Reactions of (Trihalomethyl)carbinols with Aqueous Potassium Hydroxide

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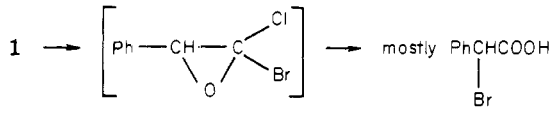
As part of our continuing investigation of the reactions of (trichloromethyl)carbinols,[1,2] we have prepared and studied other (trihalomethyl)carbinols to investigate their chemistry, particularly their reaction with cold aqueous potassium hydroxide.

Phenyl(tribromomethyl)carbinol, phenyl(dibromochloromethyl)carbinol, and phenyl(bromodichloromethyl)carbinol were all prepared by the base-catalyzed reaction of benzaldehyde with the appropriate haloform. The classical method uses powdered potassium hydroxide as the base,[3] and the first two of the above carbinols were obtained this way in yields of 22 and 7%, respectively. By use of potassium *tert*-butoxide in *tert*-butyl alcohol, the above three carbinols were obtained in yields of 60, 45, and 30%, respectively.

All underwent the intramolecular, unimolecular transformation (Jocic reaction[2]) to give an α-halo acid, as illustrated below for phenyl(dibromochloromethyl)carbinol (1) (see Table I).



One can account for the major product formed as follows. In the formation of the dihalo epoxide, bromine was displaced in preference to chlorine as would be expected. At the next stage, bromine migrates to the α carbon in preference to chlorine. The exact mechanism of this step is uncertain.[2]

Assuming the relative ease of elimination of chlorine and bromine from three-membered rings is similar to that of less strained systems, the above results suggest that a halo oxirene is not a possible intermediate in the step (**2** → **3**) where the halogen migrates to the α carbon. Hydrogen bromide would be preferentially eliminated from **2** in the formation of a halo oxirene and α-chlorophenylacetic acid should be the predominate acid formed from (dibromochloromethyl)phenylcarbinol by the halo oxirene mechanism; this is not observed.

Experimental Section

Melting points and boiling points are corrected. The infrared spectra were recorded on a Perkin-Elmer 337 spectrophotometer and the ^{1}H NMR spectra on a Varian A-60A spectrometer. Chemical shift values are expressed as δ values (ppm) downfield from tetramethylsilane as internal standard. Elemental microanalyses were performed by Mrs. Shelesa Brew.

Preparation of Phenyl(trihalomethyl)carbinols. These were prepared initially by the reaction of the haloform with benzaldehyde catalyzed by dry, powdered potassium hydroxide in low yields.[3-5] The following alternate procedure gives higher yields.

Table I. Halo Acids from Halo Carbinols

carbinol	products (composition, %)
$PhCH(OH)CBr_3$	PhCH(Br)COOH (100)
$PhCH(OH)CBr_2Cl$	PhCH(Br)COOH (83)
	PhCH(Cl)COOH (17)
$PhCH(OH)CBrCl_2$	PhCH(Cl)COOH (82)
	PhCH(Br)COOH (18)

A solution of 30 mL (0.3 mol) of benzaldehyde in 100 mL (1.2 mol) of bromoform was cooled to 0 °C and a solution of 50 g (0.45 mol) of potassium *tert*-butoxide in 300 mL of *tert*-butyl alcohol was added slowly over a period of 2 h to the stirred solution. Dry benzene (150 mL) was added and the solution stirred an additional 2 h at 0 °C. The reaction mixture was poured into 300 mL of ice–water containing 14 mL of concentrated sulfuric acid. The organic layer was washed with sodium bicarbonate solution and dried, and the excess bromoform and benzaldehyde were distilled off (15 torr) to yield 71 g of an oily residue of almost pure **phenyl(tribromomethyl)carbinol**. This soon solidified and on recrystallization from 200 mL of a 4:1 mixture of isooctane and cyclohexanol, there was obtained 65 g (60% of theory): mp 78.5–79.5 °C [lit.[4] mp 78–78.5 °C]; IR (KBr) 3550, 3500, 3020, 1480, 1440, 1375, 1290, 1190, 1050, 980, 920, 840, 760, 700, 600, 560 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.7 (m, 2, Ph), 7.4 (m, 3, Ph), 5.2 (s, 1, CHOH), 3.25 (s, 1, CHOH).

(Dibromochloromethyl)phenylcarbinol was prepared in the same way. From 0.3 mol of benzaldehyde, there was obtained 45 g (48% of theory) of recrystallized carbinol: mp 50–51 °C; IR (KBr) 3550, 3500, 3020, 1450, 1390, 1300, 1185, 1035, 825, 785, 745, 685, 560 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.7 (m, 2, Ph), 7.4 (m, 3, Ph), 5.2 (s, 1, CHOH), 3.35 (s, 1, CHOH).

Anal. Calcd for $C_8H_7Br_2ClO$: C, 30.55; H, 2.24; halogen, 62.10. Found: C, 30.48; H, 2.29; halogen, 61.47. The halogen percentage was calculated on the basis of two bromines and one chlorine being present.

(Bromodichloromethyl)phenylcarbinol was prepared by the same procedure. From 0.3 mol of benzaldehyde, there was obtained 40 g of the carbinol as an oil. Crystallization from isooctane–cyclohexanol was difficult. From 20 g of the oil, there was finally obtained 12 g (30% of theory): mp 40–41 °C; IR (KBr) 3550, 3500, 1440, 1360, 1180, 1040, 840, 800, 760, 740, 700, 570 cm^{-1}; ^{1}H NMR (CDCl,3) δ 7.7 (m, 2, Ph), 7.4 (m, 3, Ph), 5.3 (s, 1, CHOH), 3.4 (s, 1, CHOH).

Anal. Calcd for $C_8H_7BrCl_2O$: C, 35.59; H, 2.61; halogen, 55.86. Found: C, 35.48; H, 2.60; halogen, 55.78. The halogen percentage was calculated on the basis of one bromine and two chlorines being present.

Acetate esters of carbinols were prepared by refluxing 10 g of the carbinol with 75 mL of acetic anhydride for 3 h, pouring the reaction mixture into an ice–water mixture, and drying the oil which then solidified. The solids were crystallized from ethanol–water; the yields were 65 to 85% of theory. All analyzed correctly for carbon, hydrogen, and halogen. Their IR and NMR specra confirmed the structural assignments: **phenyl(tribromomethyl)carbinyl acetate**, mp 133 °C [lit.[5] 133 °C]; **(dibromochloromethyl)phenylcarbinyl acetate**, mp 116.5–117 °C; **(bromodichloromethyl)phenylcarbinyl acetate**, mp 101–102 °C.

Conversion of Phenyl(trihalomethyl)carbinols to α-Halophenylacetic Acids. This followed our standard procedure,[2] except the reaction mixtures were quenched when approximately 60% of the theoretical amount of base was consumed. This was done to minimized halogen exchange, although this has previously been shown to be a very slow reaction under these experimental conditions.[2]

To 0.0125 mol of the carbinol was added 25 mL (0.04 mol of base) of 10% potassium hydroxide solution containing 1% potassium oleate, and the mixture was stirred vigorously at −5 °C until approximately 60% of the base was consumed, determined by titrating aliquots. This took approximately 90 min. The unreacted carbinol was extracted with ether, keeping the mixture at 0 °C. The reaction mixture was acidified with 10% sulfuric acid and the acid fraction extracted with carbon tetrachloride in which mandelic acid is insoluble. The α-halophenylacetic acid mixtures were obtained in 35% yield.

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Analysis of α-Halophenylacetic Acids.[6] Total halogen was first determined by hydrolyzing 100 mg of the halo acid with 25 mL of 0.5 N sodium hydroxide solution on a stream bath for 30 min. The cold solution was acidified with dilute nitric acid and titrated with 0.02 N silver nitrate with two drops of saturated potassium chromate solution as indicator.

Bromine was determined by hydrolyzing a 50-mg sample as above, neutralizing with dilute hydrochloric acid, and adding 5 mL of 20% potassium dihydrogen phosphate solution buffer. Chlorox hypochlorite bleach (5 mL) was added, the solution was heated for 10 min on a steam bath, 5 mL of 50% sodium formate solution was added, and then 0.5 g of potassium iodide was added to the cold solution. The liberated iodine was determined by titration with standard sodium thiosulfate.

The analyses were shown to be reliable by analyzing authentic α-bromophenylacetic acid samples; theory is 37.2% bromine. Total halogen was found to be 37.0% and bromine was found to be 37.8%.

Registry No. Phenyl(tribromomethyl)carbinol, 38158-81-5; (dibromochloromethyl)phenylcarbinol, 74586-59-7; (bromodichloromethyl)phenylcarbinol, 74586-57-5; α-bromophenylacetic acid, 4870-65-9; α-chlorophenylacetic acid, 4755-72-0; benzaldehyde, 100-52-7; bromoform, 75-25-2; dibromochloromethane, 124-48-1; dichlorobromomethane, 75-27-4; phenyl(tribromomethyl)carbinyl acetate, 13136-09-9; (dibromochloromethyl)phenylcarbinyl acetate, 74586-58-6; (bromodichloromethyl)phenylcarbinyl acetate, 74586-56-4.

(6) E. C. Olson, "Treastise on Analytical Chemistry", Part II, Vol. 14, I. M. Kolthoff and P. J. Elving, Eds., Wiley-Interscience, New York, 1971, Section B-1, p 18-19.

Increased Yield of a Desired Isomer by Equilibria Displacement on Binding to Silica Gel, Applied to *meso*-Tetrakis(*o*-aminophenyl)porphyrin

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Picket-fence porphyrins have been used as model compounds to study a variety of biological processes, including heme oxygen binding,[1] porphyrin photoreactions,[2] and metallations[3,4] in organized media, and interactions of binuclear metal complexes present in enzyme active sites.[5] The fundamental building block for these syntheses has been the α,α,α,α-atropisomer of *meso*-tetrakis(*o*-aminophenyl)porphyrin, the rotational isomer with all four amino groups above the plane of the porphyrin ring. The four possible atropisomers occur at equilibrium in a 1:2:4:1 statistical mixture and are easily prepared by the method of Collman.[6] The α,α,α,α-atropisomer comprises $^1/_8$ of the mixture and is purified by silica gel chromatography. The undesired atropisomers are reequilibrated and chromatographed again; repetition of this cycle allows conversion of most of the mixture into the α,α,α,α-atropisomer. Though this method is effective, it is also quite tedious, and the quantity of α,α,α,α-atropisomer which can be easily prepared is limited. I report a facile isomerization technique which allows conversion of the random mixture of atropisomers into the α,α,α,α-atropisomer in 66% yield.

Because the interconversion of atropisomers is an equilibrium process and the α,α,α,α-atropisomer has the highest affinity for silica gel, the isomerization of atropisomers in the presence of silica gel and a suitable solvent should afford primarily the α,α,α,α-atropisomer. It is preferentially bound and thus the complex has the lowest free energy of the system. The silica gel–porphyrin slurry is then poured to form a chromatography column and eluted to obtain the α,α,α,α-atropisomer. The choice of solvent for the isomerization is crucial since it must conserve the desired most favorable binding of the α,α,α,α-atropisomer at the isomerization temperature.

When $CHCl_3$ was used as the solvent, the α,α,α,α-atropisomer was obtained in random statistical abundance. However, with benzene as the solvent, the mixture of atropisomers was converted into the α,α,α,α-atropisomer in yields of 60–70%. This is to be compared with the maximum theoretical conversion of 12.5% in each cycle of the repetitive chromatography and a maximum overall percent conversion of $100[1 - (7/8)^n]$, where n is the number of cycles performed. This technique should be of general utility for enriching mixtures of isomers in the component having the highest affinity for a given solid phase.[7]

Experimental Section

Reagent-grade benzene (85 mL) and 36 g of E. Merck SI 60 silica gel (230–400 mesh, 500 m^2/g) were added to a 250-mL three-neck round-bottom flask fitted with a nitrogen inlet and a reflux condensor. This was immersed in an oil bath maintained at 75–80 °C, with magnetic stirring and a steady flow of benzene-saturated dry nitrogen gas. After 2 h, 1 g of the mixture of atropisomers of *meso*-tetrakis(*o*-aminophenyl)porphyrin was added to the flask. After an additional 20 h, the dark slurry was cooled to room temperature and then poured into a 53-mm diameter chromatography column. The residual undesired atropisomers were eluted with benzene–anhydrous ether (1:1) until the eluant became pale red in color (about 200 mL), and then acetone–ether (1:1) was used to elute the α,α,α,α-atropisomer. The column effluent was carefully monitored by using TLC analysis (silica gel, benzene–ether (1:1)). The first fraction (215 mg) consisted primarily of the α,α,α,β-atropisomer, the final fraction (660 mg) consisted of the α,α,α,α-atropisomer, and an intermediary fraction (60 mg) consisted of both atropisomers (66% conversion, 93.5% recovery). Slight variations in the amount of benzene or silica gel used, or the duration for isomerization, caused no significant changes in the yield of the α,α,α,α-atropisomer, indicating that equilibrium has been attained. A small aliquot of the recovered α,α,α,α-atropisomer was isomerized to the expected statistical mixture of atropisomers on refluxing in toluene for 30 min. The NMR[8] and visible spectra of the recovered α,α,α,α-atropisomer were identical with those of the α,α,α,α-atropisomer obtained by repetitive chromatography: ^1H NMR (Me_2SO-d_6) δ 8.79 (s, 8 H), 7.69–6.97 (m, 16 H), 4.62 (s, 8 H), −2.78 (s, 2 H); visible spectrum (DMF), 648, 590, 553, 516, 415 nm.

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Registry No. *meso*-Tetrakis(*o*-aminophenyl)porphyrin, 52199-35-6.

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