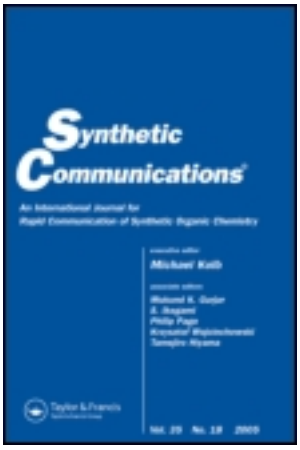

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Michele A. Weidner-Wells [a] & Stephanie A. Fraga-Spano [a]
[a] Drug Discovery, The R.W. Johnson Pharmaceutical Research Institute, 1000 Route 202, Raritan, N.J., 08869
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AN IMPROVED METHOD FOR THE PREPARATION OF 3,5-DIFLUOROSALICYLALDEHYDE AND 3,5-DIFLUOROSALICYLIC ACID#

Michele A. Weidner-Wells* and Stephanie A. Fraga-Spano

Drug Discovery, The R.W. Johnson Pharmaceutical Research Institute
1000 Route 202, Raritan, N.J. 08869

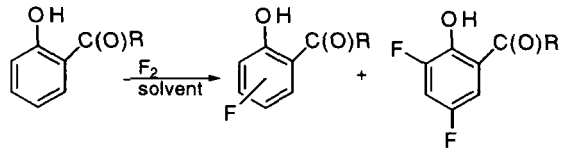
Abstract: An improved method for the synthesis of 3,5-difluorosalicylic acid (**3b**) and 3,5-difluorosalicylaldehyde (**3a**) is described. 2,4-Difluorophenol (**4**) undergoes a formylation reaction to afford aldehyde **3a** which is oxidized to the desired acid **3b**. This method avoids the use of the highly corrosive HF and fluorine gas and requires no special laboratory apparatus.

During the course of our SAR studies on salicylic acid derivatives, we found it necessary to prepare multigram quantities of 3,5-difluorosalicylic acid (**3b**). However, neither acid **3b** nor any immediate precursors were commercially available. In addition, a literature search revealed only two references[1,2] pertaining to this acid. Misaki had reported the direct fluorination of aryl oxygen compounds using fluorine gas with either anhydrous hydrofluoric acid (HF), 65% aqueous HF or acetonitrile as the solvent (Equation 1). Fluorination of salicylaldehyde (**1a**) predominately yielded the two isomeric 3- and 5-fluoroaldehydes **2a** with the difluoro compound **3a** being produced only in small

* To whom correspondence should be addressed
# Dedicated to the memory of Rosemarie R. Ungarelli, Academic Advisor, Chemistry Department, Long Island Univeristy, C.W. Post Center.

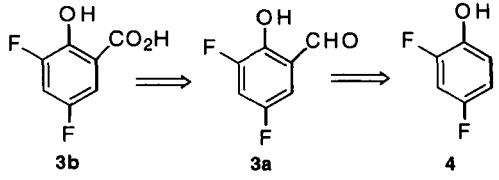
quantities (<15%). However, subjecting salicylic acid (**1b**) to various fluorinating conditions afforded, in the best case, 3,5-difluorosalicylic acid (**3b**) in 31% yield. This method[3] suffers from several drawbacks: the use of highly corrosive HF, the use of fluorine gas, low yields of the difluorinated compounds and the need for a special and impractical reaction apparatus[4].

Equation 1



We sought to find an alternative, higher yielding method for the synthesis of 3,5-difluorosalicylic acid (**3b**) without the use of highly corrosive chemicals and special reaction apparatus. The preferred synthetic route would already have the fluorine atoms incorporated on the phenyl ring (Equation 2) and would require the introduction of the acid moiety. This can be accomplished *via* a formylation/oxidation sequence commencing with 2,4-fluorophenol (**4**).

Equation 2

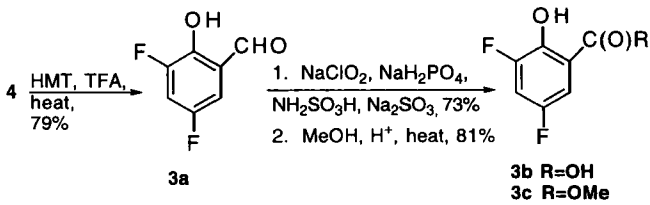


Duff[5] found that heating phenols with hexamethylenetetramine (HMT) in glycerol in the presence of glyceroboric acid followed by an aqueous workup gave salicylaldehydes in low yield (<20%). Suzuki[6] employed a modified Duff

reaction where strong acids, such as methanesulfonic, trifluoroacetic and polyphosphoric, were used as the solvent. This modification successfully formylates many electron-deficient phenols which were unreactive using the conditions of Duff.

Reaction of 2,4-difluorophenol (**4**) with HMT in warm trifluoroacetic acid furnished 3,5-difluorosalicylaldehyde (**3a**) in 79% yield (Scheme 1). This crystalline compound is extremely volatile and should remain in a tightly sealed jar. Therefore, care should be taken when attempting to dry the compound in a vacuum oven. Use of methanesulfonic acid afforded a low yield of impure product.

Scheme 1



The ^1H NMR of aldehyde **3a** in $CDCl_3$ showed two partially overlapping multiplets making the assignment of ^1H-^1H and ^1H-^{19}F coupling constants extremely difficult. A doublet, with J=1.8 Hz, is observed for the aldehyde proton due to 5-bond coupling with one fluorine atom. Five or six-bond coupling between protons and fluorine is known to be sensitive to steric effects.[7] Apparently, since the aldehyde moiety is hydrogen bonded to the ortho phenol and is unable to rotate freely, only one of the C-F bonds is in the proper orientation to overlap with the C-H bond. Dilution experiments show that the position of the phenol proton (δ 10.73) remains constant indicating that the phenol proton is hydrogen bonded to the aldehyde oxygen, as expected for a salicylaldehyde moiety.

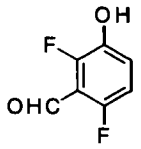
The regioisomeric identity of aldehyde **3a** was determined by careful examination of the ^{19}F-^{13}C coupling constants[8] in the proton decoupled ^{13}C

NMR (Table 1). The aldehyde carbon at δ 195.2 was observed as a triplet with $J^{19}F\text{-}^{13}C$=2.7 Hz, indicating four bond coupling with each of the two fluorines in the molecule.[9] These results can only support structure **3a** since the carbonyl carbon of the isomeric aldehydes **5** or **6** would be expected to show a triplet with three bond coupling or a doublet of doublets with three bond and five bond coupling, respectively. The coupling patterns of the two aromatic CH carbons, C-4 and C-6, also aided in the structure elucidation. The signal at δ 112.0 has coupling values indicative of two bond fluorine-carbon coupling thus demonstrating that there is a proton between the two fluorines and eliminating aldehyde **5**. The coupling of the δ 113.1 signal indicates that this hydrogen-bearing carbon is ortho to the fluorine therefore eliminating aldehyde **6**. The calculated[10] carbon chemical shifts (Table 1) are in good agreement with the experimental chemical shifts for aldehyde **3a**.

Table 1- $^{19}F\text{-}^{13}C$ coupling constants for aldehyde **3a**

C	δ exp	δ calcd[10]	m	J (Hz)
CHO	195.1	190.0	t	2.7
C-5*	154.5	156.8	dd	243.4, 9.6
C-3*	150.9	151.4	dd	253.1, 10.7
C-2	146.5	141.1	dd	12.5, 2.9
C-1	120.9	127.1	dd	7.2, 4.0
C-6	113.1	113.7	dd	22.4, 4.1
C-4	112.0	109.7	dd	21.1, 17.1

*=assignment may be interchanged



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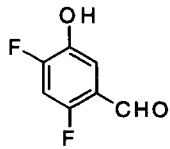

6

Attempted oxidation of aldehyde **3a** with potassium permanganate or barium permanganate led to decomposition of the aldehyde. Reaction of aldehyde **3a** with sodium chlorite and sodium phosphate monobasic (NaH_2PO_4) in aqueous dimethylsulfoxide[11] afforded acid **3b** in 49% yield. However, oxidation with sodium chlorite, sulfamic acid, sodium phosphate monobasic, and sodium sulfite in aqueous dioxane[12] produced 3,5-difluorosalicylic acid (**3b**) in 73% yield. In acid **3b**, the chemical shift difference between the two aromatic protons is significantly larger than in aldehyde **3a**, thus allowing multiplet analysis to be accomplished. The multiplet at δ 7.36 is a ddd with coupling constants of 8.6, 3.0, and 2.0 Hz indicative of ortho and para fluorine coupling along with meta hydrogen coupling[7]. The multiplet at δ 7.06 also is a ddd, but with coupling constants of 10.8, 8.0, and 3.0 Hz for the two ortho fluorines and the meta hydrogen. Acid **3b** was further characterized by esterification (sulfuric acid in methanol) to produce **3c**.

In conclusion, an improved method for the preparation of 3,5-difluorosalicylaldehyde (**3a**), 3,5-difluorosalicylic acid (**3b**) and their derivatives without the use of highly corrosive chemicals or special apparatus was been developed. The preparation of other substituted salicylic acids utilizing this methodology is under investigation.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 using tetramethylsilane as an internal reference. Melting points were performed on a Thomas-Hoover apparatus and are uncorrected.

3,5-Difluorosalicylaldehyde (3a). To 2,4-difluorophenol (6.81 g, 52.3 mmol) in neat trifluoroacetic acid (40 mL), was added hexamethylenetetramine (14.68 g, 105.0 mmol) in several portions over a period of 20 minutes. The reaction was heated at reflux under a nitrogen atmosphere for 28 h. After cooling, water (60 mL) was added followed by sulfuric acid (50%, 30 mL) and the reaction stirred at room temperature for 2 h. The acidic aqueous phase was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with

hydrochloric acid (1 N, 4 x 50 mL), water (1 x 50 mL), and dried ($MgSO_4$), filtered and evaporated. The resulting aldehyde was pure by NMR. An analytically pure sample was obtained by either trituration with methylene chloride/hexanes or recrystallization with ethyl acetate/hexanes. 6.56g (79.3% yield) of aldehyde **3a** was produced as an off-white solid. mp=87-89°C (EtOAc/Hex). *Caution*- This compound is volatile and should remain in tightly sealed jar! ^1H NMR ($CDCl_3$) δ 10.73 (s, 1H), 9.88 (d, J=1.8 Hz, 1H),7.10-7.21 (m, 2H). ^{13}C NMR δ 195.1 (t, J=2.7 Hz, CH), 154.5 (dd, J=243.3, 9.6 Hz), 150.9 (dd, J=253.1, 10.7 Hz), 146.5 (dd, J=12.5, 2.9 Hz), 120.9 (dd, J=7.2, 4.0 Hz), 113.1 (dd, J=22.4, 4.1, CH), 112.0 (dd, J=21.1, 17.1 Hz, CH). IR (KBr) 3394, 3087, 1673, 1474 cm^{-1}. MS (EI) 158 (M+). Anal. calcd. for $C_7H_4F_2O_2$: C, 53.18; H, 2.55. Found: C, 53.11; H, 2.48.

3,5-Difluorosalicylic acid (3b). To a solution of aldehyde **3a** (2.07 g, 13.1 mmol) in dioxane (150 mL) was added NaH_2PO_4 (7.08 g, 51.3 mmol) in water (50 mL) and sulfamic acid (1.86 g, 19.2 mmol). The reaction was cooled to 10°C and then $NaClO_2$ (1.86 g, 16.9 mmol) in water (7 mL) was added over a 20 minute period while keeping the temperature below 10°C. The bright yellow solution was stirred for 15 minutes. Sodium sulfite (1.95 g, 15.4 mmol) was added and stirring continued for 15 minutes. Hydrochloric acid was added to the reaction flask until pH 2 was obtained. The dioxane was evaporated and the resulting aqueous solution cooled in an ice bath. The beige solid was filtered, washed with water and dried *in vacuo* to afford acid **3b** (1.66 g, 73.1% yield, mp=185-186°C). ^1H NMR (DMSO-d_6) δ 11.14 (s, 1H), 7.36 (ddd, J=8.6, 3.0, 2.0 Hz, 1H), 7.06 (ddd, J=10.8, 8.0, 3.0 Hz, 1H). IR (KBr) 2800-3300 (br), 1686, 1484 cm^{-1}.

Methyl 3,5-difluorosalicylate (3c). 3,5-Difluorosalicylic acid (**3b**) (0.202 g, 1.16 mmol) and sulfuric acid (conc, 0.2 mL) in methanol (20 mL) were heated in an oil bath at 50°C overnight. After evaporation of the methanol, the residue was diluted with water (25 mL) and extracted with methylene chloride (3 x 50 mL). The combined organic layers were washed with water, dried ($MgSO_4$), filtered

and evaporated. Ester **3c** was isolated as pale peach crystals (mp=64-66°C, 81% yield). ^{1}H NMR ($CDCl_3$) δ 10.57 (s, 1H), 7.33 (ddd, J=8.5, 3.0, 2.0 Hz, 1H), 7.08 (ddd, J=10.3, 8.1, 3.0 Hz, 1H), 3.98 (s, 3H). IR 3089, 1693, 1632 cm^{-1}. MS (EI) 188 (M+). Anal. calcd. for $C_8H_6F_2O_3$: C, 51.08; H, 3.21. Found: C, 50.94; H, 3.40.

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