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Preparation of 4-fluorophenol and 4-fluorobenzoic acid by the Baeyer–Villiger reaction*

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Abstract

The possibility of preparing 4-fluorophenol or 4-fluorobenzoic acid via the Baeyer–Villiger reaction starting from unsymmetrical fluoroaryl ketones is discussed. Several unsymmetrical 4-fluorobenzophenones having different substituents in the fluorine-free aryl group were prepared and converted to esters by treatment with peracetic acid. The electrophilicity of the substituents influenced the molecular structure of the ester formed as a result of a carbon-to-oxygen migration, and hence 4-fluorophenol or 4-fluorobenzoic acid formation. Electron-withdrawing substituents favoured the formation of 4-fluorophenol in good yield, while electron-donating substituents formed 4-fluorobenzoic acid preferentially.

Introduction

4-Fluorophenol is a widely used intermediate in the industrial production of pharmaceutical and agrochemical specialities. Figure 1 shows methods which can be used for its preparation, where fluorine-atom introduction into the molecule occurs either during the initial (methods 1 [2] and 3 [3–5]) or final (methods 2 [6, 7] and 4 [8]) reaction steps. All these various methods display both economic or technological benefits and disadvantages, and none of them seems to be entirely satisfactory for the industrial production of this compound. Much work is being carried out to find profitable methods for 4-fluorophenol production.

The method discussed here starts from fluorobenzene, and 4-fluorophenol formation has been studied using the Baeyer–Villiger reaction with different unsymmetrical aryl ketones. This reaction [9–11] consists of an acid- or base-catalyzed oxidation of ketones to esters or lactones by peracids and/or hydrogen peroxide. According to the mechanism proposed for the acid-catalyzed reaction [12], starting from an unsymmetrical ketone R^1-CO-R^2 in the presence of a peracid $R-CO-OOH$, the reaction proceeds through an intermediate form which undergoes an intramolecular rearrangement with a carbon-to-oxygen migration of R^2 or R^1 groups, as shown in Fig. 2.

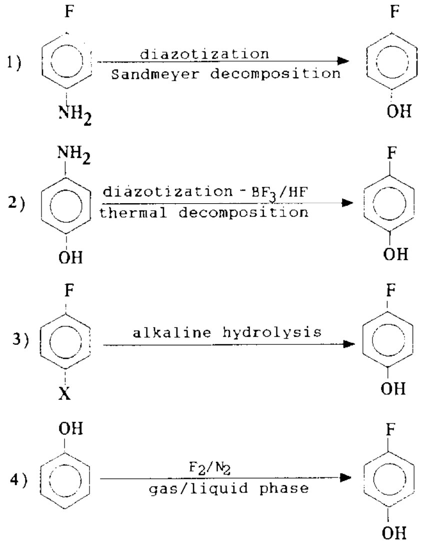

Fig. 1. Methods to produce 4-fluorophenol.

The migrating ability of the alkyl groups depends on their structure [12], while the migration of aryl groups depends on the presence of electron-donating or electron-withdrawing substituents: in particular, it is increased by electron-donating and decreased by electron-withdrawing substituents [13]. In the presence of two aromatic rings, as in benzophenones, their relative

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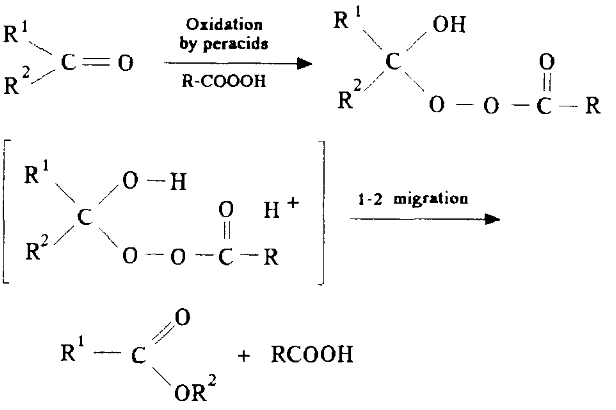

Fig. 2. Proposed mechanism for the acid-catalyzed Baeyer–Villiger reaction. Stage 1 involves oxidation by peracids (top) and stage 2 1-2 migration (bottom).

migrating ability will depend on the nature of the substituent. Thus, in the case of a 4-fluoro-4′-Z-benzophenone, $F-C_6H_4-CO-C_6H_4-Z$, migration will involve the $F-C_6H_4$ or $Z-C_6H_4$ group depending on the substituent Z being more or less electron withdrawing than F.

Since 4-$F-C_6H_4$-group migration will lead to 4-fluorophenol (after hydrolysis of the corresponding ester), it should be possible to favour the formation of the 4-fluorophenol or 4-fluorobenzoic acid by a suitable choice of the Z substituent. In order to confirm this, several 4-fluoro-4′-Z-benzophenones, having different Z substituents, were prepared and subjected to the acid-catalyzed Baeyer–Villiger reaction in the presence of peracetic acid produced *in situ* from hydrogen peroxide and acetic acid [14]; the esters obtained in this manner were then converted by hydrolysis to the corresponding phenols and benzoic acids.

Experimental

The method involves a three-step procedure:

(1) Friedel–Crafts acylation reaction with 4-Z-benzoyl or acetyl chloride on fluorobenzene to give the corresponding unsymmetrical bis-arylketone.

(2) Peracid oxidation of the ketone to give an intermediate from which the ester forms via a carbon-to-oxygen intramolecular migration.

(3) Base hydrolysis of the ester to give the corresponding phenol and carboxylic acid.

Because of the competitive character of the migration involving the F-phenol and X groups, both possible esters were nearly always obtained. In these cases, a mixture of two phenols and two carboxylic acids was found.

Materials

All reagents used were of a commercial grade quality.

Analytical

Reaction products were identified by means of a Carlo Erba GC–MS spectrometer model MCF 500/QMD 1000 (30 m × 0.5 mm capillary fused silica column packed with PS 264 using different operational conditions according to the sample tested) and a Perkin-Elmer IR spectrometer model 782.

For quantitative determination of the products in the final reaction mixture, a GLC internal method [15, 16] was used. Benzoic acids required preliminary esterification before estimation. Gas–liquid chromatography was undertaken using a Shimadzu thermal conductivity instrument fitted with a 1 m × 2 mm stainless-steel column packed with FS on 100–120 mesh Chromosorb P (different temperatures and helium flow rates depending on the sample tested).

General procedure

The substituent Z in the unsymmetrical 4-fluoro-4′-Z-benzophenones synthesized was Cl, CH_3 or NO_2; 4-$F-C_6H_4-CO-C_6H_5$ and 4-$F-C_6H_4-CO-CH_3$ were also prepared for comparative purposes.

Different results were obtained in the conversion of benzophenones into the corresponding esters, probably due to insufficient amounts of reagent being sometimes used in the experiments. In fact, the success of the reaction depends on the presence of a sufficient concentration of peracid, which is best prepared *in situ* by reaction of a carboxylic acid with 30% hydrogen peroxide. Since the concentration of the peracid generated depends on the amount of water present, higher conversion of the peracid can be obtained by replacing part of the carboxylic acid with its anhydride [17].

The usual synthetic procedure for Friedel–Crafts acylation reactions [18–20] was used in order to prepare the investigated benzophenones from fluorobenzene and the appropriate acyl chloride. Ester hydrolysis, the third step in the procedure, was accomplished by treatment with NaOH followed by acidification in order to separate phenols and carboxylic acids formed; quantitative evaluation of the latter was undertaken after their esterification with methanol.

Peracid oxidation of benzophenones was accomplished making some modifications to the method reported for ketones [21]. The oxidation of 4-fluoro-4′-nitrobenzophenone is described in detail below and was representative of the procedure used for other benzophenones.

Peracid oxidation of 4-fluoro-4′-nitrobenzophenone

To a stirred and ice-cooled solution consisting of 30 g of crude benzophenone in 186 ml of acetic acid and

131 ml of acetic anhydride was added 86 ml of 96% H_2SO_4 with the temperature being maintained below 30 °C. After 30 min stirring, 26 g of 40% H_2O_2 were added slowly and carefully, the temperature being always kept below 30 °C. The well-stirred reaction mixture was allowed to stand for 4 h at room temperature and then poured into a solution of 16 g of Na_2SO_3 in 600 ml of ice and water. After filtration, 31.7 g of a solid were isolated.

Results and discussion

Figure 3 outlines the reaction pathway leading to 4-fluorophenol or 4-fluorobenzoic acid depending on the relative migration ability of the X group compared to the $F-C_6H_4$ group. The step-by-step yields determined experimentally are reported in Table 1; the values shown were calculated assuming that the compounds isolated were pure.

It is clear from these data that the degree of conversion of ketones to esters was very high in every case (the determined values were always higher than 92%). However, the first step (formation of the ketone) exhibited a very high conversion only for 4-chloro- and 4-nitro-benzoyl chlorides; in addition, the third step (hydrolysis of the esters) exhibited low yields generally, except for those esters derived from benzoyl and 4-nitro-benzoyl chlorides.

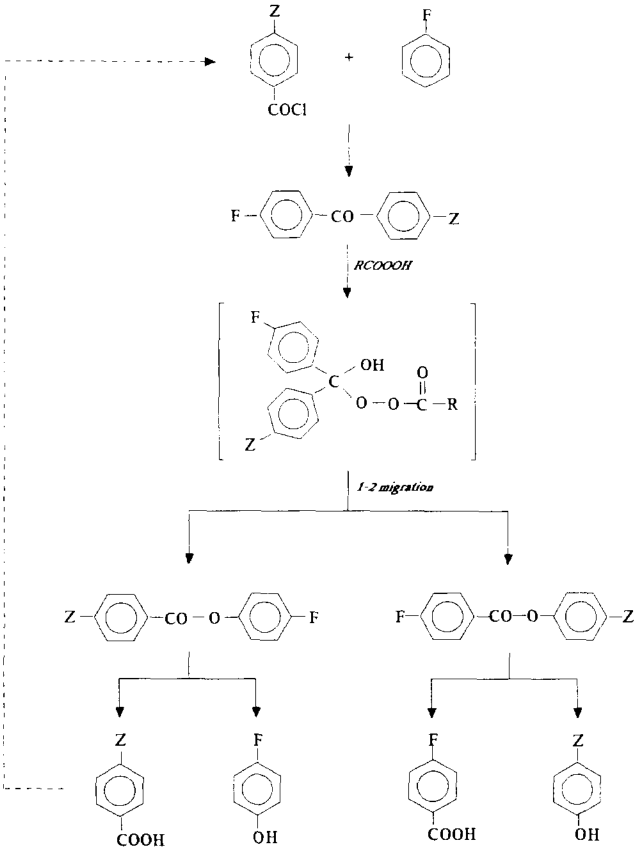

Fig. 3. Outline of reaction pathway for the 4-fluorophenol or 4-fluorobenzoic acid formation. Dashed line concerns the recycling of benzoic acid formed.

TABLE 1. Preparation of phenols and carboxylic acids from acyl chlorides X−COCl (step-by-step yields given)

Compound	X^a=				
	NO_2–C_6H_4	CH_3–C_6H_4	Cl–C_6H_4	H–C_6H_4	CH_3
X–COCl	55.6	47.0	44.0	49.2	71.0
	0.300	0.304	0.251	0.350	0.904
Ketone	71.8	55.4	51.6	43.8	114.5
	0.293	0.259	0.220	0.219	0.830
	97.7	85.2	87.6	62.6	91.8
Esters	75.9	58.4	54.4	46.1	117.0
	0.291	0.254	0.217	0.213	0.760
	99.3	98.1	99.1	97.3	92.0
F–Ph[b]	26.1	1.01	6.2	11.6	23.5
	0.233	0.009	0.055	0.104	0.210
	80.0	3.5	25.3	48.8	27.6
X–OH	–	17.2	2.4	9.7	–
	–	0.159	0.019	0.103	–
	–	62.6	8.7	48.3	–
F–Ac[c]	–	21.3	3.4	14.0	–
	–	0.152	0.024	0.100	–
	–	59.8	11.0	47.3	–
X–COOH[d]	39.6	1.2	10.3	12.7	–
	0.237	0.009	0.066	0.104	–
	81.5	3.5	30.3	48.8	–

[a] Amounts (g, mol) and yields (%) listed in each case where appropriate.

[b] 4-Fluorophenol.

[c] 4-Fluorobenzoic acid (data based on GLC analysis of the corresponding methyl ester).

[d] Carboxylic acid (data based on GLC analysis of the corresponding methyl ester).

For the preparation of 4-fluorophenol in good yield, the best results were undoubtedly obtained starting from 4-nitrobenzoyl chloride as the acylating agent. In fact, 4-fluorophenol was the only phenol formed in this case indicating that the oxidation of the corresponding benzophenone only involved migration of the $4-F-C_6H_4$ group. Acetyl chloride also only gave 4-fluorophenol but in a much lower yield.

In contrast, the other acyl chlorides gave a mixture of the corresponding phenol and 4-fluorophenol, with different relative amounts depending on the Z substituent. Thus, with 4-methyl-benzoyl chloride, the yield of the 4-cresol formed was higher than that of the 4-fluorophenol, while with 4-chlorobenzoyl chloride the opposite result was observed. Finally, with benzoyl

TABLE 2. Comparison of the migrating ability between X and F–Ph groups

X	Overall yield of phenols (%)	Quantity of phenols found (mol)		% migration[a]	
		F–Ph (*a*)	X–OH (*b*)	F–Ph (*c*)	X (*d*)
NO_2–C_6H_4	77.7	0.233	–	100	–
CH_3–C_6H_4	55.3	0.009	0.159	5.3	94.7
Cl–C_6H_4	29.5	0.055	0.019	74.3	25.7
H–C_6H_4	59.1	0.104	0.103	50.2	49.8
CH_3	23.2	0.021	–	100	–

[a] $c = 100[a/(a+b)]$; $d = 100[b/(a+b)]$.

TABLE 3. Percentage overall yield of final products from the Baeyer–Villiger reaction

Compound	X =				
	NO_2–C_6H_4	CH_3–C_6H_4	Cl–C_6H_4	H–C_6H_4	CH_3
F–Ph[a]	77.7	3.0	21.9	29.7	23.2
X–OH	–	52.3	4.0	29.4	–
F–Ac[b]	–	50.0	9.6	28.6	–
X–COOH[c]	79.0	3.0	26.3	29.7	–

[a] 4-Fluorophenol.
[b] 4-Fluorobenzoic acid.
[c] Carboxylic acid.

chloride, similar amounts of phenol and 4-fluorophenol were obtained.

The experimental data listed in Table 2 allow a comparison to be made between the migrating ability of the acyl groups studied. From the mole quantities and relative amounts found for each phenol formed, it is possible to calculate the percentage migrating ability for the X groups. As can be seen, in the case of 4-nitrobenzoyl chloride the 4-fluorophenyl group shows higher migrating ability than the 4-nitrophenyl group so that only the 4-fluorophenol is formed. The same also occurs with acetyl chloride. A methyl group in the *para* position favours the migration of the CH_3-C_6H_4 group while the presence of chlorine in the same position favours the migration of the 4-F$-$$C_6H_4$ group. In the absence of substituents, the C_6H_5 and 4-F$-$$C_6H_4$ groups exhibit the same migrating ability.

Less favourable results were found in the formation of 4-fluorobenzoic acid. As can be seen from Table 3, this compound is formed preferentially only in the case of 4-methyl-benzoyl chloride and then not in a high yield.

Conclusions

The experimental data reported show that it is possible to prepare the 4-fluorophenol in good yield via the Baeyer–Villiger reaction starting from unsymmetrical benzophenones possessing an electron-withdrawing substituent in the position *para* of the acyl group. The following migration sequence was observed with respect to the F-phenyl group: methylphenyl > phenyl > chlorophenyl > nitrophenyl, methyl.

The most effective acyl agents for 4-fluorophenol formation were 4-nitrobenzoyl and acetyl chlorides, but the former gave better yields. The reverse situation is valid for 4-fluorobenzoic acid, whose formation was favoured in the case of 4-methylbenzoyl chloride.

The prospect of a practical application for this method is at present limited by the large amounts of reagent required in the oxidation of the ketone to the ester. A reduction in these amounts and an improvement in the yields could make this a possible successful method on an industrial scale.

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