[CONTRIBUTION FROM THE MALLINCKRODT CHEMICAL LABORATORIES, HARVARD UNIVERSITY]

The Meerwein Reaction. Catalysis by Cuprous Chloride

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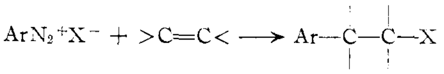
The Meerwein reaction which previously had been postulated as being a cupric-catalyzed reaction is shown to be a cuprous-catalyzed reaction. This reaction is thus mechanistically put into the same category as the Sandmeyer reaction in the reactions of aromatic diazonium salts.

The Meerwein reaction[1] can be formulated in its most general form as the reaction of an aromatic diazonium halide with an aliphatic unsaturated compound to yield substituted α-halo-β-phenyl alkanes and alkenes



$$ArN_2^+X^- + {>}C{=}C{<} \longrightarrow Ar{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}X$$

With certain olefins, products corresponding to the dehydrohalogenated adduct or decarboxylated alkene are obtained. The reaction is carried out in aqueous acetone solutions in which the diazotized amine solution has been neutralized with sodium acetate. Catalytic amounts of cupric chloride are necessary for the reaction. The myriad of unsaturated compounds to which this reaction has been applied runs the gamut of simple ethylenes,[2] aromatic ethylenes,[3] α,β-unsaturated carbonyl compounds, including chalcones,[4a] cinnamic acid and its derivatives,[1,4e] coumarins,[1] acrylic acids[4b] and ketones,[2a] acrylonitriles,[2a,4a,c,d] acetylenes,[1,2a] and conjugated dienes.[5]

The mechanism of this interesting and versatile reaction has been the subject of considerable speculation.[4c,4d] The primary questions revolved essentially around two points: (a) the homolytic or heterolytic (if either) character of the reaction and (b) the role of divalent copper and the specificity of acetone in promoting the decomposition of the diazonium salt.

We have investigated the catalysis by cupric chloride and find that under the conditions of the experiment cupric chloride is reduced readily to cuprous chloride by acetone.[7] The reaction is given by the equation

$$2CuCl_2 + CH_3COCH_3 \longrightarrow 2CuCl + ClCH_2COCH_3 + HCl$$

The reaction proceeds at its maximum rate under the conditions originally specified by Meerwein, *et al.*,[1] for the diazonium reaction, *viz.*, buffering with sodium acetate, optimum acetone concentrations (limited by solubility of salts) and high chloride ion concentrations.

The cuprous chloride formed under these conditions possesses an extraordinary catalytic power to decompose diazonium ions. Whereas the usual conditions of the Sandmeyer reaction often call for high temperatures and molar amounts of cuprous chloride we have found that extremely small amounts (0.05 equivalent or less) of cuprous chloride are efficacious at 0–25° in thoroughly deoxygenated aqueous acetone solutions. The use of acetone thus greatly facilitates the preparative Sandmeyer reaction.[8] Under these conditions the Sandmeyer product is formed in excellent isolated yield, accompanied by a small amount of reduced product and little or no undesirable azo compounds.

In the presence of olefin the Meerwein reaction takes precedence over the Sandmeyer reaction and the aryl halide is formed usually only as the side product despite the preponderant chloride concentration. For example, crystalline *p*-chlorobenzenediazonium chloride dissolved in a lithium chloride solution of 75 volume per cent. acetone–water liberates a quantitative volume of nitrogen with cupric chloride; the organic product, *p*-dichlorobenzene, is isolable in greater than 90% yield. If the diazonium salt is decomposed in a similar manner in a solution containing an amount of styrene equivalent to the diazonium compound, α,4′-dichlorobibenzyl is formed in 68% yield. If an oxidizing agent such as potassium permanganate or oxygen is added to the reaction initially the rate of nitrogen evolution is inhibited.[9]

Similarly catalytic amounts of cuprous chloride can be added to an anaerobic aqueous acetone solution containing only lithium chloride and *p*-chlorobenzenediazonium chloride; the Sandmeyer product is isolable in excellent yield. If cuprous chloride is added dropwise to *p*-chlorobenzenediazonium chloride and styrene in aqueous acetone at 0°, α,4′-dichlorobibenzyl is formed in 75% yield.

When the Meerwein reaction is catalyzed by cuprous chloride, acetone is desirable but not necessary for the reaction. Diazotized *p*-chloroaniline reacts with styrene in approximately 75 volume per cent. ethanol–water to give 28% of α,4′-dichlorobibenzyl. Similarly this diazonium salt adds to acrylonitrile in aqueous solutions containing no organic

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(1) H. Meerwein, E. Buchner and K. van Emster, *J. prakt. Chem.*, **152**, 237 (1939).

(2) (a) E. Müller, *Angew. Chem.*, **61**, 179 (1949); (b) S. Cristol and W. Norris, THIS JOURNAL, **76**, 3005 (1954).

(3) (a) W. Brunner and J. Kustascher, *Monatsh.*, **82**, 100 (1951); (b) W. Dale and C. Ise, THIS JOURNAL, **76**, 2259 (1954); (c) W. Freund, *J. Chem. Soc.*, 3068 (1952); 2889 (1953); (d) F. Bergmann, E. Dimant and H. Japhe, THIS JOURNAL, **70**, 1618 (1948); (e) D. Brown and G. Kon, *J. Chem. Soc.*, **224**, 2147 (1948).

(4) (a) P. L'Ecuyer and C. Olivier, *Can. J. Research*, **27B**, 689 (1949); (b) J. Rai and K. Mathur, *J. Indian Chem. Soc.*, **24**, 413 (1947), and earlier papers; R. Fusco and S. Rossi, *Gazz. chim. ital.*, **78**, 524 (1948); (c) W. Brunner and H. Perger, *Monatsh.*, **79**, 187 (1948); (d) C. Koelsch and V. Boekelheide, THIS JOURNAL, **66**, 412 (1944); C. Koelsch, *ibid.*, **65**, 57 (1943); (e) F. Bergmann and D. Schapiro, *J. Org. Chem.*, **12**, 57 (1947); F. Bergmann, *et al.*, *ibid.*, **9**, 408, 415 (1944); P. L'Ecuyer, C. Oliver, E. Giguere, F. Turcotte and P. Roberge, *Can. J. Research*, **26B**, 70 (1948); R. Fuson and H. Cooke, THIS JOURNAL, **62**, 1180 (1940); P. L'Ecuyer and C. Oliver, *Can. J. Research*, **28B**, 648 (1950); F. Waring and D. Bell, *J. Chem. Soc.*, 1025 (1948).

(5) E. Coyner and G. Ropp, THIS JOURNAL, **70**, 2283 (1948); E. Müller, "Action of Aromatic Diazo Compounds on Aliphatic Unsaturated Compounds," PB 737, Office of Technical Services, Department of Commerce, Washington, D. C.; E. Braude and J. Fawcett, *J. Chem. Soc.*, 3113 (1951).

(7) Kochi, THIS JOURNAL, in press.

(8) Unpublished results.

(9) *Cf.* E. Pfeil and O. Velten, *Ann.*, **565**, 182 (1949), and earlier papers.

solvent to give 68% yield of α,*p*-dichlorohydrocinnamonitrile. Rai and Mathur[4b] report that they were able to get better yields of cinnamic acid from diazonium salts and maleic acid when the reaction was run with cupric chloride in water than when gross acetone was used. In certain cases gross acetone concentrations may adversely affect the solubility problem. The effectiveness of acetone over other organic solvents in the cuprous chloride catalyzed reaction may merely be a solvent effect. Attempts to achieve the reaction in the absence of copper in aqueous acetone solutions from which oxygen had been scrupulously eliminated were unsuccessful.[4c]

Our experiments indicate that the effective catalytic species in the Meerwein reaction is the univalent form of copper, and not one of the chlorocupric anions previously suggested. The process can then be given as

$$2CuCl_2 + CH_3COCH_3 \longrightarrow 2CuCl + ClCH_2COCH_3 + HCl \quad (1)$$

$$ArN_2{}^+Cl^- \cdot + >C{=}C< \xrightarrow{CuCl} Ar{-}\underset{|}{\overset{|}{C}}{-}\underset{|}{\overset{|}{C}}{-}Cl$$

A kinetic study of the Sandmeyer and related Meerwein reaction will be published shortly.

Experimental

***p*-Chlorobenzenediazonium Chloride.**—Crystalline *p*-chlorobenzenediazonium chloride was prepared from the amine hydrochloride and amyl nitrite in ethanol.[10] It was recrystallized several times from ethanol–ether solutions; the colorless platelets were analyzed for ionic chloride potentiometrically.

Anal. Calcd. for $C_6H_4N_2Cl_2$: Cl, 20.3. Found: Cl, 21.0.

Method I.—The *p*-chlorobenzenediazonium chloride (10 g.) was dissolved in a solution containing 100 ml. of acetone, 28 ml. of water and 5 ml. of 1.2 *M* lithium chloride contained in a 100-ml. round-bottomed standard taper flask equipped with a side arm (8 mm. tubing) capped with a skirt type rubber stopper (Cenco 44181). Through the stopper was attached a stopcock by which the flask was degassed by repeated freezings and evacuations at 0.01 μ. The flask and contents then were brought to room temperature, purified nitrogen introduced into the flask and oxygen-free aqueous cupric chloride solution introduced with a hypodermic syringe. The nitrogen evolution was measured in an eudiometer. After the nitrogen evolution was complete, water was added to the reaction mixture and the whole extracted with ether. The ether extracts were dried over calcium chloride and the ether carefully distilled. Small amounts of chloroacetone co-distilled with the ether, and it also was present in the aqueous mother liquors (infrared spectrum and 2,4-dinitrophenylhydrazone). The residue on cooling crystallized; after one recrystallization from aqueous ethanol, m.p. 52°, yield 92%.

Method II.—If crystalline *p*-chlorobenzenediazonium chloride was treated with 6.0 g. of styrene (freshly distilled) in a manner similar to method I, α,4′-dichlorobibenzyl was formed. The crude oil solidified on cooling; crystallization from petroleum ether (b.p. 20–40°) gave colorless needles melting at 76–77°,[11] yield 68%.

Anal. Calcd. for $C_{14}H_{12}Cl_2$: Cl, 28.2. Found: Cl, 28.0.[12]

Method III.—Crystalline *p*-chlorobenzenediazonium chloride (12.5 g.) was dissolved in a mixture containing 8 g. of freshly distilled styrene, 100 ml. of reagent acetone (redistilled from chromic anhydride) and 28 ml. of water at 0° in a 250-ml. standard taper erlenmeyer flask equipped with a nitrogen inlet at the bottom of the flask and a standard taper Y-tube head. One end of the head led to a eudiometer and to the other end was attached a 50-ml. standard taper dropping funnel. Fifteen drops of a solution containing 0.07 g. of CuCl (purified by the standard method[13]) in 2.5 ml. of acetone and 0.8 ml. of 1.1 *M* lithium chloride was added intermittently over a period of an hour to the magnetically stirred diazonium solution. The mixture immediately turned deep wine red and began to evolve nitrogen. The reaction was complete in one hour at 10–20° and was green-black finally. Excess water was added to the reaction mixture and the product worked up in the usual manner. The brown oil left after the distillation of the ether crystallized on standing; crude weight 16 g., yield of recrystallized material 75%. Small amounts of chloroacetone (<0.5 g.), *p*-dichlorobenzene (1.0 g.) and chlorobenzene (0.3 g.) were isolated from the aqueous solution and mother liquors.

Method IV.—A mixture of 10.8 g. of *p*-chloroaniline and 18 ml. of concentrated hydrochloric acid was chilled in an ice–HCl-bath and diazotized with 6.0 g. of sodium nitrite in 10 ml. of water. The excess nitrite was cut with a saturated solution of urea until the diazo solution gave a negative starch–iodide test. After decolorization with Norite the clear colorless solution (33 ml.) was added to a chilled solution of 100 ml. of acetone and 8.9 g. of styrene. Purified nitrogen was bubbled through the solution for 15 minutes, and 25 drops of a solution of 0.07 g. of CuCl in 1.5 ml. of acetone and 0.5 ml. of 1.2 *M* lithium chloride was added dropwise over an hour to the stirred solution. The solution turned magenta as before and evolved 1950 ml. of gas in 1.5 hours. Excess water was added to the two-layered reaction mixture and the product worked up as described earlier. The dried ethereal solution was distilled; it left a brown oil which crystallized. Recrystallization from petroleum ether (b.p. 20–40°) gave colorless prisms (15.2 g.) melting at 75–76°.

Method V. Effect of Solvent.—The process outlined in method IV was repeated using 95% ethanol (distilled from potassium hydroxide) instead of acetone. When the cuprous chloride solution was added dropwise to the reaction mixture, the solution turned dark purple immediately. The solution evolved 1525 ml. of nitrogen in one hour, turned dark brown and precipitated a large amount of black tar. Addition of water followed by extraction with ether gave a black ethereal solution. The solution, after drying and distillation of the ether, yielded a dark brown intractable tar. The oil was taken up partially by 75 ml. of ligroin (b.p. 80–110°) and chromatographed with petroleum ether (b.p. 30–60°) as eluent. One pass gave crystalline material (28%) melting at 75–76°. The black oil, which was eluted with benzene, and the petroleum ether insoluble resin were not characterized.

Method VI. Acrylonitrile in Water.—A mixture of 16.2 g. of *p*-chloroaniline and 27 ml. of concentrated hydrochloric acid was diazotized with 9.0 g. of sodium nitrite in the usual manner (see method IV). The diazo solution was diluted to 110 ml. with water and decolorized. Through the clear colorless solution was bubbled purified nitrogen for 20 minutes at 0°; 8 g. of freshly distilled acrylonitrile was added and the bubbling continued for an additional five minutes. Cuprous chloride (0.77 g.) dissolved in 15 ml. of oxygen-free 1.2 *M* lithium chloride solution was added dropwise to the stirred light yellow diazonium–olefin solution. The solution turned bright yellow and slowly evolved nitrogen. The cuprous chloride solution was added at the rate of 5 ml. per hour at 0–10°. As the reaction progressed an orange amorphous solid precipitated. Extraction with ether was incomplete. Approximately 0.1 g. of ether and water-insoluble light brown material was filtered. It probably was the acrylonitrile polymer. The orange ethereal solution was washed repeatedly with water and dried. Evaporation of the ether left an orange liquid which slowly crystallized. The amorphous material was extracted twice with 25-ml. portions of petroleum ether (b.p. 20–40°). The petroleum ether solution was then chromatographed

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[10] M. Crossley, R. Kienle and C. Benbrook, THIS JOURNAL, **62**, 1400 (1940).

[11] The Meerwein reaction between styrene and diazonium salts leads to α-chlorobibenzyls and not to the stilbenes as reported by Brunner and Kustascher (ref. 3a). With styrene and benzenediazonium chloride the product is α-chlorobibenzyl which slowly loses hydrogen chloride on standing to give *trans*-stilbene. The α-chlorobibenzyl obtained in the Meerwein reaction solvolyzed at the same rate in 50% aqueous acetone at 55° as the chloride obtained by treating phenylbenzylcarbinol with thionyl chloride.

[12] Microanalysis was carried out by Mr. S. Nagy, Massachusetts Institute of Technology.

[13] W. Fernelius, Editor, "Inorganic Syntheses," Vol. 2, McGraw-Hill Book Co., Inc., New York, N. Y., 1946, p. 1.

directly. It yielded 2.8 g. of *p*-dichlorobenzene, 0.5 g. of chlorobenzene, 0.6 g. of orange crystalline material (not identified) and 2.0 g. of α,p-dichlorohydrocinnamonitrile. The petroleum ether insoluble material on vacuum distillation gave 17.4 g. of orange oil, α,p-dichlorohydrocinnamonitrile, which boils at 128–132° (5 mm.).[3a] The oil, 4.1 g., was refluxed with 60 g. of 10% sodium hydroxide for two hours. The sodium salt was filtered, acidified with hydrochloric acid and recrystallized twice from absolute ethanol. The colorless needles (88%) melted at 249.5–250°.[4a,4b]

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

The Methyl Esters of 3-Hydroxyphthalic Acid. Selective Reduction of Monomethyl Phthalates with Lithium Aluminum Hydride

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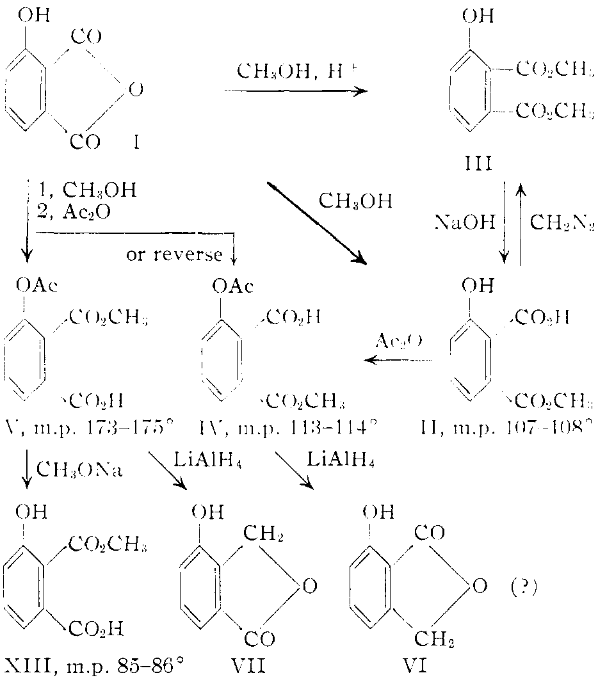
Reaction of 3-hydroxyphthalic anhydride with methanol gives the 1- and 2-methyl esters in about a 3:2 ratio. A method for reducing methyl phthalate to phthalide in good yield by means of lithium aluminum hydride is described.

In connection with another problem we were interested in the monomethyl esters of 3-hydroxyphthalic acid. Treatment of the anhydride I with hot methanol gave material melting over a wide range from which the pure half-ester II could be isolated only with considerable loss. The same material was obtained in very low yield by the saponification of the diester III with one equivalent of sodium hydroxide.

When the crude monomethyl ester was acetylated, a mixture resulted from which *both* monomethyl esters (IV and V) of 3-acetoxyphthalic acid could be isolated by crystallization. The lower melting of these (IV) proved to be identical with material obtained in good yield from the pure methyl 3-hydroxyphthalate (II) by acetylation. This ester IV was isolated in 44% yield, the yield of the higher melting isomer V being 25%. The formulas summarize the reactions so far outlined and some others described in the experimental part. Structures are assigned on the basis of the evidence given.



Attempts to prove the structures of the half-esters IV and V by decarboxylation failed, since saponification of the decarboxylation product of either IV *or* V appeared to give mainly 3-hydroxybenzoic acid.[2] A structure proof based on the selective reduction of the ester groups of IV and V by means of lithium aluminum hydride so as to obtain 7- (VI) and 4-hydroxyphthalide (VII), respectively, was then considered. The selective reduction of the ester group of an ester-acid with lithium aluminum hydride at low temperatures was first suggested in 1947.[3] Later, the reduction of methyl phthalate to phthalide was actually performed,[4] but no experimental details are available. The only other selective reduction of an ester-acid reported seems to be that of 1-methyl 3-chlorophthalate (VIII) to the corresponding phthalide IX,[5] but in this case steric factors may be partly responsible for the incomplete reduction, in view of the fact that an excess of the hydride was employed and that the isomeric 2-methyl 3-chlorophthalate (X), under the same conditions was reduced all the way to 3-chloro-*o*-xylylene glycol (XI).[5]

In our hands, reduction of methyl phthalate in ether at −60° by the addition of the theoretical amount of ethereal lithium aluminum hydride failed to yield any phthalide. When the methyl phthalate was dissolved in tetrahydrofuran instead of ether at −60°, phthalide was formed in 32% yield. Satisfactory results were finally obtained by dissolving the half-ester in tetrahydrofuran and carrying out the reaction at −30°, the yield of the phthalide in this case being 72%. Apparently the success of the selective reduction goes hand in hand with the *absence* of the formation of a heavy precipitate in the reaction mixture. With ether as a sol-

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[1] Reilly Fellow, 1949–1951, National Institutes of Health Fellow 1951–1952.

[2] This acid was identified with certainty only in the case of V which should *not* have yielded 3-hydroxybenzoic acid by simple decarboxylation. Presumably, at the temperature required for decarboxylation, IV and V are interconvertible and the more labile carboxyl group *ortho* to the acetyl function is lost in either case.

[3] R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 2548 (1947).

[4] G. Papineau-Couture, E. M. Richardson and G. A. Grant, *Can. J. Res., Sect. B*, **27**, 902 (1949).

[5] R. F. Bird and E. E. Turner, *J. Chem. Soc.*, 5050 (1952).