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Halogens halt aromatic group migration in Baeyer–Villiger oxidation

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Abstract

Oxidation of a dihalogenated benzaldehyde under Baeyer–Villiger conditions led to the aromatic carboxylic acid as opposed to the desired phenol. Fluorine was located at the *para*-position of the benzaldehyde, halting migration of the aryl group and thus resulting in the carboxylic acid product.

Keywords: Fluorobenzaldehyde; Fluorocarboxylic acid; Baeyer–Villiger oxidation mechanism

1. Introduction

Our group has been involved in studying syntheses of several aromatic amines of biological interest, especially those with fluorine on the aromatic ring [1–3]. As part of these studies, we needed the novel bromofluorophenol (**1**) as a reagent. We proposed synthesizing it by Baeyer–Villiger oxidation [4–6] of 3-bromo-4-fluorobenzaldehyde (**2**).

Several oxidizing agents such as *meta*-chloroperoxybenzoic acid (MCPBA), peroxyacetic acid and trifluoroperoxyacetic acid were examined in the reaction (Table 1). The reactivities of those reagents decreased in the order of peroxytrifluoroacetic acid (synthesized from trifluoroacetic anhydride and H_2O_2)>MCPBA>peroxyacetic acid (synthesized from acetic anhydride and H_2O_2). Reaction of peroxyacetic acid with the aldehyde required long time and was not complete. Reaction of MCPBA with it was carried out in chloroform or methylene chloride and heated to different temperatures. The reaction gave a high yield (62%). However, the product was 3-bromo-4-fluorobenzoic acid (**3**) and not the desired phenol (**1**). Using trifluoroperoxyacetic acid gave the same compound but in shorter time. Reaction with this oxidizing agent was complex and resulted in many side-products. Some of these may involve oxidations of the benzene ring to form phenols.

In the mechanism (Scheme 1), we propose that migration of the aromatic group of oxazon ion (**4**) was hindered by the electron withdrawing fluorine, with possible contribution by the bromine. Hydride was therefore able to migrate much faster, leading to the acid observed [7,8]. We are currently examining other methods of obtaining the desired phenol.

2. Experimental

Melting points were determined on a Mel temp II capillary melting point apparatus. IR spectra were recorded on a Perkin-Elmer 457 spectrometer. ^{1}H NMR spectra were recorded on Bruker AC250 (250 MHz) spectrometer. MS spectra were obtained by electrospray method using the Finnigan TSQ-700 mass spectrometer. Elemental analyses were performed by Galbraith laboratories, Knoxville, TN, and the observed values were within ±0.4% of theoretical values.

2.1. Oxidation by MCPBA

A solution of 3-bromo-4-fluorobenzaldehyde (1.00 g, 5 mmol), and 60% MCPBA (3.0 g, 10 mmol) in CH_2Cl_2 (30 ml) was refluxed for 24 h. After the solvent was evaporated, saturated $NaHCO_3$ solution (30 ml) was added to the residue, and the mixture was extracted by AcOEt (2×30 ml). The organic extracts were combined, dried over Na_2SO_4 and the solvent was evaporated to yield a white powder (0.92 g, 84%). A solution of the solid in MeOH (10 ml) and 10% KOH solution (3 ml) was stirred for 1 h at room temperature. After the solvent was evaporated, and the pH of the residue was adjusted to 2 with 2 N HCl solution. The mixture was extracted with AcOEt (3×30 ml). The organic extracts were combined, dried over Na_2SO_4 and the solvent was evaporated to yield 0.81 g (74%) of a white solid 3-bromo-4-fluorobenzoic acid (**3**). Further, character-

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Table 1
Oxidation of 3-bromo-4-fluorobenzaldehyde by different peroxyacids

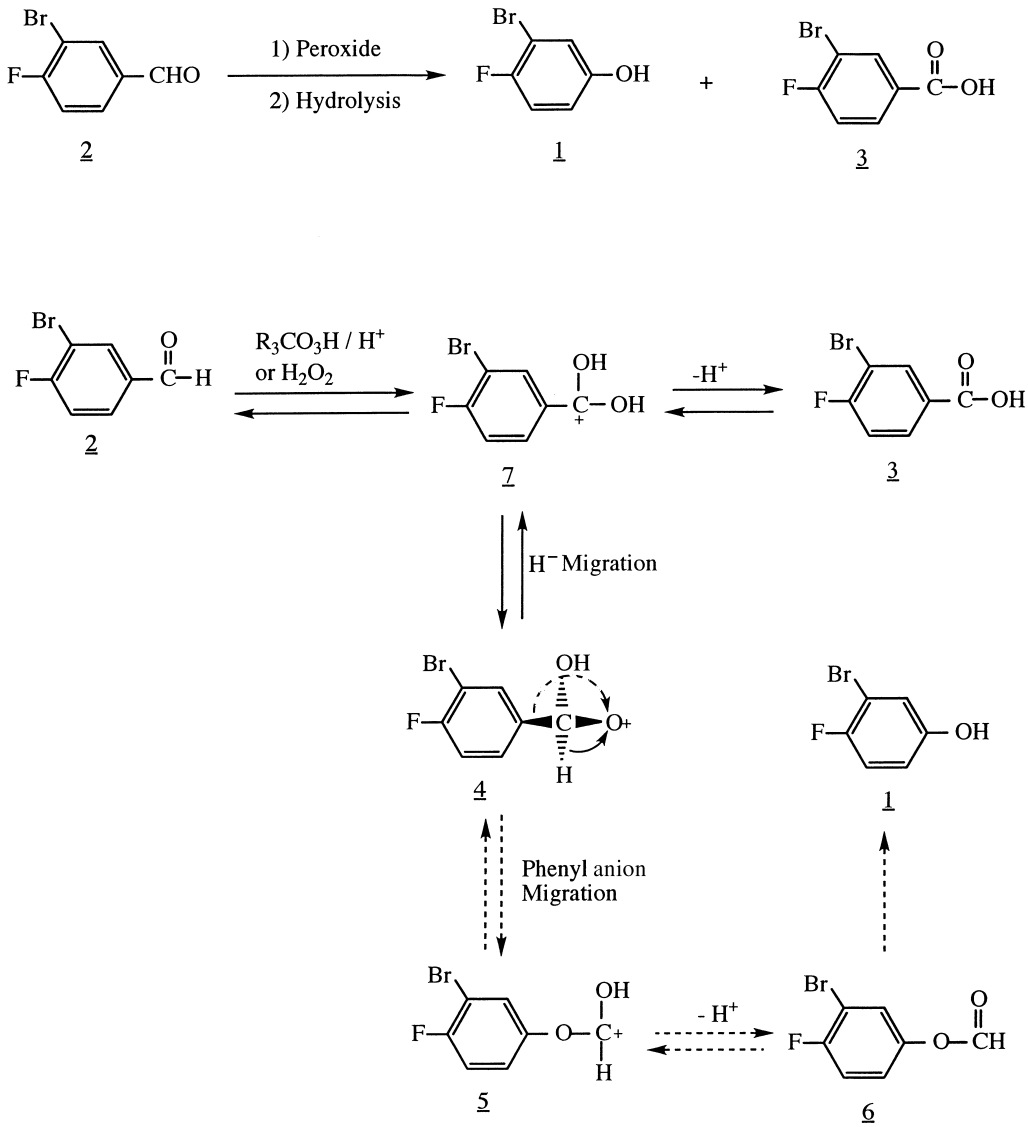
Type of peroxyacids	Catalyst	Solvent	Time (h)	Yield[a] (%)
meta-chloroperoxybenzoic acid	No	$CHCl_3$	12	62
Acetic anhydride/H_2O_2	H_2SO_4	CH_2Cl_2	48	48
Trifluoroacetic acid/H_2O_2	H_2SO_4	CH_2Cl_2	4	36
Trifluoroacetic anhydride/H_2O_2	No	CH_2Cl_2	0.5	36

[a] The yields refer to the amounts of the acid formed.

ization was consistent with the proposed acid, mp=136–140°C; ([7], mp=137°C) IR ($CHCl_3$) cm^{-1}: 1695 (COOH); ^1H NMR ($CDCl_3$): 9.70–9.25 (s, ^1H, COOH), 7.90–7.30 (m, 3H, 3×Ar-H).

2.2. Oxidation by trifluoroperoxyacetic acid

30% H_2O_2 (0.65 ml, 5.8 mmol) was slowly added to the mixture of trifluoroacetic acid (10 ml) and H_2SO_4 (0.5 ml) at 5°C to generate the trifluoroperoxyacetic acid in situ. A solution of 3-bromo-4-fluorobenzaldehyde (1.02 g, 5 mmol) in CH_2Cl_2 was added with vigorous stirring. The reaction was complete in 15 min, and the mixture was filtered to yield 0.98 g (91.0%) of a white solid trifluoroacetate ester, mp=106–108°C, ^1H NMR ($CDC1_3$): 7.80–7.58 (d, 1H), 7.55–7.00 (m, 2H), 6.85 (s, 1H). A solution of this solid in MeOH (20 ml) and 10% KOH (10 ml) was refluxed for 2 h, and then concentrated. The residue was acidified with



Scheme 1. Possible mechanism to explain formation of phenol (**1**) and acid (**3**).

2 N HCl solution and extracted with AcOEt (2×30 ml). The organic extracts were combined, dried over Na_2SO_4 and the solvent was evaporated to yield 0.38 g of a white solid (40.0%) 3-bromo-4-fluorobenzoic acid (**3**). Results of the characterization were consistent with the compound prepared by the MCPBA method, mp=138–141°C; IR ($CHCl_3$) cm^{-1}: 1710 (COOH); ^1H NMR ($CDCl_3$): 9.50–9.20 (s, 1H, COOH), 7.70–7.10 (m, 3H, 3×Ar-H). MS ESI: *m/z* 218 ($M+H^+$, base), 217. Anal. Calc. for $C_7H_4O_2BrF$: C, 38.39; H, 1.84; F, 8.67. Found: C, 38.79; H, 2.01; F, 8.27.

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