

Selective Bromination with Copper(II) Bromide¹

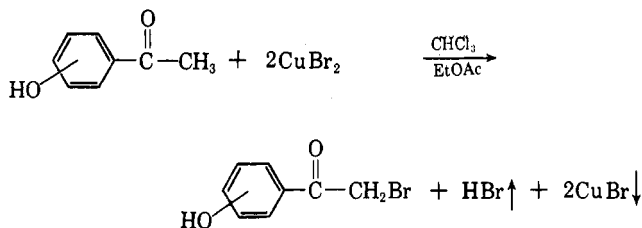
L. CARROLL KING AND G. KENNETH OSTRUM²

Chemistry Department, Northwestern University, Evanston, Illinois 60201

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A heterogeneous system consisting of copper(II) bromide in chloroform-ethyl acetate will effect selective bromination of ketones. This system is the cleanest and the most direct for selective bromination reported to date. In the present paper the selective bromination of hydroxyacetophenones is reported.

A suspension of copper(II) bromide in chloroform-ethyl acetate reacts with ketones to give the corresponding α -bromo ketones. This reaction system is highly selective when used to brominate hydroxyacetophenones and gives nearly quantitative yields of the α -bromohydroxyacetophenones, hydrogen bromide, and copper(I) bromide according to the following equation.



The reaction is best carried out by adding 1 mole of ketone to a suspension of 2 moles of copper(II) bromide in refluxing chloroform-ethyl acetate. Under these conditions the reaction proceeds rapidly with evolution of hydrogen bromide and conversion of black copper(II) bromide to white copper(I) bromide. Completion of the reaction is indicated by cessation of hydrogen bromide evolution, disappearance of all the black solid, and a color change in the solution from green to amber.

When carried out under these conditions, the reaction possesses practical experimental advantages not available with other bromination procedures. (1) The reaction is selective. The test for this selectivity was made using hydroxyacetophenones. When hydroxyacetophenones are brominated, only side-chain monobromination products are observed, and there is no indication of nuclear bromination. This selectivity was established by conversion of the bromo ketones to derivatives identical with compounds previously prepared in this laboratory by known reactions.^{3,4} (2) The by-products of the reaction can be separated readily from the desired α -bromo ketone. Hydrogen bromide is only slightly soluble in the solvent system used and escapes from the reaction vessel.⁵ The copper(I) bromide is insoluble and is easily removed by filtration. (3) The resulting solution of the α -bromo ketone can be used directly for the preparation of derivatives without isolation of the lachrymatory product.

(1) Presented at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept., 1964, paper 170.

(2) Abstracted from the forthcoming Ph.D. Thesis of G. K. O., Northwestern University.

(3) (a) L. C. King, *J. Am. Chem. Soc.*, **66**, 894 (1944); (b) L. C. King, M. McWhirter, and D. M. Barton, *ibid.*, **67**, 2089 (1945).

(4) F. Kröhnke, *Angew. Chem.*, **65**, 605 (1953).

(5) (a) J. J. Howland, Jr., D. R. Miller, and J. W. Willard [*J. Am. Chem. Soc.*, **63**, 2807 (1941)] studied the solubility of hydrogen bromide in chloroform. (b) W. Gerrard and E. Macklen [*J. Appl. Chem.* (London), **6**, 241 (1956)] studied the solubility of hydrogen chloride in ethyl acetate. In later studies W. Gerrard, A. M. A. Mincer, and P. L. Wyvill [*ibid.*, **10**, 115 (1960)] found that the solubility of hydrogen bromide in a series of solvents was always greater than that of hydrogen chloride.

If desired, the solvents may be removed under reduced pressure (except for low molecular weight aliphatic bromo ketones where fractional distillation must be used) so that the α -bromo ketone itself may be isolated or a change of solvent accomplished. (4) The extent of reaction can be determined by titration of the liberated hydrogen bromide, after sweeping out the system to ensure complete removal, and/or from the amount of copper(I) recovered. If the reaction is interrupted before completion, the extent of reaction can be estimated from the weight of the mixture of copper(II) and copper(I) bromides recovered.

Copper(II) halides in aqueous solution, alcoholic solution, dimethylformamide solution, or dioxane solution have been used to halogenate a variety of ketones.⁶⁻¹² There has been no report of both selectivity and high yield of product when the reaction is carried out in these homogeneous systems, and other experimental disadvantages, especially in the ease of isolation of products, are inherent in these systems. Doifode and Marathe¹² brominated 4'-methoxy-2'-hydroxyacetophenone, and two analogs, with copper(II) bromide in dioxane, and their results indicate a selectivity of the type we have found. However, the yields they obtained are somewhat lower than those expected with the heterogeneous system reported herein. Kosower, *et al.*,¹¹ used copper(II) halides in dimethylformamide solution and showed that under these conditions phenols are halogenated at rates significantly faster than those observed for aliphatic ketones. Fort⁷ used methanolic solutions of copper(II) bromide and concluded that this system had no selectivity, but rather gave the same products as obtained from molecular bromide. Fort,⁷ Sollman and Dodson,⁸ and Glazier¹⁰ also noted that methanolysis of the bromo ketone product occurred in certain favorable cases. These results are in sharp contrast with the results obtained in this study and illustrate the marked influence of the solvent on the course of the reaction. The choice of solvent is also critical in the heterogeneous bromination of ketones using copper(II) bromide. Apparently a polar solvent is required since Nonhebel¹³ reported that acetone in carbon tetrachloride did not react with copper(II) chloride. We have observed this phenomenon also. 2'-Hydroxyacetophenone does not react with copper(II) bromide at an observable rate in carbon tetrachloride, but reacts readily in chloroform and/or ethyl acetate. The

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(11) E. M. Kosower, W. J. Cole, G.-S. Wu, D. E. Cardy, and G. Meisters, *ibid.*, **28**, 630 (1963).

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TABLE I
PREPARATION OF 2-BROMOHYDROXYACETOPHENONES

Substituted acetophenone	Acetophenone formed	Time required	Yield, ^a %	M.p., ^b °C.
2'-Hydroxy-	2-Bromo-2'-hydroxy-	3-5 hr.	ca. 100	40 ^c (45) ^d (70-71) ^e
3'-Hydroxy-	2-Bromo-3'-hydroxy-	20-40 min.	ca. 100	(...) ^f (...)
4'-Hydroxy-	2-Bromo-4'-hydroxy-	15-20 min.	ca. 100	124-126 (130) ^g (128-129) ^h
2',4'-Dihydroxy-	2-Bromo-2',4'-dihydroxy-	3-5 hr.	ca. 100 ⁱ	144-145 ^j (127) ^k
2',5'-Dihydroxy-	2-Bromo-2',5'-dihydroxy-	3-5 hr.	74-87 ^l	112-113 ^m (117.5-119) ⁿ

^a Yield based on weight of crude product isolated and amount of copper(I) bromide recovered. ^b Literature values in parenthesis. ^c Not completely crystalline. ^d N. P. Buu-Hoi and D. Lavit, *J. Chem. Soc.*, 18 (1955). ^e L. Vargha, J. Ramonczai, and J. Bathory, *J. Am. Chem. Soc.*, 71, 2652 (1949). ^f Isolated as a liquid which decomposed upon attempted vacuum distillation. ^g N. P. Buu-Hoi, N. D. Xuong, and D. Lavit, *J. Chem. Soc.*, 1034 (1954). ^h D. D. Mukerji, *Ann.*, 619, 189 (1958). ⁱ Isolated ca. 40% as crystalline product. ^j After several recrystallizations from benzene; crude product m.p. 128-138°. ^k A. Sonn and S. Falkenheim, *Ber.*, 55, 2975 (1922). ^l Isolated crystalline product. ^m Slightly contaminated with unreacted starting material as indicated by C and H analysis and thin layer chromatography. ⁿ M. C. Kloetzel, R. P. Dayton, and B. Y. Abadir, *J. Org. Chem.*, 20, 38 (1955).

TABLE II
PREPARATION OF SUBSTITUTED 1-BENZOYL METHYL PYRIDINIUM SALTS^a

Compd. ^b	Yield, ^c %	Bromide m.p., °C. ^d	Iodide m.p., °C. ^d	Perchlorate m.p., °C. ^d
2'-Hydroxy-R	85-93	197-200 (...)	212-217 (211-215) ^e	201-202 (193-196) ^e
3'-Hydroxy-R	68-93	222.5-224 dec. (218-219) ^g	236-239 dec. ^f (223-228) ^e	222-224 (224-226) ^e
4'-Hydroxy-R	84-99	248-250 dec. (...)	221-223 dec. (215-219) ^e	180-182 (181-183) ^e
2',4'-Dihydroxy-R	66-72	253-254.5 dec. (...)	243.5-245.5 (241-242) ^e	240-242 ^f (253-255) ^e
2',5'-Dihydroxy-R	75-83	235-238 (...)	237-239 dec. (...)	272-274 dec. (...)

^a Bromide salts were converted to the less soluble iodide and perchlorate salts by the method of King.³ ^b R = benzoylmethylpyridinium salt. ^c Represents lowest and highest yields of the bromide salt obtained in a minimum of three preparations. ^d Literature values in parenthesis. ^e Ref. 3b. ^f Infrared spectrum was superimposable on that of an authentic sample. ^g T. Goto, *J. Pharm. Soc. Japan*, 74, 318 (1954).

mixture of chloroform and ethyl acetate was used throughout this study since preliminary work indicated that this mixed solvent system gave cleaner products than either solvent alone. We thus conclude that the present heterogeneous method using copper(II) bromide in chloroform-ethyl acetate is the cleanest, the most convenient, and the most direct reported to date for the preparation of α -bromo ketones in general.

The hydroxyacetophenones were brominated with copper(II) bromide under the heterogeneous conditions described and the crude α -bromo ketones isolated by removal of the solvents under reduced pressure, or converted directly to the corresponding β -ketoalkylpyridinium bromides (see Tables I and II). The β -ketoalkylpyridinium bromides were converted to the known iodide or perchlorate salts by the method of King.^{3a} The salts produced by these reactions gave characteristic hydroxybenzoic acids when cleaved by aqueous alkali (see Table III). Further evidence for this selectivity was obtained by the conversion of 2-bromo-2'-hydroxyacetophenone to the known coumaran-3-one with aqueous base by the method of Fries and Pfaffendorf.¹⁴

TABLE III
CLEAVAGE OF SUBSTITUTED 1-BENZOYL METHYL PYRIDINIUM SALTS

Salt hydrolyzed ^a	Substituted benzoic acid formed ^b	Yield, ^c %	M.p., °C. ^d
2'-Hydroxy-R	2-Hydroxy-	53	156-158 (156-158) ^e
3'-Hydroxy-R	3-Hydroxy-	67	201-203, 205 ^f (197-201) ^e
4'-Hydroxy-R	4-Hydroxy-	98	213-215, 218 ^f (212-213) ^e
2',4'-Dihydroxy-R	2,4-Dihydroxy-	62	211-213 ^f (218-219) ^e (208) ^g
2',5'-Dihydroxy-R	2,5-Dihydroxy-	35	201-203 ^f (201) ^{f,h}

^a R = benzoylmethylpyridinium bromide. ^b All had infrared spectra which were superimposable with those of authentic samples. ^c Optimum yields were not sought. ^d Literature values in parenthesis. ^e Ref. 3b. ^f Sublimed sample. ^g R. Kuhn, F. Zilliken, and H. Trischmann, *Ber.*, 83, 304 (1950). ^h S. C. Bhattacharyya and D. E. Seymour, *J. Chem. Soc.*, 1139 (1950).

Experimental

All melting points were taken on a Fischer-Johns melting point apparatus and are uncorrected. Structure assignments were supported by infrared spectra taken on a Baird Associates

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double beam infrared spectrophotometer in potassium bromide pellets. Analyses were by Micro-Tech Laboratories, Skokie, Ill. Satisfactory analyses were obtained for all new compounds reported.

General Procedure for Heterogeneous Bromination Using Copper(II) Bromide.—The copper(II) bromide (Matheson Coleman and Bell or Baker and Adamson reagent grades) was routinely ground, without drying, in a mortar and pestle to ca. 80 mesh to ensure a large surface area for reaction. Copper(II) bromide (0.050 mole) was placed in an erlenmeyer flask fitted with a reflux condenser, and ethyl acetate (25 ml.) was added and brought to reflux on a magnetic stirrer-hot plate. The compound to be brominated (0.030 mole; it is advisable to use a slight excess to avoid the possibility of dibromination) was dissolved in or diluted with hot chloroform (25 ml.) (or an additional 25 ml. of ethyl acetate if the compound were not soluble in chloroform) and added to the flask. The resulting reaction mixture was refluxed with vigorous stirring to ensure complete exposure of the copper(II) bromide to the reaction medium until the reaction was complete as judged by a color change of the solution from green to amber, disappearance of all black solid, and cessation of hydrogen bromide evolution. With numerous compounds the bromination was estimated, from the composition of the mixed copper bromides recovered, to be 90–95% complete in 30–60 min. even though the deep green color persisted much longer. This color could be removed by decoloration with Norit A after removal of the copper(I) bromide by filtration. An induction period which varied with the starting material was observed in each case. The copper(I) bromide was collected by filtration and washed well with ethyl acetate. Recovery of copper(I) bromide was 96–100% in every case. The solvents were removed from the filtrate under reduced pressure, except when the product had a low boiling point, a property which required fractional distillation.

Bromination of Hydroxyacetophenones.—The above procedure was used, the time required for typical runs being noted in Table

I. The crude products could be recrystallized from benzene except as noted in Table I. Table I also gives physical characteristics of the compounds prepared.

Preparation of the Substituted 1-Benzoylmethylpyridinium Salts.—The pyridinium bromides could be prepared directly from the filtrate containing the crude α -bromo ketone by addition of a slight excess (0.03 mole) of pyridine followed by heating on the steam bath. An alternate procedure was to remove the chloroform-ethyl acetate under reduced pressure and dissolve the crude α -bromo ketone in acetone before addition of the pyridine. The latter method sometimes gave crude products which were less discolored and had higher melting points. Both methods gave good yields. The pyridinium bromides were converted to the corresponding pyridinium iodides or perchlorates by the method of King^{3a} (see Table II).

Alkaline Cleavage of the Substituted β -Ketoalkylpyridinium Salts.—About 1 g. of the pyridinium salt was dissolved in water and heated with 1 g. of sodium hydroxide as described by King.^{3a} The alkaline solution was treated with Norit A, and the acid fraction was separated and purified by recrystallization from water and/or sublimation (150° at 1.0 mm) (see Table III).

Preparation of Coumaran-3-one.—This compound was prepared from 2-bromo-2'-hydroxyacetophenone by the method of Fries and Pfaffendorf¹⁴ in 48–80% yield. The crude yellow product melted at 94–99°. After sublimation (50° at 1.0 mm), the essentially colorless crystals melted at 101–102° (lit.¹⁵ m.p. 100–101.5°). The infrared spectrum of the sublimed sample corresponded to that reported by Bose and Yates.¹⁵

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Decompositions of Hydroperoxides in Oxidizing Olefins

R. HIATT, CONSTANCE WILLARD GOULD, AND FRANK R. MAYO

Stanford Research Institute, Menlo Park, California

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We have examined the reactions at 60° of combinations of styrene, oxygen at a total pressure of 1 atm., and either *t*-butyl or α -tetralyl hydroperoxide. *t*-Butyl hydroperoxide has a half-life of only about 100 min. under these conditions. Several lines of evidence indicate that the hydroperoxide reacts mostly by chain transfer with the peroxy radicals in oxidizing styrene producing styrene polyperoxide with hydroperoxide end groups. Later, some styrene oxide and *t*-butyl alcohol appear. Both chain initiation and peroxide disappearance are initially autocatalytic; the oxidation later becomes slower, but does not stop, as the original free hydroperoxide is exhausted. Formaldehyde forms addition compounds with hydroperoxides and complicates analytical problems and interpretation of the results. So far, these accelerated interactions of unsaturated compounds with hydroperoxide and oxygen have been most marked with styrene. They have not complicated the oxidations of alkenes, where high yields of hydroperoxides have been obtained in oxidations. Butyl methacrylate oxidized too slowly to give a marked effect. Indene gave only a moderate effect, possibly because it produces little or no formaldehyde during its oxidation.

Previous workers have shown that cyclohexyl¹ and *t*-butyl^{2,3} hydroperoxide decompose with unexpected rapidity in styrene and thereby initiate polymerization rather rapidly. Farkas and Passaglia¹ showed that cyclohexyl hydroperoxide disappeared and also initiated polymerization at 80° although the decomposition of this peroxide is negligible at this temperature in other solvents. Walling and Chang³ found similar effects with *t*-butyl hydroperoxide and styrene and detected *t*-butyl alcohol and styrene oxide among the products. This work has been extended recently by Heaton.⁴ She reported that the reaction is complex,

and complicated by complexes of hydroperoxide with itself and with styrene; only a small fraction of the decomposing hydroperoxide produces free radicals which initiate polymerization. Brill and Indictor⁵ have studied the decomposition of *t*-butyl hydroperoxide in olefins as a means of producing epoxides. Yields were generally poor. For 1-octene the rate was first order in both hydroperoxide and olefin. They suggested that the epoxidation is polar in nature.

From our study of oxidation of mixtures of styrene and tetralin, we eventually found that complicated reactions like those above also occur in the presence of oxygen, and much faster. This paper describes our efforts to determine the nature and scope of hydroperoxide-olefin-oxygen interactions.

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