluation of the contribution of the present results to organic chemistry would be difficult to make at this time. However, some general aspects of the contribution may be indicated. They are concerned with both the theory and practice of organic chemistry.

A. Mechanisms and Factors Governing Reactions.-- The mechanisms of several reactions have been elucidated including the boron fluoride method of acylation of ketones (27), the displacement of carbanions from silicon by the amide ion (12,13), the beta-eliminations of alkyl halides (14, 20, 31) and ethers (30), and especially the Stevens 1,2-shift of benzyl ethers (10,28, 29) and the ortho substitution rearrangement of benzyl quaternary ammonium ions (11, 19).

The factors governing several reactions have been established or indicated including the rearrangements mentioned above, the acylations of ketones (9, 24), the cyclizations of aminopyridine derivatives (6), and certain reactions by basic reagents in which the metallic cation plays an important role (12, 26). These contributions to the theory of reactions are of importance not only in themselves but also for the advancement of synthesis.

B. Syntheses.-- Many new compounds have been synthesized and even certain ~~new types~~ new types have been prepared. Probably the most significant contribution from the practical standpoint was the discovery of several essentially new methods of synthesis which has made possible the preparation of many new compounds. A particularly important method involves the ortho substitution rearrangement (11, 17, 19) which may be employed not only for the preparation of the vicinal alkyl aromatic tertiary amines resulting from the rearrangement but also for the synthesis of various related compounds including

alcohols and carboxylic acids. Several new applications of this method are being made.

Two useful developments involve the synthesis of alpha-dialkyl-aminobenzyl n-butyl ethers and their condensations with Grignard reagents to form tertiary amines some of which are difficult to prepare by other methods (22).

Methods for preparing silicon compounds include the silico-alkylation of sodio esters (15) and of potassium diphenylmethide and triphenylmethide with trimethylchlorosilane (12), and the reactions of the Grignard reagents of alpha-halosilanes with certain compounds (13).

Other methods include the syntheses of diacetates (2), ketones (4,5), naphthyridines (6), beta-iminonitriles and 2-hydroxy-4-amino-pyridines (8), beta diketones and beta-keto esters (3, 9, 24), cyclic ethers and phenanthrenes (18), tertiary amines and quaternary ammonium compounds (11, 19) and primary amines and alcohols (23).

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