Chlorination of *m*-Hydroxyacetophenone[1]

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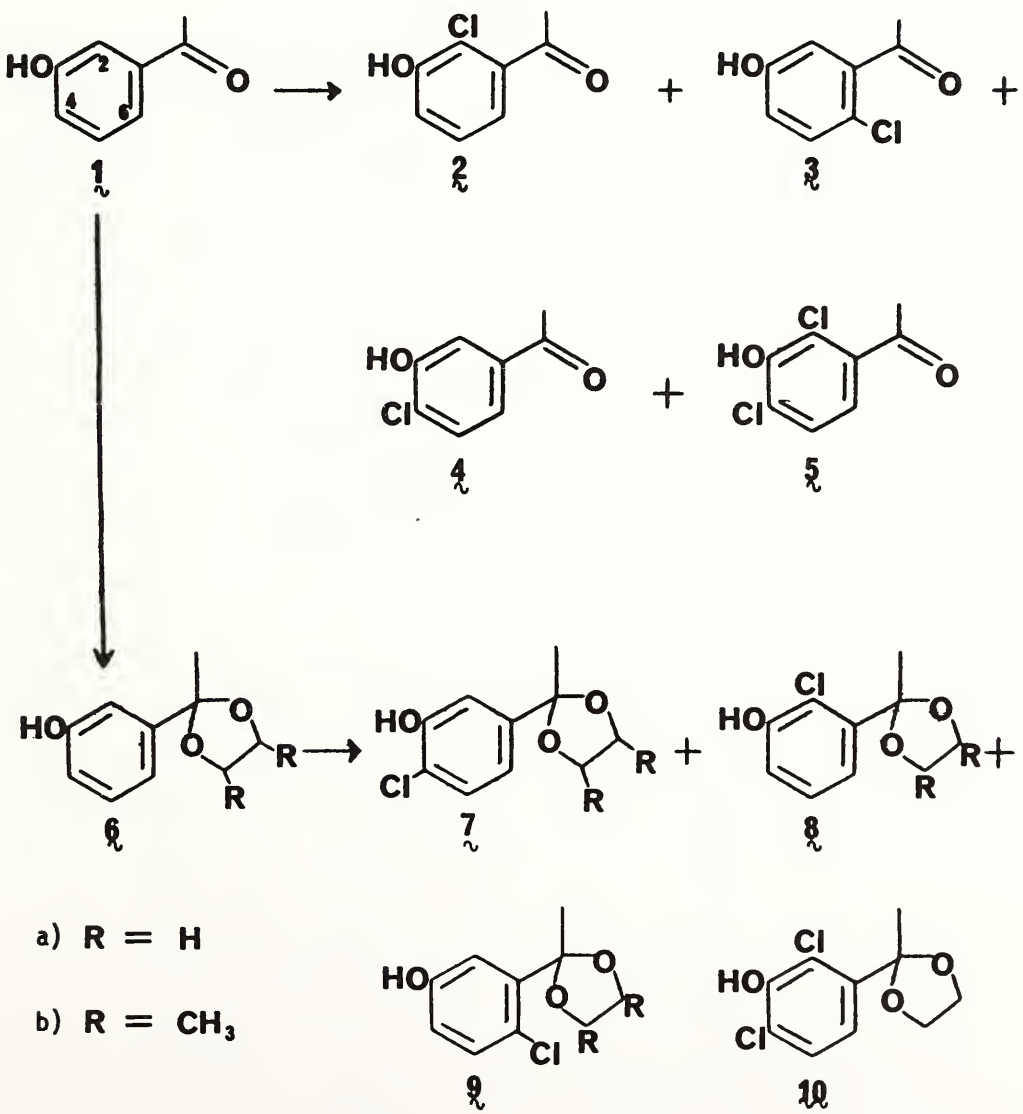
Introduction

In connection with another problem (2), we required a quantity of 3-hydroxy-4-chloroacetophenone (compound 4, scheme 1). A search of the literature,

Scheme 1



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including formula indices of Beilstein and Chemical Abstracts, indicated that this was apparently a new compound, and a method for its synthesis was needed. In view of the structure of *m*-hydroxyacetophenone (compound 1, scheme 1), and the known propensity of phenol to chlorinate in the *ortho* and *para*-positions, it was assumed that direct chlorination of 1, which is commercially available, with *t*-butyl hypochlorite, which is reported (4) to favor *ortho* chlorination in phenols, would lead to the desired 4-chloro compound 4 as the major product. Indeed, Ginsberg (4) claimed to obtain 2-hydroxy-3-chlorobenzoic acid in 75% yield on chlorination of salicylic acid with *t*-butyl hypochlorite. The presence of the more bulky acetyl group at the *meta*-position in 1 should also favor chlorination at the less hindered 4-position of 1, despite the statement of Harvey and Norman (5) that they had obtained only a 50/50 *ortho/para* ratio on chlorination of phenol in inert solvents with *t*-butyl hypochlorite.

Discussion

Chlorination of *m*-hydroxyacetophenone with *t*-butyl hypochlorite in chloroform solution gave mainly the 2-chloro compound 2 (Table 1, exp. 1) representing substitution at the more hindered position *ortho* to the phenol function, in keeping with Ginsberg's (4) results. It was possible to crystallize some of 2 from the crude mixture, and characterize it as 2-chloro-3-hydroxyacetophenone by spectral data and conversion to the known 2-chloro-3-hydroxybenzoic acid (6). Recrystallized 2 gave a glc peak identical to that of the major component in the product mixture.

We then turned our attention to the ethylene ketal 6a, on the assumption that a more bulky and less polar group at this position should favor chlorination at the 4-position over the 2- and 6-positions favored in the simple ketone. Ketalization of 1 in ethylene glycol using the usual acid catalyst, *p*-toluenesulfonic acid (9) gave considerable trouble, even under nitrogen. Some polymerization occurred, and the reaction reached equilibrium at only about 60% conversion. The maximum yield of vacuum-distilled material was 48%. However, the reaction gave complete conversion using a zinc chloride-phosphoric acid catalyst (8), and pure

TABLE 1. *Chlorination with t-Butyl Hypochlorite*

Expt.	Sub.-strate	Solvent	Temp., C°	Crude product compn., %[a]				
				Starting Material	2/8a	3/9a	4/7a	5/10
1	1	$CHCl_3$	15	13	49	24	6	9
2	6a	THF	0	11	10	33	46	–
3	6a	$CHCl_3$	25	3	31	16	48	–
4	6a	$CHCl_3$	0	4	22	20	54	2
5	6a	$CHCl_3$	-20	4	20	19	56	–
6	6a	C_6H_6-Toluene 9:1	0	5	24	9	62	–
7	6a	C_6H_6-$CHCl_3$, 9:1	0	–	24	11	65	–
8	6a[b]	C_6H_6-$CHCl_3$ 9:1	0	~30	~20	–	~20	~30

[a] Analysis of volatile products by glc using area normalization.
[b] Undistilled ketal 6a was used in this experiment.

6a was obtained in high yield by recrystallization. This avoided the distillation process, which caused decomposition of the ketal, due to the acid character of the phenol.

Indeed, chlorination of 6a gave much more 4-substitution (table 1). Selectivity for the 4-position was better in less polar solvents at lower temperatures. A 9:1 (v:v) mixture of benzene and chloroform at 0° was shown to give 65% of 7a in the crude product mixture (Table 1, exp. 7). Certain samples of 6a, even after repeated recrystallization, gave a much different product mixture, containing substantial amounts of dichloroketal 10 and starting material (Table 1, exp 8), and a reaction rate about ten times faster. The selective monochlorinations listed in experiments 2-7 (Table 1) could only be consistently obtained using samples of ketal that had been distilled from a flask containing potassium carbonate and recrystallized from carbon tetrachloride. We attribute the dichlorination to the presence of traces of base, leading to the formation of phenolates which are much more reactive than unionized phenols (5). In addition, monochloro products 7 and 8, being more acidic, are more easily converted to phenolates, which chlorinate further to 10. Support for the basecatalyzed side reaction was provided by an experiment in which distilled ketal 6a was chlorinated in the presence of a quaternary ammonium hydroxide. Substantial dichlorination was observed. Also, dichlorination was decreased by using undistilled ketal that had been recrystallized from carbon tetrachloride containing acetic acid. However, acid-recrystallized material was not stable on storage.

Selective hydrolysis of a crude chloroketal mixture, prepared as in experiment 7 (Table 1), was carried out under mild conditions. With dilute acetic acid in a water-tetrahydrofuran mixture at reflux for four hours, ketal 7a was completely hydrolyzed, with little or no hydrolysis of 8a or 9a. The latter two ketals, with chlorine *ortho* to the ketal-containing side chain, may be stabilized by the steric or electronic effects of the chlorine atom. Following selective hydrolysis, pure ketone 4 was crystallized, and its structure proven by conversion to the known 4-chloro-3-methoxybenzoic acid (3). Augmentation of the glc peak assigned to 4 with an authentic sample confirmed the analytical assignments (Table 1).

Keton 4 was prepared much more cleanly, and in better yield, from ketal 7b. Chlorination of ketal 6b, derived from 2,3-butylene glycol, with *t*-butyl hypochlorite still gave a mixture of products having about the same distribution among the isomers 7b (65%) 8b and 9b. Thus the more bulky 2,4,5-trimethyl-1,3-dioxolane group did not alter the chlorination ratios appreciably. However, this approach offered the advantage of isolating the pure 4-chloro derivative 7b. While hydrolysis of this compound was more difficult, it was not necessary to use care to avoid hydrolysis of unwanted isomers, as was the case with hydrolysis of 7a. Thus recrystallized 7b, obtained in about 60% yield, was converted to 4 in nearly quantitative yield.

The structural assignments of ketones 2 and 4 were further confirmed by a study of dichlorination products. Treatment of ketone 1 with two equivalents of *t*-butyl hypochlorite resulted initially in formation of 2, as shown by glc. As this peak waned, the peak assigned to 2,4-dichloro-3-hydroxyacetophenone (5) increased. Dichloroketone 5 was isolated as its 4-nitrophenylhydrazone, which had a doublet of doublets, $j = 8$ Hz, in the pmr assigned to vicinal hydrogens on the phenol ring. Thus compound 5 was either the 2,4- or 2,6-dichloroketone. However, the identical *p*-nitrophenylhydrazone was obtained by dichlorination of ketal 6a, followed by hydrolysis. Since ketal 6a is known to give mainly the 4-chloro derivative 7a on monochlorination, dichlorination must produce 10, the 2,4-dichloro derivative. Therefore compound 2 must have a chlorine at position 2.

Experimental

Melting points were determined on a "uni-melt" Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 137-B infrared spectrometer. Nuclear magnetic resonance spectra were obtained on a Varian T-60A spectrometer and in certain instances on a Varian 220 MHz spectrometer. Mass spectra were obtained on a Hewlett-Packard Model 5992A GC/MS mass spectrometer or on a Varian CH7 mass spectrometer. Gas chromatograph analysis was accomplished using a Varian Model 3700 gas chromatograph equipped with a flame ionization detector, with a 3 ft. x 1/8 in. column packed with 5% Carbowax 20 M on Gas Chrom Q, initial temp 150°, increased on 16°/min to 220°. Elemental analyses were performed by Midwest Microlab, Indianapolis.

Chlorination of 3-Hydroxyacetophenone.

A solution of 2.72 g (20 mmole) of 3-hydroxyacetophenone (1)[3], dissolved in 20 mL of chloroform, was cooled to about 15°, and 2.17 g (20 mmole) of *t*-butyl hypochlorite (7) was added dropwise in subdued light, with cooling to maintain temperature at about 15°C. The mixture was allowed to stand overnight in the dark. Concentration on the rotary evaporator gave an oily residue, which was analyzed by glc, using area normalization. It contained 13% of 1, 49% of 2, 24% of 3, 6% of 4 and 9% of 5. When the residue was cooled overnight, part of it crystallized to give 1 g of material, melting at 61-63°, that gave a glc peak identical to the major component of the crude product. It was identified as 2-chloro-3-hydroxyacetophenone (2) in the following way.

Ketone 2 had the following properties: ir 3225 (OH), 1665 cm^{-1}(CO); pmr (acetone-d_6) δ 7.4-6.8 (m, large single peak at 7.10, 3H, ArH), 2.58 (s, 3H, CH_3).

2-Chloro-3-hydroxyacetophenone 4-Nitrophenylhydrazone.

A small sample of 2 was converted to the 4-nitrophenylhydrazone, (10) m.p. 188-189° after two recrystallizations from alcohol; pmr (acetone-d_6) δ 9.40 (s, 1H, NH), 8.17 (d,2H, J = 9 Hz), 7.13 (d, 2H, J = 9 Hz, ArH), 7.2-6.7 (m, 3H, ArH), 3.6-2.4 (br, 1H, OH, D_2O exchangeable), 2.37 (s, 3H, CH_3).

Anal. calc'd for $C_{14}H_{12}N_3O_3Cl$: C, 55.08; H, 3.93; N, 13.77. Found: C, 55.11; H, 4.12; N, 13.87.

2-Chloro-3-hydroxybenzoic Acid.

Oxidation of ketone 2 with sodium hypochlorite solution gave a crystalline acid, recrystallized from toluene-hexane mixture, and melting at 164-166°. Beyer (1) reported m.p. 158-159° for this acid, 219-220° for 4-chloro-3-hydroxybenzoic acid, and 178-179° for 6-chloro-3-hydroxybenzoic acid. However, Hodgsen and Rosenberg (6) give 161.5° as m.p. of 2-chloro-3-hydroxybenzoic acid.

2-(3'-Hydroxyphenyl)-2-methyl-1,3-dioxolane (6a).

A. *Use of Toluenesulfonic Acid.* A mixture of 150 g (1.1 mole) of 1, 70 g of ethylene glycol, 2.3 g of *p*-toluenesulfonic acid monohydrate, and 1.5 liter of benzene was refluxed until no further water collected in the Dean-Stark trap

3. Technical grade *m*-hydroxyacetophenone, m.p. 86-88° (Aldrich) was recrystallized from toluene or hot water to melting point 94-96°. However, the hot water recrystallization, using activated carbon, gave purer product with less tars carried along.

(100 h). The acid was neutralized with 2.3 g sodium methoxide, the warm mixture filtered through a fluted filter, washed with brine, and concentrated on a rotary evaporator to give 139 g (70%) of pale yellow crystals, m.p. 83-85°. The crude product, mixed with 0.7 g potassium carbonate, was distilled at 1 torr using a short column and air-cooled condenser, to give a colorless oil, b.p. 130-140°, which solidified. Recrystallization from carbon tetrachloride gave 93 g (47%) of white crystals of 6a, m.p. 90-91°; ir (KBr) 3250 (OH), 1140-1070 (ketal CO)cm^{-1}, pmr (DMSO-d_6) δ 9.1 (1H, OH), 7.3-6.5 (m, 4H, ArH), 4.2-3.6 (m, 4H, -CH_2-), 1.65 (s, 3H, CH_3).

Anal. calc'd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71; M.W. 180. Found: C, 66.48; H, 6.54; M^+ 180.

B. *Use of Phosphoric Acid/Zinc Chloride.* In a 500 mL 3-neck flask, equipped with magnetic stirrer, nitrogen inlet and Dean-Stark trap was placed 13.6 g (0.1 mole) of 1, 31 g (0.5 mole) of ethylene glycol, 0.2 g of anh. zinc chloride, 0.2 mL of 85% phosphoric acid and 70 mL of toluene. The mixture was refluxed until tlc showed no ketone present. The mixture was cooled, 100 mL of ether added, and the solution washed with aqueous bicarbonate solution. The aqueous layer was washed once with ether, and the combined ether extracts dried ($MgSO_4$) and concentrated (rotary evaporator) to give 16.1 g (89%) of white crystalline 6a, melting at 87-91°. Recrystallization from cyclohexane gave white crystals melting at 89-91°, identical in ir spectrum to 6a prepared above.

3-Hydroxy-4-chloroacetophenone (4).

A. *By Hydrolysis of 7a.* In a three-neck flask with drying tube and mechanical stirrer, a solution of 15 g (83 mmol) of 6a in 270 mL of benzene and 30 mL of chloroform was cooled in an ice-bath. In dim light, a mixture of 9.49 g (87 mmoles) of *t*-butyl hypochlorite in 30 mL of 9/1 benzene/chloroform was added dropwise. After 4 h, the mixture was allowed to stand at room temperature overnight. Analysis by glc showed a mixture containing approximately 65% of 7a, with 24% of 8a and 11% of 9a. The oily residue, obtained on removal of solvents under vacuum, was refluxed for 3 h in a heterogeneous mixture of 250 mL THF, 250 mL water and 25 mL glacial acetic acid. The aqueous solution was extracted with ether, and the ether extracts combined, washed with brine, saturated sodium bicarbonate, water, and then dried ($MgSO_4$). Concentration gave a semi-solid residue that recrystallized from toluene to give 7.3 g (48%) of 4, m.p. 101-103°. Several recrystallizations from toluene gave an analytical sample, m.p. 106-107°; ir 3290, 1660 cm,s^{-1}; pmr (acetone-d_6) δ 2.54 (s, 3H, CH_3), 7.46 (s, 2H, ArH), 7.58 (s, 1H, ArH), 7.5-8.5 (broad, 1H, OH).

Anal. Calc'd for $C_8H_7O_2Cl$: C, 56.33; H, 4.14; M.W., 170. Found: C, 56.15; H, 4.21; M^+, 170.

The identity of the 4 peak in the glc of the chlorination mixture of 1 was established by augmenting this peak with an authentic sample of 3-hydroxy-4-chloroacetophenone, prepared as described.

B. *By Hydrolysis of 7b.* A solution of 11.5 g (0.047 mole) of 7b (see below) in a mixture of 100 mL of THF, 80 mL of water and 20 mL of conc. HCl was refluxed for 2 hrs. The solution was then concentrated on a rotovap, extracted three times with ether, and the combined ether extracts washed with water, then saturated sodium bicarbonate solution, and finally with brine. After drying over anhydrous $MgSO_4$, concentration of the ether gave 7.6 g (94%) of 3-hydroxy-4-chloroacetophenone (4), melting at 101-104°.

3-Hydroxy-4-chloroacetophenone 4-Nitrophenylhydrazone.

A sample of 4 was converted to the 4-nitrophenylhydrazone, m.p. 231-232°.

Anal. calc'd for $C_{14}H_{12}N_3O_3Cl$: C, 55.08; H, 3.93; N, 13.77. Found: C, 54.80; H, 4.07; N, 13.58.

3-Methoxy-4-chlorobenzoic Acid.

Treatment of 4 with methyl sulfate and potassium carbonate in acetone, followed by oxidation with sodium hypochlorite solution, gave 3-methoxy-4-chlorobenzoic acid, m.p. 212-214°. Gibson (3) gives m.p. 211° for this acid, 160° for 3-methoxy-2-chlorobenzoic acid and 173° for 3-methoxy-6-chlorobenzoic acid.

2,4-Dichloro-3-hydroxyacetophenone 4-Nitrophenylhydrazone.

An authentic sample of 5 was prepared by treating 3.0 g (16 mmol) of ketal 6a in 50 mL benzene and 6 mL of chloroform with 3.9 g (35 mmols) of *t*-butyl hypochlorite in 9 mL of benzene and 1 mL of chloroform, added dropwise, with cooling. After 4 hrs., the mixture was allowed to come to room temp and let stand overnight. Total hydrolysis of this mixture with dilute hydrochloric acid and THF gave an oil, the main constituent of which had a retention time identical to the peak assigned structure 5.

Chlorination of 1 with two equivalents of *t*-butyl hypochlorite, as described above, gave essentially one product, an oil which also had the identical glc retention time as 5. Treatment of this oil with 4-nitrophenylhydrazine gave the 4-nitrophenylhydrazone of 2,4-dichloro-3-hydroxyacetophenone, melting at 245-246° after recrystallization from ethanol-water: pmr (acetone-d_6) δ 8.11, 7.31 (dd, J = 9 Hz, 4H, Ar'H-2',3',5',6', 7.39, 7.04 (dd, J = 8 Hz, 2H, Arh-5,6), 2.34 (s, 3H, CH_3).

Anal. calc'd for $C_{14}H_{11}O_3N_3Cl_2$; C, 49.43; H, 3.26; N, 12.35; M.W. 339. Found: C, 49.27; H, 3.30, N, 12.11; M^+, 339.

2-(3'-Hydroxyphenyl)-2,4,5-trimethyl-1,3-dioxolane (6b).

A mixture of 13.6 g (0.1 mole) of 1, 12.5 g (0.15 mole) of technical grade 2,3-butanediol (a mixture of stereoisomers), 0.2 g of anh. zinc chloride, 0.2 mL of 85% phosphoric acid and 70 mL of toluene was refluxed till all ketone had disappeared (by tcl). After cooling, 100 mL of ether was added, and the mixture worked up as above, to give 18.3 g (88%) of white crystals. Twice recrystallized from carbon tetrachloride, the material melted at 100-103°; pmr (acetone-d_6) δ 1.1 (d, 3H, CH_3), 1.2 (d, 3H,CH_3), 1.53 (s, 3H, CH_3), 3.3-4.3 (m, 2H, =CH-), 6.6-7.3 (m, 4H, ArH), 8.2 (s, 1H, OH).

This compound showed only one spot on tlc. The broad melting point is due to the presence of stereoisomers, as it is a mixture of 2 *meso* and one *dl*-pair of compounds.

Anal. calc'd for $C_{12}H_{16}O_3$; C, 69.23; H, 7.69; M.W. 208. Found: C 69.13; H, 7.84; M^+, 208.

2-(4'-Chloro-3'-hydroxyphenyl)-2,4,5-trimethyl-1,3-dioxolane (7b).

A solution of 6b (20.8 g, 0.1 mole) in 400 mL of a 9:1 benzene/chloroform mixture was cooled to 0°, and 12.3 g (0.11 mole) of t-butyl hypochlorite added dropwise with vigorous stirring. Addition of the hypochlorite required about 1.5-2.0 hrs, after which stirring at 0° was continued for 2 hrs, then continued while the reaction mixture was allowed to come to room temperature overnight. Solvents were removed on a rotovap, and the residual oil was triturated with petroleum

ether, and stored in the cold overnight. The white solid was collected and washed with cold petroleum ether, to give 14.6 g (60%) of 7b, melting at 89-93°. An analytical sample, recrystallized from carbon tetrachloride/petroleum ether melted at 92.5-95°: pmr ($CDCl_3$); δ 1.14 (d, 3H, CH_3), 1.26 (d, 3H, CH_3), 1.6 (s, 3H, CH_3), 3.73 (m, 2H, CH), 5.82 (s, 1H, OH), 7.01 (dd, 1H, ArH-6'), 7.21 (d, 1H, ArH-2'), 7.25 (d, 1H, ArH-5').

Anl. calc'd for $C_{12}H_{15}ClO_3$: C, 59.39; H, 6.19; Cl; 14.62. Found: C, 59.33; H, 6.26; Cl, 14.64.

Summary

3-Hydroxy-4-chloroacetophenone has been prepared from m-hydroxyacetophenone, by chlorination of its ketal derived from 2,3-butylene glycol, using t-butyl hypochlorite. Direct chlorination of m-hydroxyacetophenone gave a mixture, in which 2-chloro-3-hydroxyacetophenone predominated, with some 6-chloro-3-hydroxyacetophenone, and only a little of the desired 4-chloro isomer. 4-Chloro-3-hydroxyacetophenone and 2-chloro-3-hydroxyacetophenone have been isolated and characterized, and their structures confirmed by spectral data, and conversion to known derivatives. 2,4-Dichloro-3-hydroxyacetophenone was isolated as its p-nitrophenylhydrazone, and its structure confirmed by spectral data and alternate synthetic pathways.

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