A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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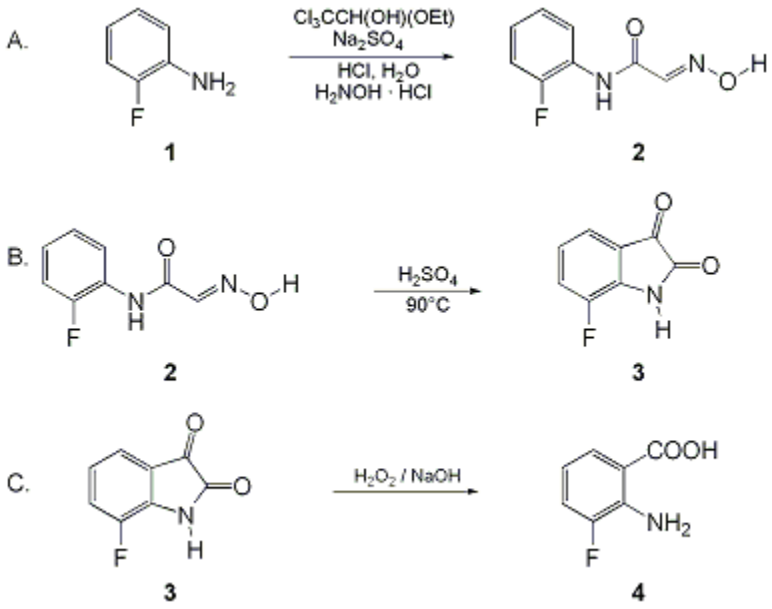
2-AMINO-3-FLUOROBENZOIC ACID

[Benzoic acid, 2-amino-3-fluoro-]



Submitted by Martin Kollmar, Richard Parlitz, Stephan R. Oevers, and Günter Helmchen[1] .
Checked by Hui Li and Marvin J. Miller.

1. Procedure

A. N-(2-Fluorophenyl)-2-(hydroxyimino)acetamide (**2**). Solution A: A 2-L, three-necked, round-bottomed flask fitted with a condenser and a thermometer is charged with 62.0 g (0.89 mol) of hydroxylamine hydrochloride , 256.7 g (1.80 mol) of anhydrous sodium sulfate , 79.5 g (0.41 mol) of 2,2,2-trichloro-1-ethoxyethanol (Note 1) and 1125 mL of water. To aid dissolution, the mixture is heated to approximately 40°C and stirred vigorously with the help of a mechanical stirrer (Note 2). Solution B: 30 g (0.27 mol) of 2-fluoroaminobenzene (Note 3) is added dropwise slowly into a 500-mL, one-necked, round-bottomed flask containing a vigorously stirred mixture of 150 mL of water and 75 mL of concd hydrochloric acid (Note 4). Solution B is added in one portion to solution A. The mixture is vigorously stirred and heated to reflux. After 1 to 2 min the mixture turns milky and a white precipitate accompanied by a small amount of brown by-product is formed (Note 5). The oil bath is removed and the flask is cooled rapidly (ice bath) to room temperature (20°C) (Note 6). After 60 hr at room temperature the precipitate is removed by filtration and washed with ice-cold water (Note 7). After drying over phosphorus pentoxide (P_4O_{10}), 43.6 g (86%) of product, mp 116-117°C, is obtained (Note 8). Crystals glued together by brown by-product, mainly consisting of the product, can be used in the next step without further purification. Nearly colorless product is obtained by recrystallization from ethanol .

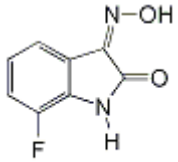
B. 7-Fluoroisatin (**3**) . A 250-mL, three-necked, round-bottomed flask fitted with a condenser and a thermometer is charged with 100 mL of concd sulfuric acid . After heating to 70°C, 30.0 g (0.165 mol) of anilide **2** (Note 9) is added over a period of 1 hr. The resulting deep red solution is heated to 90°C (Note 10) for 60 min (Note 11) and then is cooled to room temperature (20°C) over an ice bath (Note 12). The mixture is then added rapidly to a vigorously stirred mixture of 1.0 L of ice water and 200 mL of ethyl acetate (Note 13). The organic phase is separated and the almost black aqueous phase is extracted twice with 200 mL of ethyl acetate (Note 14). The combined red organic phases are dried with sodium sulfate . The solvent is removed under reduced pressure and the crude product is dried at low pressure, whereupon 12.9 to 15.7 g (47-57%) of an orange powder, mp 186-190°C, is obtained (Note

15). The crude product is sufficiently pure for the next step. Further purification is possible by recrystallization from acetone/water.

C. 2-Amino-3-fluorobenzoic acid (**4**) . A 500-mL, three-necked, round-bottomed flask fitted with an addition funnel and a thermometer, is charged with 15.0 g (0.09 mol) of 7-fluoroisatin (**3**) and 200 mL of 1 M aqueous sodium hydroxide solution (Note 16); 22 mL of hydrogen peroxide (30%) solution (0.20 mol hydrogen peroxide) is added dropwise over 45 min. The temperature of the reaction mixture rises to 30° or 40°C. After 1.5 hr the reaction is complete (Note 17). To the pale orange, clear reaction mixture 3 M hydrochloric acid is added until a pH of ca. 7.5 is reached. The mixture is treated with charcoal, stirred for a while, filtered and the clear filtrate is further acidified to pH 4-5, when the now pale yellow solution becomes cloudy again. Finally, at pH 1 the beige 3-fluoroanthranilic acid (**4**) precipitates. Bubbles are observed during acidification. After an hour of stirring, the product is collected on a funnel and dried over P_4O_{10}; yield: 11.64 to 13.3 g (84-96%) of pure 3-fluoroanthranilic acid (**4**), mp 182-184°C (Note 18).

2. Notes

1. *CAUTION: 2,2,2-Trichloro-1-ethoxyethanol is toxic.* 2,2,2-Trichloro-1-ethoxyethanol was obtained from Aldrich Chemical Company, Inc.
2. The salts can also be dissolved at room temperature. Warming to ca. 40°C facilitates dissolution. Note that complete dissolution and observance of precise concentration of the solution are essential for the success of the procedure.
3. The quality of the commercially available (colorless) 2-fluoroaminobenzene (**1**) is sufficient (Fluka Chemical Company). Older or colored material requires distillation prior to use (bp 171°C, d = 1.15).
4. Dissolution of aniline **1** is exothermic and it should therefore be added in small portions. Complete dissolution is essential in order to avoid the formation of dark tar-like by-products.
5. The longer the solution boils the more tar-like by-product is formed. One to two min of boiling are necessary and sufficient for complete conversion of the reactants.
6. The reaction mixture must not be cooled to 0°C as this leads to the precipitation of inorganic salts.
7. The long period is necessary to obtain maximum yield.
8. Spectral characteristics are as follows: IR (KBr) cm^{-1} : 3390 m (O-H), 1660 s (C=O), 1618 s (C=N), 1546, 1486, 1460 s (C=C), 1260 s (C-F)], 1021 m [ν(N-O)], 756 s [$\nu(C\text{-}H)_{arom}$] ; ^1H NMR (CD_3OD, 500.13 MHz) δ: 7.09 (m, 3 H, H-3, H-4, H-5), 7.53 (s, 1 H, HC=NOH), 7.94 (m, 1 H, H-6) ; ^{13}C NMR (CD_3OD,75.47 MHz) δ: 116.33 (d, $^2J_{F,3}$ = 19.8, C-3), 124.76 (C-5), 125.47 (d, $^3J_{F,6}$ = 4.0, C-6), 126.53 (d, $^2J_{F,1}$ = 11.3, C-1), 126.99 (d, $^3J_{F,4}$ = 7.9, C-4), 144.01 (HC=NOH), 155.42 (d, $^1J_{F,2}$ = 245.3, C-2), 162.88 (C=O) .
9. Anilide **2** has to be completely dry. Residual water reacts violently with the acid with heat generation causing decomposition.
10. By-products form if the temperature is too high. Anilide **2** does not dissolve completely if the temperature is below 50°C and then the reaction does not go to completion.
11. The progress of the reaction can be monitored by hydrolysis of a sample, extraction with ethyl acetate , and TLC [silica gel Macherey, Nagel & Co. "Polygram Sil G/UV 254", petroleum ether/ethyl acetate/acetic acid 99:50:1, UV visualization, R_f (**2**) = 0.40, R_f (**3**) = 0.31 (yellow spot)].
12. If the temperature is too high, tar-like by-products form. If the solution is cooled to 0°C, hydrolysis does not take place because the sulfuric acid does not mix with the hydrolysis solution and mainly oxime **5** is obtained.
13. The presence of ethyl acetate is essential as otherwise the yellow oxime **5** (mp 233-235°C) is formed in yields of 20-30%. Ethyl acetate is added in order to extract the isatin **3** from the aqueous phase immediately upon formation. Oxime **5** is probably formed by reaction of isatin **3** with hydroxylamine generated by decomposition of unreacted anilide **2**.[2]



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Spectral characteristics of 7-fluoroisatin 3-oxime (**5**) are as follows: TLC: silica gel Macherey, Nagel & Co. "Polygram Sil G/UV 254", petroleum ether/ethyl acetate PE/EE 2:1 elution, 2 drops of glacial acetic acid , UV visualization, R_f = 0.19; IR (KBr) cm^{-1}: ≈3500 m, br (OH), 1723 s (C=O), 1640 s (C=N), 1596, 1494, 1445 m (C=C), 1208 m (C-F), 942 m (N-O), 794 w νC-H_{arom}) ; ^{1}H NMR (acetone-d_6, 500.13 MHz) δ: 7.06 (ddd, 1 H, $^4J_{5,F}$ + 4.6, $^3J_{4,5}$ = 7.5, $^3J_{5,6}$ = 8.5, H-5), 7.20 (ddd, 1 H, $^4J_{4,6}$ =1.1, $^3J_{5,6}$ = 8.5, $^3J_{6,F}$ = 10.1, H-6), 7,83 (dd, 1 H, $^4J_{4,6}$ = 1,0, $^3J_{4,5}$ = 7.0, H-4), 10.14 (bs, 1 H, N-H), 12.75 (bs, 1H, N-OH) ; ^{13}C NMR (acetone-d_6, 125.76 MHz) δ: 115.75 (d, $^3J_{F,3}$ = 4.2, C-3a), 115.96 (C-6), 120.33 (C-5), 120.43 (C-4), 126.40 (d, $^2J_{F,8}$ = 13.4, C-7a), 140.65 (d, $^4J_{F,2}$ = 4.1, C-3), 143.85 (d, $^1J_{F,7}$ = 243,2, C-7), 161.71 (C-2) ; HR-MS (EI, direct insert): m/z 180.03322 (M^+ exact mass calcd for $C_8H_5O_2N_2F$: 180.0335), 163.0070 (M^+ - OH), 152.0365 (M^+ - CO), 135.0359 (M^+ - CO_2H), 108.0271 (M^+ - CO - OH - HCN). Anal. Calcd for $C_8H_5FN_2O_2$: C, 53.43; H, 2.80; N, 15.55. Found: C, 53.34; H, 3.08; N, 15.28.

14. If the aqueous phase is extracted more than twice, the yield may rise, but the oxime **5** and other by-products are extracted as well.

15. Spectral characteristics are as follows: IR (KBr) cm^{-1}: 3446 w (NH-CO), 1737 s (C3=O), 1637 s (C2=O), 1602, 1495, 1452 m (C=C), 1209 m (C-F), 780 w (C-$H)_{arom}$; ^{1}H NMR (acetone-d_6, 500.13 MHz) δ: 7.14 (ddd, 1 H, $^4J_{5,F}$ = 4.2, $^3J_{4,5}$ = 7.7, $^3J_{5,6}$ = 8.3, H-5), 7.39 (dd, 1 H, $^4J_{4,6}$ = 1.1, $^3J_{4,5}$ = 7.4, H-4), 7.48 (ddd, 1 H, $^4J_{4,6}$ = 1.0, $^3J_{4,5}$ = 8.4, $^3J_{6,F}$ = 10.2, H-6), 10.45 (bs, 1 H, N-H) ; ^{13}C NMR (acetone-d_6, 125.76 MHz) δ: 119.15 (d, $^3J_{F,3}$ = 3.4, C-3a), 119.26 (d, $^4J_{F,4}$ = 3.5, C-4), 122.52 (d, $^3J_{F,5}$ = 5.3, C-5), 123.57 (d, $^2J_{F,6}$ = 17.6, C-6), 136.20 (d, $^2J_{F,8}$ = 13.9, C-7a), 146.38 (d, $^1J_{F,7}$ = 246.8, C-7), 157.29 (C-2), 181.70 (d, $^4J_{F,2}$ = 4.5, C-3) .

16. Previously[3] 3 N or 10 N NaOH was used. The submitters found that this reaction also proceeds to completion at room temperature in 1 N NaOH solution.

17. Monitoring was carried out by extracting acidified samples with ethyl acetate and TLC [silica gel Macherey, Nagel & Co. "Polygram Sil G/UV 254", petroleum ether/ethyl acetate/acetic acid 99:50:1, visualization of spots by UV R_f = 0.37 (spot shows strong blue fluorescence)].

18. Spectral characteristics of **4** are as follows: IR (KBr) cm^{-1}: 3500-3391 m (NH_2), 3085 m, br (CO_2-H), 1678 s (C=O), 1630 w (C-NH_2)], 1590, 1562, 1476 m (C=C)], 780 w (C-H_{arom}) ; ^{1}H NMR (acetone-d_6, 500.13 MHz) δ: 6.58 (ddd, 1 H, $^4J_{5,F}$ = 4.9, $^3J_{5,6}$ = 7.9, $^3J_{4,5}$ = 8.0, H-5), 6.84 (bs, 1 H), 7.19 (ddd, 1 H, $^4J_{4,6}$ = 1.3, $^3J_{4,5}$ = 8.0, $^3J_{4,F}$ = 11.6, H-4), 7.31 (bdd, 1 H), 7.63 (bd, 1 H), 7.67 (ddd, 1 H, $^3J_{6,F}$ = 1.3, $^4J_{4,6}$ = 1.3, $^3J_{5,6}$ = 7.9, H-6) ; ^{13}C NMR (acetone-d_6, 125.76 MHz) δ: 108.71 (d, $^3J_{F,1}$ = 4.5, C-1), 110.30 (d, $^3J_{F,5}$ = 7.0, C-5), 114.51 (d, $^2J_{F,4}$ = 18.5, C-4), 122.97 (d, $^4J_{F,6}$ = 3.0, C-6), 136.35 (d, $^2J_{F,2}$ = 14.0, C-2), 147.55 (d, $^1J_{F,3}$ = 237.4, C-3), 165.27 (d, $^4J_{F,7}$ = 3.4, C-7) .

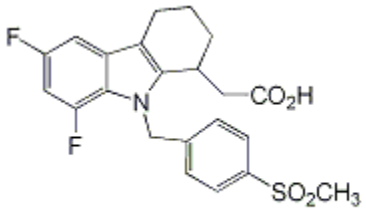
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

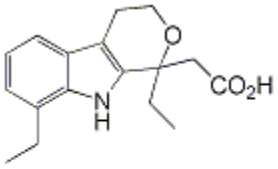
3. Discussion

Anthranilic acids are important intermediates for the preparation of heterocycles. The previously described procedure,[3] used here as the starting point, works well for compounds not containing electron-withdrawing substituents. This modified procedure thus extends the range of applicability.

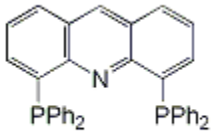
2-Amino-3-fluorobenzoic acid is an important intermediate in the synthesis of derivatives of indole , such as the potent and selective thromboxane/prostaglandin endoperoxide receptor antagonist L-670,596[4] or the anti-inflammatory agent Etodolac.[5] Compounds of this type have therapeutic applications. 2-Amino-3-fluoro-benzoic acid is also an important precursor for the synthesis of fluoroacridines, which can be converted to interesting tridentate ligands, such as Acriphos.[6]



L-670,596



Etodolac



Acriphos

The steps described above at least triple yields that were previously reported;[3] in particular the yield of the second step is improved significantly. No chromatography is required for purification and all reactions can be carried out on a larger scale, the only limiting factor being the scale of the laboratory equipment. Of advantage is the use of water as solvent in all three steps.

In order to assess the generality of this procedure for the preparation of acceptor-substituted anthranilic acids it was applied to 2-amino-3-chlorobenzoic acid , which was obtained with excellent overall yield of 53% (lit.[3]: 16%).

References and Notes

1. Organisch-Chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany and (S.R.O.) Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470 Mühlheim an der Ruhr, Germany.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-Amino-3-fluorobenzoic acid:
Anthranilic acid, 3-fluoro- (8);
Benzoic acid, 2-amino-3-fluoro- (10); (825-22-9)

N-(2-Fluorophenyl)-2-(hydroxyimino)acetamide:
Acetamide, N-(2-fluorophenyl)-2-(hydroxyimino)- (9); (349-24-6)

Hydroxylamine hydrochloride (8);
Hydroxylamine, hydrochloride (9); (5470-11-1)

2,2,2-Trichloro-1-ethoxyethanol:
Ethanol, 2,2,2-trichloro-1-ethoxy- (8,9); (515-83-3)

2-Fluoroaminobenzene:
Aniline, o-fluoro- (8);
Benzenamine, 2-fluoro- (9); (348-54-9)

7-Fluoroisatin:
1H-Indole-2,3-dione, 7-fluoro- (8,9); (317-20-4)

Hydrogen peroxide (8,9); (7722-84-1)

7-Fluoroisatin 3-oxime:
1H-Indole-2,3-dione, 7-fluoro-, 3-oxime (13); (143884-84-8)