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# *p*-Fluorobenzaldehyde and *p*-fluorobenzoic acid by oxidation of *p*-fluorobenzyl derivatives

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### Abstract

Experiments on the oxidation reactions of p-fluorobenzyl alcohol and chloride were carried out. Several oxidizing agents (manganese dioxide, 30% hydrogen peroxide and hypochlorite solutions at different concentrations) were used, and a mixture of p-fluorobenzaldehyde and p-fluorobenzoic acid in different proportions was obtained. In the case of p-fluorobenzyl chloride, some p-fluorobenzyl alcohol was also found in the reaction mixture. The experimental conditions required to obtain an increase in the yield of the aldehyde or acid were also studied.  $\bigcirc$  1998 Elsevier Science S.A.

Keywords: p-Fluorobenzaldehyde; p-Fluorobenzoic acid; p-Fluorobenzyl derivatives; Oxidation

## 1. Introduction

The production of fluoroaromatic compounds has become increasingly important in view of their application as agrochemicals, drugs, textile chemicals, etc. [1]. The presence of carbon-fluorine bonds enhances certain molecular properties (e.g. lipid solubility, bioactivity, reduced toxicity, oxidative stability) so that these compounds are often preferred to their non-fluorinated homologues.

Of the fluoroaromatics, *p*-fluorobenzaldehyde and *p*-fluorobenzoic acid are important due to their extensive use as intermediates for pharmaceuticals. Their preparation includes side-chain methyl oxidation, chlorination and hydrolysis, leading to side-products which influence the yield and chemical quality. Due to the particular use of these two compounds as bioactive molecules, the presence of by-products cannot be accepted, so that a major research effort has been made to find alternative procedures for their preparation in high purity.

Many methods have been proposed to prepare p-fluorobenzaldehyde [2–6], but some present difficulties and others are non-selective or dangerous [7]. As an alternative route, an extension of the Gatterman–Koch reaction from fluorobenzene and the oxidation of p-fluorobenzyl alcohol or chloride with different oxidizing agents were investigated.

## 2. Experimental details

# 2.1. Reagents

Fluorobenzene and nitrobenzene, used in the Gatterman-Koch reaction, were Aldrich (99% pure) and C. Erba (99.5% pure) products respectively.  $MnO_2$  was a C. Erba product (92% pure).  $H_2O_2$  was a Prolabo Rhone-Poulenc 30 vol.% aqueous solution, and NaClO was a commercial 6%–13% active chlorine aqueous solution.

*p*-Fluorobenzyl chloride was a Miteni product (98% pure), while *p*-fluorobenzyl alcohol was prepared from the corresponding chloride by the following representative procedure: 120 g (0.83 mol) of *p*-fluorobenzyl chloride and a solution of 140 g (0.49 mol) of sodium carbonate decahydrate in 120 g of water were placed in a two-necked, round-bottomed Pyrex glass vessel (11) equipped with a mechanical stirrer and a water condenser; the reaction mixture was maintained at reflux temperature for 6 h; after cooling, the organic phase (114 g) was separated and dried over MgSO<sub>4</sub>; 78 g (0.62 mol) of *p*-fluorobenzyl alcohol (99% pure; gas–liquid chromatography (GLC)) was recovered by fractional distillation in 75% yield.

#### 2.2. Analysis

Analysis was by a Perkin–Elmer Sigma 3 gas chromatography (GC) instrument ( $1 \text{ m} \times 2 \text{ mm}$  stainless-steel column

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packed with OV 101 on 100–120 mesh Chromosorb P), equipped with a thermal conductivity detector and connected to a Sigma 1 GC system for quantitative evaluation (toluene as external standard). The operational conditions were as follows: 270 °C for injector and detector; column temperature programme, 10 °C min<sup>-1</sup> from 80 to 250 °C and this temperature for 10 min; gas carrier (He) flow rate, 30 ml min<sup>-1</sup>. Product identity was confirmed by gas chromatography–mass spectrometry (GC–MS) (C. Erba model MFC 500/QMD 1000, equipped with a 30 m×0.25 mm capillary fused silica MEGA PS 264 column) and, for *p*-fluorobenzoic acid, by its IR spectrum recorded on a 782 Perkin–Elmer spectrometer.

The hypochlorite concentration of the aqueous solutions was evaluated by the iodometric titration method using thiosulphate.

### 2.3. General procedures

The typical procedures representative of the experiments carried out are reported below.

### 2.3.1. The Gatterman-Koch reaction

Fluorobenzene (100 g, 1.04 mol) was placed in a 250 ml, three-necked, round-bottomed Pyrex glass vessel equipped with a water condenser and two gas inlet tubes, through which  $151 h^{-1}$  of HCl and  $301 h^{-1}$  of CO were admitted separately. The temperature rose to 60 °C and was maintained below 70 °C in order to avoid exothermic side-reactions. The reaction was stopped after 2 h and the organic phase was recovered and analysed. The experiment was also carried out in the presence of a solvent (nitrobenzene).

#### 2.3.2. Oxidation reactions

#### 2.3.2.1. Oxidation by $MnO_2$

*p*-Fluorobenzyl alcohol (20 g, 0.16 mol), MnO<sub>2</sub> (7 g, 0.08 mol) and acetone (or ethylmethylketone) (50 ml) were placed in a 250 ml, three-necked, round-bottomed Pyrex glass vessel equipped with a mechanical stirrer and water condenser and maintained at reflux temperature for 5 h. The reaction mixture was then filtered and the organic phase was analysed after solvent removal. The experiment was also carried out with the addition of 5 ml of H<sub>2</sub>SO<sub>4</sub> (97%).

#### 2.3.2.2. Oxidation by $H_2O_2$

*p*-Fluorobenzyl chloride (30.3 g, 0.21 mol) (or 26.5 g of *p*-fluorobenzyl alcohol), 30%  $H_2O_2$  aqueous solution (23.6 g, 0.21 mol) and HCl (10 g) were placed in a 250 ml Pyrex glass vessel equipped with a water condenser and magnetic stirrer and maintained at reflux temperature for 3 h. The organic phase (28.3 g from *p*-fluorobenzyl chloride, 25.7 g from *p*-fluorobenzyl alcohol) was then separated, dried on MgSO<sub>4</sub> and analysed.

#### 2.3.2.3. Oxidation by aqueous sodium hypochlorite

All the oxidations carried out with this oxidizing agent were accomplished in a 250 ml, three-necked, round-bottomed Pyrex glass vessel equipped with a mechanical stirrer and water condenser, with about 0.1 mol of the principal reagent (*p*-fluorobenzyl alcohol or *p*-fluorobenzyl chloride), variable amounts of the oxidizing agent and, when required, other components (solvent, additives). On completion, after cooling, the pH and residual hypochlorite concentration of the solution were measured and the reaction mixture was acidified in order to separate benzoic acid. By solvent (diethyl ether) extraction, the organic phase was recovered, dried on MgSO<sub>4</sub> and analysed.

## 3. Results and discussion

## 3.1. The Gatterman-Koch reaction

This reaction, accomplished with chlorobenzene at atmospheric pressure in nitrobenzene, gave p-chlorobenzaldehyde in 70% yield [8]. As an extension of this procedure, fluorobenzene was treated with HCl and CO either in the absence or presence of a solvent (nitrobenzene), but no significant amounts of p-fluorobenzaldehyde were obtained, and 1-fluoro-4-chlorobenzene was the only compound produced in any quantity.

# 3.2. p-Fluorobenzyl alcohol oxidation

#### 3.2.1. Oxidation with $MnO_2$

Manganese dioxide gave only small amounts of *p*-fluorobenzaldehyde under all conditions.

## 3.2.2. Oxidation with $H_2O_2$

This oxidizing agent is readily available and cheap, but the use of a 30% aqueous solution of hydrogen peroxide alone did not lead to the oxidation of p-fluorobenzyl alcohol to the corresponding acid or aldehyde. However, different amounts of p-fluorobenzaldehyde and p-fluorobenzoic acid were found when the reaction was carried out in the presence of HCl (Table 1); in particular, increasing amounts of HCl favoured the acid rather than the aldehyde. Large amounts of p-fluorobenzyl chloride, resulting from nucleophilic substitution of the –OH group with Cl<sup>-</sup>, were always found.

## 3.2.3. Oxidation with aqueous sodium hypochlorite

Our experiments with benzyl alcohol as substrate confirmed the possibility of obtaining the corresponding aldehyde. However, with *p*-fluorobenzyl alcohol, *p*-fluorobenzoic acid was mainly formed (Table 2), especially at high concentrations of hypochlorite, as presumably fluorine makes this alcohol more oxidizable. In the presence of equimolar amounts (with respect to the alcohol) of NaHCO<sub>3</sub>, *p*-fluorobenzaldehyde was the main product of oxidation.

Table 1				
Oxidation of	p-fluorobenzyl alcohol	with	hydrogen	peroxide

Experiment	Molar ratio	······	Reaction time	Conversion	Molar yield (%)			
	HC1/alcohol	Alcohol/H <sub>2</sub> O <sub>2</sub>	(11111)	(%)	Acid	Aldehyde	Chloride	
1	0.5	1	180	28.7	49	8	43	
2	1.5	1	180	61.2	70	4	26	

Table 2

Oxidation of p-fluorobenzyl alcohol with aqueous sod um hypochlorite; additive, NaHCO3; molar ratio hypochlorite/alcohol, 1:1

Experiment	Hypochlorite concentration $(\%)$	Molar ratio additive/alcohol	Reaction time	Conversion	Molar yield (%)	
	(70)		(1111)	(-70)	Acid	Aldehyde
1	7.6	_	80	100	100	_
2	3.8	_	20	56.6	75	25
3	7.6	1	240	70.0	22	78

Table 3

Oxidation of p-fluorobenzyl chloride with aqueous sodium hypochlorite: effect of the ratio of the reagents. Reaction time, 150 min

Experiment	Hypochlorite concentration	Molar ratio hypochlorite/chloride	Conversion	Molar yi	ield (%)		
	(70)		( <i>n</i> )	Acid	Aldehyde	Alcohol	
1	9.0	1	71	66	16	18	
2	9.0	2	93	69	31	~	
3	8.8	3	99	50	12	38	

Table 4

Oxidation of p-fluorobenzyl chloride with aqueous sodium hypochlorite; molar ratio hypochlorite/chloride, 1:1; reaction time, 150 min

	Hypochlorite concentration	Conversion	Molar yield (%)				
	(%)	(%)	Acid	Aldehyde	Alcohol		
1	2.8	99	40	24	36		
2	6.3	79	53	47	-		
3	9.0	71	66	16	18		
4	12.3	36	47	44	9		

#### 3.3. p-Fluorobenzyl chloride oxidation

## 3.3.1. With 30% hydrogen peroxide

None of the required oxidation products were found in the reaction mixture.

#### 3.3.2. With aqueous sodium hypochlorite

On varying the hypochlorite/chloride molar ratio at constant concentration of aqueous hypochlorite, different amounts of the corresponding aldehyde and acid were found, together with *p*-fluorobenzyl alcohol derived from the hydrolysis of the chloride (Table 3); in particular, increasing oxidation was observed with increasing amount of hypochlorite, but the highest yield of the oxidation products (aldehyde and acid) was found with a 2 : 1 hypochlorite/chloride molar ratio. On varying the hypochlorite concentration in the aqueous solution with an equimolar ratio of hypochlorite/chloride, a decrease in conversion was observed as the hypochlorite concentration increased (Table 4).

This latter experiment showed the particular effect of the stability of the hypochlorite solution on the conversion. This stability depends on the temperature and pH (aqueous solutions of hypochlorite are unstable at pH <8 [9]). In particular, the stability at the temperature used (reflux) was tested on two aqueous hypochlorite solutions with different initial concentrations (7.1% and 3.1%, pH 14) maintained at reflux for some time. The hypochlorite concentration and pH were measured at regular time intervals. While the pH remained almost constant, the hypochlorite concentration of the solution decreased with time as shown in Fig. 1; in particular, the most dilute solution showed the best stability.



Fig. 1. Percentage reduction of hypochlorite concentration vs. time for aqueous sodium hypochlorite at different initial concentrations.

These results showed that a considerable decomposition of the hypochlorite solution could be expected at the temperature (higher than 70 °C) used in our experiments. Thus, in other experiments carried out by feeding the reagents separately, particular attention was paid to the final pH and the residual hypochlorite concentration of the solution (Table 5). On feeding continuously the hypochlorite solution alone (over 2 h), the final reaction mixture was somewhat acidic (pH 2) and the residual hypochlorite concentration of the solution was still appreciable; in these conditions, almost equal amounts of alcohol and acid were found, together with minor amounts of aldehyde. On feeding the chloride alone (in 30 min), the final reaction mixture was almost neutral (pH 6), but the residual hypochlorite concentration was very low; in these conditions, *p*-fluorobenzoic acid was the main product and the corresponding aldehyde was formed in very small amounts. Finally, on feeding the hypochlorite solution in two portions, the pH and residual hypochlorite concentration, together with minor amounts of alcohol.

The effect of additives on the oxidation reaction was also studied (Table 6). In the presence of sodium phosphates, low conversions were obtained, and alcohol was always the main product; moreover, when the pH was maintained at rather high values (pH 10–12), almost equimolar amounts of acid and alcohol were obtained. In the presence of sodium bicarbonate, conversion was nearly complete and acid was the main product, whereas, in the presence of sodium hydroxide, a rather low pH was measured on completion with the formation of equimolar amounts of acid and alcohol. In these conditions, aldehyde formation was not favoured.

Finally, some experiments were carried out in order to attempt to maximize acid formation by using a 3 : 1 hypochlorite/chloride molar ratio (Table 7). The yield of acid was dependent on the feed mode of the hypochlorite solution. Thus the highest yield was obtained by feeding the hypochlorite solution in two portions, with intermediate cooling

Table 5

Oxidation of *p*-fluorobenzyl chloride with aqueous sodium hypochlorite: effect of the feed mode. Molar ratio hypochlorite/chloride, 2 : 1; reaction time, 150 min

Experiment	Initial hypochlorite	Final pH	Residual hypochlorite concentration (%)	Conversion	Molar yi	ield (%)	
	concentration (%)			(%)	Acid	Aldehyde	Alcohol
] <sup>a</sup>	8.0	2	3.4	91	37	25	38
2 <sup>b</sup>	6.0	6	0.4	99	57	3	40
3°	7.6	1	0.8	97	54	26	20

<sup>a</sup> Dropwise addition of hypochlorite alone (in 2 h).

<sup>b</sup> Dropwise addition of *p*-fluorobenzyl chloride alone (in 30 min).

<sup>c</sup> Hypochlorite fed in two portions.

Table 6

Oxidation of p-fluorobenzyl chloride with aqueous sodium hypochlorite: effect of additives. Molar ratio hypochlorite/chloride, 1 : 1; reaction time, 150 min

Experiment	Initial hypochlorite concentration (%)	Additive	Final pH	Residual hypochlorite	Conversion	Molar yield (%)		
				concentration (%)	(%)	Acid	Alcohol	
1	6.3	Na <sub>2</sub> HPO <sub>4</sub> · 2H <sub>2</sub> O	8	2.1	69	36	9	55
2	6.3	NaH <sub>2</sub> PO <sub>4</sub> .H <sub>2</sub> O	5	2.1	51	10	11	79
3	6.3	Na <sub>3</sub> PO <sub>4</sub> · 12H <sub>2</sub> O	12	_	79	39	17	44
4	8.0	NaHCO <sub>3</sub>	9	1.9	99	60	16	24
5	9.0	NaOH	3	0.5	99	44	15	41

Experiment	Reaction time	Final pH	Residual hypochlorite	Conversion	Molar yield (%)			
	(min)		concentration (%)	(76)	Acid	Aldehyde	Alcohol	
1 <sup>a</sup>	150	1	1.6	99	49	13	38	
2 <sup>h</sup>	240	6	1.1	99	87	6	7	
3°	270	6	0.5	99	93	5	2	

Oxidation of *p*-fluorobenzyl chloride with aqueous sodium hypochlorite: selectivity towards acid. Hypochlorite concentration, 8.8%; molar ratio hypochlorite/ chloride, 3 : 1

<sup>a</sup> Hypochlorite fed alone.

Table 7

<sup>b</sup> Hypochlorite fed in two portions with intermediate cooling of the reaction mixture.

<sup>e</sup> Hypochlorite fed in two portions with intermediate cooling of the reaction mixture and dropwise addition of the second portion.

of the reaction mixture and dropwise addition of the second portion.

## 4. Conclusions

The above data show that the experimental oxidation reactions always gave aldehyde and acid as the reaction products. The relative amounts of these products in the reaction mixture principally depended on the oxidizing agent and the reagents used. Commercial aqueous hypochlorite solutions were the best oxidizing agents. *p*-Fluorobenzyl alcohol gave the corresponding acid as the main product; however, aldehyde was obtained in satisfactory yield in the presence of additives, such as sodium bicarbonate, which were able to maintain high pH values (pH > 10). In the case of *p*-fluorobenzyl chloride, the corresponding alcohol, formed from concomitant hydrolysis, was also found in the reaction mixture and *p*-fluorobenzoic acid was once again the main product. The selectivity towards this product was dependent on the feed mode of the hypochlorite solution.

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