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Regio-selective hydroxysubstitution of fluorobenzoic acid derivatives: facile synthesis of fluorosalicylic acid derivatives

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Abstract

Ortho-substituted fluorine in 2,4-difluorobenzoic acid was found to be regio-selectively replaced to hydroxide by solid sodium hydroxide in 1,3-dimethyl-2-imidazolidinone, to afford 4-fluoro-2-hydroxybenzoic acid in high yield. Several multi-fluoro-substituted benzoic acid derivatives were effectively transformed to the corresponding salicylic acid derivatives under the similar conditions.

Keywords: Ortho-substitution; 2,4-Difluorobenzoic acid; 4-Fluoro-2-hydroxybenzoic acid; Solid sodium hydroxide

1. Introduction

In the course of our synthetic program for a pharmaceutical intermediate, an efficient method has been sought to produce a large quantities of 4-fluoro-2-hydroxybenzoic acid (**2a**). Although several methods are reported such as Kolbe–Schmidt reaction of 3-fluorophenol [1], Baltz–Schimann reaction followed by hydrolysis of methyl-4-amino-2-hydroxybenzoate [2], and an oxidation process with protection and deprotection or 2-hydroxy group of 4-fluoro-2-hydroxytoluene [3], the yields are not satisfactory, the corresponding starting precursors are not easily available and/or the synthesis requires multi-steps (Scheme 1).

We desired a synthetic method which would overcome these difficulties and provide **2a** in large quantities. Ipso substitution of 2-fluorobenzophenone derivatives with potassium anion of acetone oxime was reported [4]. We therefore addressed to hydrolyze 2,4-difluorobenzoic acid (**1a**), which is easily available on a large scale from 2,4-dichlorobenzoyl chloride by Halex fluorination [5]. Treatment of **1a** with aqueous sodium hydroxide, however, gave a mixture of **2a** and 2-fluoro-4-hydroxybenzoic acid (**3a**), where undesired **3a** was a major product. In sharp contrast, non-aqueous treatment of **1a** with solid sodium hydroxide in 1,3-dimethyl-2-imidazolidinone (DMI) was found to afford **2a** in high regio-selectivity and excellent yield. We now present the details of these findings.

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2. Results and discussion

Our preliminary results are shown in Table 1. Treatment of **1a** in 4 eq. of aqueous sodium hydroxide (about 7% concentration) proceeded slowly even at reflux temperature (about 103 °C). Only 18% of **1a** was reacted after 7 h and the product ratio of **2a**:**3a** was about 19:81. On the other hand, when a mixture of **1a** with 4 eq. of solid sodium hydroxide in DMI (NaOH/DMI (w/w) is about 7%) was stirred at 120 °C for 16 h, **2a** was formed exclusively without leaving the substrate **1a**. Being encouraged by this successful result, we next tried the optimization of the hydroxylation under substantially anhydrous conditions. Employment of solid sodium hydroxide in DMI at 130 °C was finally found to afford a 97% yield of **2a** in only 1.5 h (Table 2). Several dipolar aprotic solvents such as 1-methyl-2-pyrolidone (NMP), sulfolane, dimethylsulfoxide (DMSO) were next examined and all furnished in good to excellent yields of **2a**. In these cases, almost pure **2a** was precipitated by an acidification of the crude residue. However, a reaction in dimethylformamide (DMF) left most of the starting material intact. The results for solvent effect are summarized in Table 2. Based on these findings, we succeeded in a development of a practical synthetic process for multi-kilogram scale without chromatographic separation of **2a**.

In a similar manner, several ortho-fluorobenzoic acid derivatives were treated with solid sodium hydroxide in DMI to give the corresponding salicylic acid derivatives in good to excellent yields, except for fluorobenzoic acid derivatives having a 5-position of fluorine atom, as indicated in Table 3.

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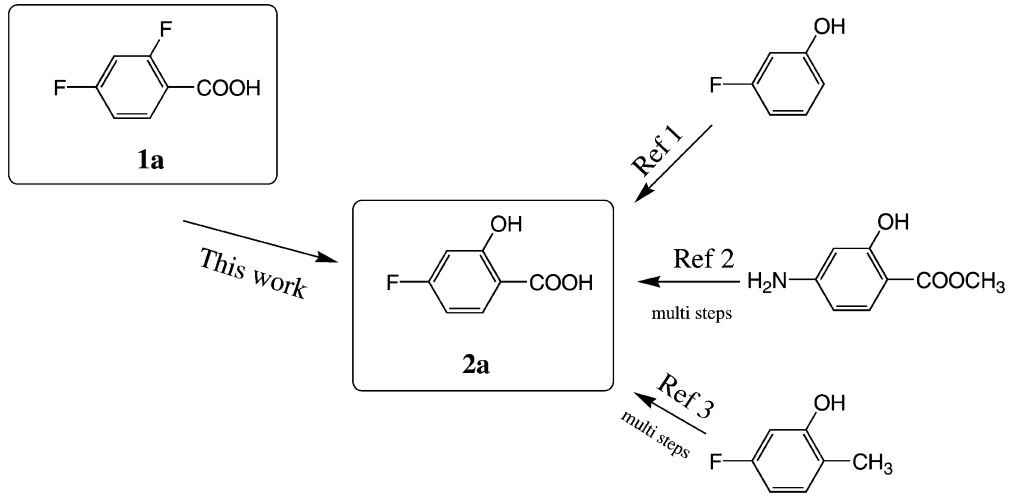

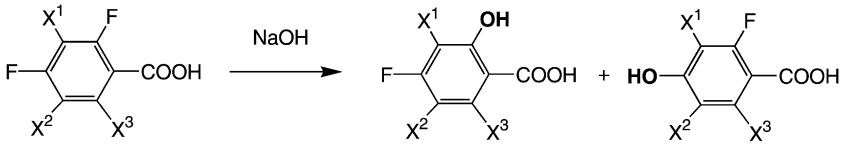

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	X^1	X^2	X^3		X^1	X^2	X^3
a	H	H	H	**e**	H	H	F
b	F	H	H	**f**	H	F	H
c	H	Cl	H	**g**	F	F	H
d	Cl	Cl	H	**h**	F	F	F

Scheme 1.

3. Experimental

3.1. 4-Fluoro-2-hydroxybenzoic acid (*2a*)

In a 1 l four-necked flask equipped with a mechanical stirrer, a thermometer, a condenser, 2,4-difluorobenzoic acid (**1a**) (31.6 g, 0.200 mol), 99% beaded sodium hydroxide (32.3 g, 0.800 mol) and 1,3-dimethyl-2-imidazolidinone (DMI) (400 ml) were charged. When the whole mixture was stirred at 130 °C, analysis of the organic layer (GLC) revealed a 100% conversion after 4 h. After DMI was removed in vacuo, the residue was poured into 3% hydrochloric acid

Table 1
Ortho-selective hydroxylation of **1a**

Solvent	Temperature (°C)	Time (h)	Yield of **2a** + **3a** (%)[a]	Ratio of **2a**:**3a**	Recovery of **1a** (%)
H_2O[b]	Reflux	7	16	19:81	82
DMI[c]	120	16	97	99:1	–

[a] HPLC external standard method.
[b] **1a** (0.1 mol), NaOH (0.4 mol), H_2O (200 ml).
[c] **1a** (0.1 mol), NaOH (0.4 mol), DMI (200 ml).

Table 2
Solvent effects on ortho-hydroxylation of **1a** with solid NaOH

Solvent	Temperature (°C)	Time (h)	Yield of **2a** (%)[a]	Product ratio **2a**:**3a**	Recovery of **1a** (%)
DMI	130	1.5	97	99:1	–
NMP	150	1.0	94	99:1	–
Sulfolane	150	4.0	89	98:2	–
DMSO	130	3.0	98	99:1	–
DMAC[b]	150	1.5	60	99:1	13
Diglyme	150	1.5	–[c]	88:12	63
DMF	150	1.5	–	–	98

[a] HPLC external standard method.
[b] *N*,*N*-Dimethylacetamide.
[c] Not determined.

Table 3
Examples of ortho-hydroxylations

Substrate	Product ratio of **2**:**3**	
	Solid NaOH in DMI[a]	Aqueous NaOH[b]
1a	99:1 (95)[c]	20:80
1b	99.8:0.2 (95)[c]	25:75
1c	93:7 (88)[c]	3:97
1d	92:8 (87)[c]	9:91
1e	97:3 (87)[c]	–
1f	72:28	2:98
1g	67:33	–
1h	Complex mixture	–

[a] Product ratios after completion of the reaction.
[b] Product ratios after 7 h under reflux condition (a large amount of the starting materials (~80%) were remained). Though the reactions in aqueous NaOH were generally slow under reflux conditions, we did not further investigate due to our research interest for the preparation of salicylic acid derivatives.
[c] Yields in parenthesis are referred to isolated yields of **2** (see experimental).

solution (2.50 l) with stirring at room temperature. The generated precipitates were collected, washed with water, and dried to give (**2a**) (29.7 g, 95.1%), and the purity was determined as 99.2% by HPLC. Recrystallization from a mixture of 2-propanol and water (1:3) gave a pure **2a** having mp 185.1–185.3 °C ([2] mp 185 °C).

The 300 MHz ^{1}H NMR ($CDCl_3$) δ: 6.67 (ddd, J = 10.2, 9.0, 2.4 Hz, 1H), 6.70 (dd, J = 10.2, 2.4 Hz, 1H), 7.93 (dd, J = 9.0, 6.6 Hz, 1H), 10.67 (brs, 1H).

IR (KBr) (cm^{-1}): 3261, 3006, 1671, 1624, 1598, 1509, 1441, 1327, 1251, 1208, 1170, 1153, 1134, 887, 852, 795, 772, 669, 613.

LC mass spectrum m/z: 156 (M^+), 138, 110.

3.2. 3,4-Difluoro-2-hydroxybenzoic acid (*2b*)

A mixture of 2,3,4-trifluorobenzoic acid (**1b**) (1.76 g, 10.0 mmol), 99% sodium hydroxide (1.62 g, 40.0 mmol), and DMI (20.0 ml) was stirred at 150 °C for 2 h. After a part of DMI was removed in vacuo, water (500 ml) and 10% HCl were added up to pH 1. The generated precipitate was collected by filtration, washed with water, dried to give **2b** (1.66 g, 95.1%) having mp 176.8–178.2 °C. The 60 MHz ^{1}H NMR (DMSO-d6 + $CDCl_3$: δ: 6.63–7.20 (m, 1H), 7.47–7.90 (m, 1H), 8.33 (brs, 2H). IR (KBr) (cm^{-1}): 3431, 3211, 3104, 3079, 3022, 2942, 2864, 2677, 2546, 2343, 1658, 1573, 1540, 1512, 1470, 1445, 1384, 1316, 1277, 1214, 1200, 1149, 1054, 909, 831, 785, 716, 689, 609.

3.3. 5-Chloro-4-fluoro-2-hydroxybenzoic acid (*2c*)

In the same manner, a mixture of 5-chloro-2,4-difluorobenzoic acid (**1c**) (1.93 g, 10.0 mmol), 99% NaOH (1.62 g, 40.0 mmol), and NMP (20.0 ml) was stirred at 130 °C for 3 h. 5-Chloro-4-fluoro-2-hydroxybenzoic acid (**2c**) was given in 87.6% yield (1.67 g), mp 200.0–201.2 °C. The 60 MHz ^{1}H NMR (DMSO-d6 + $CDCl_3$) δ: 6.79 (d, J = 10.3 Hz, 1H), 7.92 (d, J = 8.8 Hz, 1H), 9.46 (brs, 2H). IR (KBr) (cm^{-1}): 3630–3280, 1669, 1616, 1590, 1491, 1475, 1449, 1377, 1276, 1248, 1212, 1166, 849, 703, 611.

3.4. 3,5-Dichloro-4-fluoro-2-hydroxybenzoic acid (*2d*)

It was obtained from 3,5-dichloro-2,4-difluorobenzoic acid (**1d**) (10.0 mmol) in 86.7% yield, mp 119.4–120.9 °C. The 60 MHz ^{1}H NMR (DMSO-d6 + $CDCl_3$) δ: 7.39 (brs, 2H), 7.89 (d, J = 8.2 Hz, 1H). IR (KBr) (cm^{-1}): 3451, 3428, 1674, 1641, 1607, 1543, 1474, 1458, 1432, 1307, 1292, 1241, 1057, 1432, 1307, 1292, 1241, 1057, 810, 720, 659.

3.5. 4,6-Difluoro-2-hydroxybenzoic acid (*2e*)

One fluorine out of three was selectively replaced to hydroxide from a mixture of 2,4,6-trifluorobenzoic acid (**1e**) (10.0 mmol), 99% NaOH (40.0 mmol) in NMP in 86.7% yield, mp 180.8–183.4 °C. The 60 MHz ^{1}H NMR (DMSO-d6 + $CDCl_3$) δ: 6.27–6.80 (m, 2H), 7.20 (brs, 2H). IR (KBr) (cm^{-1}): 3421, 3274, 3106, 3005, 2964, 2929, 1667, 1632, 1598, 1561, 1509, 1465, 1436, 1365, 1325, 1253, 1178, 1137, 1065, 854, 830, 787, 612.

4. Conclusion

Regio-selective ortho-substitution of multi-fluorobenzoic acid derivatives was demonstrated by sodium hydroxide under substantially anhydrous conditions to afford the corresponding salicylic acid derivatives in good yields. This process which is operationally simple, chromatographic-free preparation, and gives excellent yields of fluorosalicylic acid derivatives, is suitable for large scale synthesis.

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