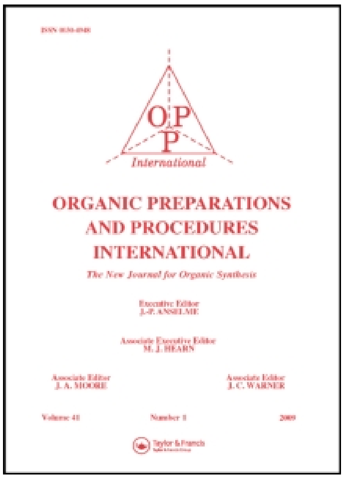

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SYNTHESIS OF 2-HALO-4,5-DIFLUOROBENZOIC ACIDS

Tamim F. Braish[a]; Darrell E. Fox[a]
[a] Central Research Division, Pfizer Inc., Process Research and Development, Groton, CT

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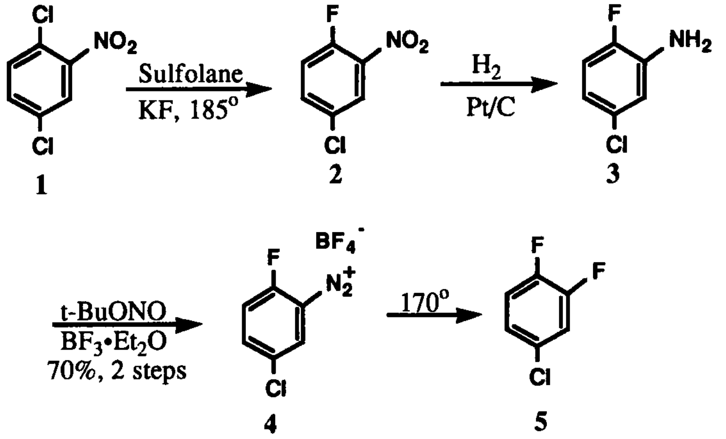
SYNTHESES OF 2-HALO-4,5-DIFLUOROBENZOIC ACIDS

Submitted by (05/09/91)
Tamim F. Braish* and Darrell E. Fox

Central Research Division
Pfizer Inc., Process Research and Development
Groton, CT 06340

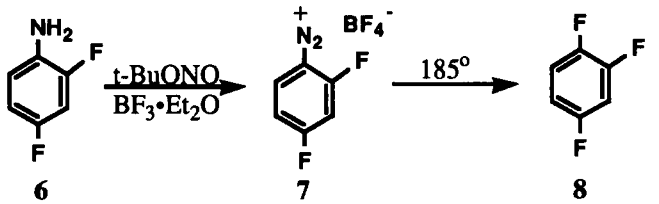
Most of the reported syntheses of trihalobenzoic acids suffer from being lengthy or the use of expensive starting materials[1]. Recently, O'Rielly *et al.* described an expedient route to 2,4,5-trifluorobenzoic acids[2] based on the selective monodechlorination of tetrachlophthalic anhydride to 3,4,6-trichlorophthalic acid.[3] Herein we report efficient syntheses of 2-chloro-4,5-difluoro- and 2,4,5-trifluorobenzoic acids from readily available starting materials, by utilizing halogen-fluorine exchange and the Balz-Schiemann reaction[7] to introduce the fluorines.

1,4-Dichloro-2-nitrobenzene was first heated in sulfolane in the presence of KF for 24 h at 190°, to give 1-fluoro-4-chloro-2-nitrobenzene in 52% yield. Nitro group activation of the *ortho* and *para* positions in aromatic rings towards halogen-fluoride exchange is well documented.[4] One important observation worth mentioning is the fact that this reaction is extremely moisture sensitive: it was necessary to treat solutions of **1** in sulfolane with 4A° molecular sieves for 24 hrs prior to heating them with dry potassium fluoride. The resulting nitro compound was hydrogenated over platinum on carbon to provide the compound **3**[5] in 80% yield. Compound **3** was treated with *t*-butyl nitrite in the presence of boron trifluoride etherate[6] to provide the diazonium tetrafluoroborate salt **4** in 97% yield. Pyrolysis of **4** neat at 165° in a flask fitted with a distillation head afforded 1-chloro-3,4-difluorobenzene in 49% yield.



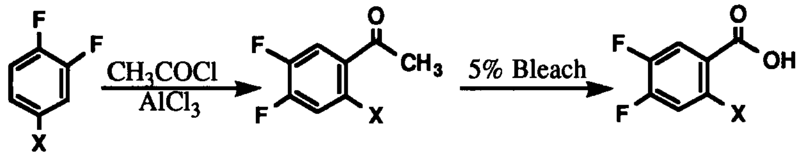
2,4,5-Trifluorobenzoic acid was synthesized in a similar fashion. This synthesis was more straightforward since 2,4-difluoroaniline (**6**) is commercially available. In this case, 1,2,4-trifluorobenzene (**8**) was distilled from the pyrolysis reaction of the diazonium tetrafluoroborate **7**.

This constitutes a more direct and efficient synthesis of this compound than that reported by Schiemann.[7]



6 7 8

Friedel-Crafts acylation of **5** or **8** with acetyl chloride in the presence of aluminum chloride provided the acetophenones **9** (80%) and **10** (87%) respectively.[8] Oxidation of the acetophenones with 5% bleach (Haloform Reaction[9]) provided the desired trihalobenzoic acid **11**[10] and **12** in excellent yields.



5 X = Cl
8 X = F

9 X = Cl, 80%
10 X = F, 87%

11 X = Cl, 90%
12 X = F, 95%

EXPERIMENTAL SECTION

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on a Brucker 300MHz spectrometer using TMS as an internal standard. Infrared spectra were recorded on a Perkin-Elmer 283B spectrophotometer in $CHCl_3$. Microanalyses were performed by the Pfizer Analytical Department. All reagents were used as received without any purification.

2-Fluoro-4-chloronitrobenzene (**2**).- To a solution of 2,5-dichloronitrobenzene (50g, 262 mmol) in 180 ml of sulfolane was added 5g of powdered 4A° sieves and the mixture was allowed to stir for 24 hrs and was then filtered through a minimum amount of Celite. To the filtrate were added 1.2 g of 18-crown-6 and KF (30.4g, 523 mmol) and the mixture was heated at 180° for 32 hrs. The reaction was then quenched with 200 ml of water and extracted with hexane (6 x 200 ml). The combined organic layers were washed with water (2 x 50 ml) and dried over $MgSO_4$. The solvent was then evaporated and the product was distilled through a 10 cm column of glass beads to give 23.9 g (52%) of a tan oil, bp. 68°/2.2 mm. Hg. ^{1}H NMR ($CDCl_3$): δ 8.04 (m, 1H); 7.6 (m, 1H); 7.28 (m, 1H).

Anal. Calcd for $C_6H_3ClFNO_2$: C, 41.05; H, 1.72; Cl, 20.2; F, 10.81; N, 7.98

Found: C, 41.10; H, 1.70; Cl, 20.1; F, 10.75; N, 7.90

2-Fluoro-5-chlorophenyldiazonium Tetrafluoroborate (**4**).- To 2-fluoro-4-chloronitrobenzene (10.0 g, 57.1 mmol) was added 80 ml of dimethoxyethane and 1 g of 5% Pt on carbon catalyst (50% wet) and the mixture was hydrogenated under 50 psi of hydrogen using a Parr shaker. After 24 hrs, the reaction mixture was filtered under nitrogen and the filtrate was cooled to -20° before boron trifluoride etherate (10.6 ml, 85.7 mmol) was added. The reaction was allowed to stir at 20° for 15 min, and *t*-butyl nitrite (8.11 ml, 68.5 mmol) in 10 ml of dimethoxyethane was then added over a period of 30 min. The reaction mixture was then warmed to -5° and allowed to stir for 1 hr. The precipitate formed was collected and air dried to give 13.5 g (97%) of the diazonium salt, mp. 145° (dec.). ^{1}H NMR (D_2O): δ 8.70 (m, 1H), 8.40 (m, 1H), 7.86 (t, 1H). After 4 hrs in D_2O, the corresponding difluorophenol began to form.

3,4-Difluoro-1-chlorobenzene (**5**).- 2-Fluoro-5-chlorophenyldiazonium tetrafluoroborate (6.0 g, 24.5 mmol) in a flask fitted with a distillation head was heated to 185° (oil bath temperature, 170° internal temperature) for 30 min after which an oil began to distill, bp. 118-120°. This oil (1.79 g, 49%) was identical in all respects to an authentic sample purchased from Aldrich. NMR ($CDCl_3$): δ 7.15 (m, 1H), 7.08 (m, 2H).

3,4-Difluorophenyldiazonium Tetrafluoroborate (**7**).- 2,4-Difluoroaniline (10.0 g, 77.5 mmol) was dissolved in 20 ml of dimethoxyethane and added to a cold (-5°C) solution of boron trifluoride·etherate (16.5 g, 116 mmol) in 35 ml of dimethoxyethane. After 30 min the reaction was cooled to -15° and *t*-butyl nitrite (9.58 g, 93.0 mmol) in 30 ml of DME was added (30 min) and the reaction was allowed to warm to -5°. The diazonium salt precipitated out of the reaction mixture over a period of 1 hr and was then collected and dried (16.9 g, 96% yield). ^{1}H NMR (D_2O): δ 8.78 (m, 1H), 7.78 (m, 1H), 7.63 (m, 1H).

1,2,4-Trifluorobenzene (**8**).- The Diazonium salt **7** (5.0 g, 21.9 mmol) was heated neat in a flask fitted with a short path distillation head at 185° for 1 hr. The trifluorobenzene distilled at 86-88° and was trapped at 0° (1.50 g, 52% yield). The sample was identical in all respects to an authentic sample purchased from Aldrich.

2,4,5-Trifluoroacetophenone (**10**).- 1,3,4-Trifluorobenzene (10.0 g, 75.7 mmol) and aluminum trichloride (15.1 g, 113.2 mmol) and acetyl chloride (5.92 ml, 83.3 mmol) were mixed in a sealed tube and heated to 80° for 24 hrs. The reaction mixture was cooled and quenched with 200 g of ice and extracted with CH_2Cl_2 (3 X 100 ml). The combined organic layers were dried and evaporated to afford 11.5 g (87%) of a colorless oil.[10] ^{1}H NMR ($CDCl_3$): δ 7.75 (m, 1H); 7.01 (m, 1H); 2.62 (d, 3H).

Anal. Calcd for $C_8H_5F_3O$: C, 55.18; H, 2.89; F, 32.73 Found: C, 55.10; H, 2.79; F, 32.69

2,4,5-Trifluorobenzoic Acid (**12**).- 2,4,5-Trifluoroacetophenone (30.0 g, 172 mmol) and 1.2 l of 5% NaOCl (Clorox brand bleach) were heated to reflux for 6 hrs. The reaction was cooled and the pH of the reaction was adjusted to 1 with conc. HCl solution. The mixture was then extracted with 200 ml of CH_2Cl_2 and dried over $MgSO_4$. Evaporation of the solvent provided 28.8 g (95%) of a colorless solid, mp. 95-96°, lit.[11] mp. 93-95°. ^{1}H NMR ($CDCl_3$): δ 7.88 (m, 1H); 7.03 (m, 1H).

Anal. Calcd for $C_7H_3F_3O_2$: C, 47.75; H, 1.72; F, 32.37 Found: C, 47.82; H, 1.70; F, 32.43

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AN IMPROVED PREPARATION OF QUINUCLIDIN-3-THIOL

Submitted by
(12/12/90)

S. D. Aster*, S. S. Yang and G. D. Berger

Merck Sharp and Dohme Research Laboratories
P. O. Box 2000, RY121E-2236
Rahway, NJ 07065-0900

In the course of an ongoing synthesis program, we desired multigram quantities of quinuclidin-3-thiol (**1**). This compound has previously been prepared by Shaw[1] and by Barriere.[2]