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SYNTHESIS OF 2-BROMO-4,5-DIFLUOROBENZOIC ACID

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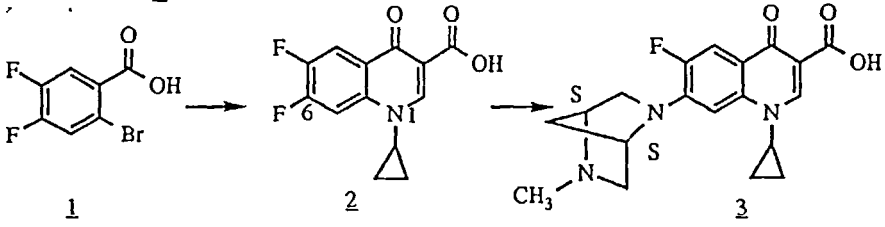
Abstract: The synthesis of 2-bromo-4,5-difluorobenzoic acid was achieved from difluorophthalic anhydride by either using a Losen rearrangement or the Barton bromodecarboxylation reaction.

Introduction:

2-Halo-4,5-difluorobenzoic acids[1] are important starting materials in the synthesis of the difluoroquinolone 2. Reaction of 2 with (S,S)-2-methyl-2,5-diazabicyclo[2.2.1] heptane[2] provides the totally synthetic quinolone antibacterial danofloxacin 3[3].



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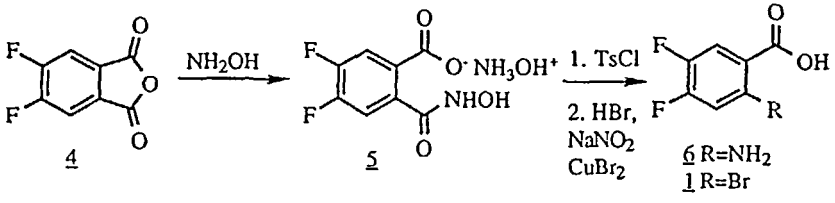
The synthesis of the nucleus 2, from trihalobenzoic acids has been accomplished using several well established methods[4]. Most of the reported syntheses of trihalobenzoic acids suffer from being lengthy or the use of expensive starting materials and difficult to execute reactions on large scales[5,6].

Recently, a report by O'Rielly *et al*[7] described an expedient route to 2,4,5-trifluorobenzoic acids based on the selective monodechlorination of tetrachlophthalic anhydride to 3,4,6-trichlorophthalic acid[8].

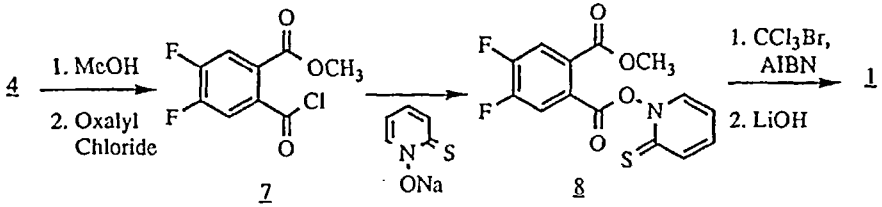
This report prompted us to communicate our results in this area and herein two efficient syntheses of 2-bromo-4,5-difluorobenzoic acid from one common intermediate 4,5-difluorophthalic anhydride 4 are described.

4,5-Difluorophthalic anhydride 4 is a readily available starting material produced by the chlorine-fluorine exchange of dichlorophthalic anhydride, and its conversion to 4,5-difluoroanthranilic acid via a Hoffman rearrangement is known[9]. In our hands this process could not be successfully scaled up[10] and we therefore sought modifications to this chemistry. Treatment of the anhydride 4 with hydroxylamine provided the hydroxamic acid hydroxylamine salt 5 in 78% yield. When 5 was treated with p-toluenesulfonyl chloride in the presence of aqueous base, the Losen rearrangement[11] product 6 was obtained in 80% yield (from 5). The sequence (4 to 6) may be achieved in one pot and an overall yield of 55%. Sandmeyer reaction with *t*-butylnitrite in the presence of copper (II) bromide[5] provided the title compound 1 in 72%.



4 5 6 R=NH2 1 R=Br

Alternatively, the anhydride of 4 was treated with methanol followed by oxalyl chloride to obtain 7 in quantitative yield. Attempts to decarbonylate 7 to methyl-2-chloro-4,5-difluorobenzoate with Wilkinson's catalyst failed[12]. Treatment of 7 with the sodium salt of 2-thio-1-hydroxypyridine provided 8 in 75% yield. Heating 8 in trichlorobromomethane in the presence of AIBN[13] followed by saponification of the resulting ester provided 1 in 45% overall yield from 4.



The two procedures could be easily scaled up to make multigram quantities of the title compound without any complications.

EXPERIMENTAL

Melting points were determined with Thomas-Hoover capillary melting point apparatus and were uncorrected. NMR spectra were recorded on a Brucker 300MHz spectrometer in $CDCl_3$ unless noted otherwise. Infrared spectra were recorded on a Perkin-Elmer 283B spectrophotometer in $CHCl_3$. Microanalyses were performed by the Pfizer Analytical Department. 2,2'-Azobis-2-methyl propionitrile (AIBN) was purchased from Pfaltz &Bauer. All other reagents were purchased from Aldrich. All reagents were used as they were received without any purification.

Synthesis of 4,5-difluoroanthranilic acid 6 from 4,5-dichlorophthalic anhydride:

To 4,5-dichlorophthalic anhydride (1.0 g, 4.61 mmol) in 4 ml of dry sulfolane[14] was added potassium fluoride (0.94 g, 16.1 mmol) and the reaction was heated to

185°C for 2 h. The reaction was then cooled to room temperature and hydroxylamine.hydrochloride (0.64g, 9.22 mmol) was added as a solution in 4.6 ml of 3M KOH. The reaction was allowed to stir at room temperature for 2 additional hours. To this mixture was added more KOH (0.74 g) and p-toluenesulfonyl chloride (2.2 g, 11.53 mmol), and stirring was continued overnight. The pH of the reaction was adjusted to 12 with KOH and the sulfolane was extracted with 4X15 ml portions of diisopropyl ether. The pH was then adjusted to 4 with 10% HCl solution and extracted with 4X15 ml of diisopropyl ether. The combined organic layers were dried and evaporated to provide 245 mg of 4,5-difluoroanthranilic acid which represented a 31% yield. NMR($CDCl_3$): 7.70 (dd, 1H), 6.44 (dd, 1H).

Synthesis of intermediate 5:

Sodium methoxide was generated by the addition of Na (6.37 g, 277 mmol) to 250 ml of methanol at room temperature. To this was added hydroxylamine hydrochloride (19.2 g, 277 mmol) in 100 ml of methanol over a period of 30 min. A white precipitate formed and was removed by filtration. The filtrate was cooled with an ice bath (5°C) and 4,5-difluorophthalic anhydride 4 (17.0 g, 92.3 mmol) was added in portions (15 min). The reaction was allowed to warm to room temperature and allowed to stir for 3 h. A precipitate formed which was isolated by filtration and dried at 40°C *in vacuo* to provide 17.5 g of 5 (78% yield).

Synthesis of 4,5-difluoroanthranilic acid 6 from 5:

The hydroxamic acid 5 (1.0 g, 4.00 mmol) was added to 15 ml of 10% NaOH aq. solution. A transient red-colored solution developed which turned to a pale amber color. The reaction was cooled to 0°C and p-toluenesulfonyl chloride

(1.68 g, 8.80 mmol) was added. The reaction was allowed to stir for 16 h. The pH was then adjusted to 4.5 using 1N aq. HCl solution and the reaction was extracted with isopropylether (2X50 ml). The combined organic layers were dried ($MgSO_4$) and evaporated to provide 550 mg of 6 as a white solid (80% yield) which required no purification. M.P.= 171-172°C (Lit 176-178°C[5]). NMR($CDCl_3$): 7.70 (dd, 1H), 6.44 (dd, 1H).

Synthesis of 2-bromo-4,5-difluorobenzoic acid 1 from 6:

A slurry of anhydrous copper (II) bromide (7.45 g, 33.0 mmol) in 150 ml of anhydrous acetonitrile was cooled to 0°C and 90% t-butyl nitrite (5.68 ml, 43.0 mmol) was added. The mixture turned dark green and the 4,5-difluoroanthranilic acid (5.0 g, 29.0 mmol) was added in portions over a period of 5 min. After 2 h at 0°C the reaction was warmed to room temperature and allowed to stir overnight. The solvent was then evaporated to half the original volume and 70ml of 1M HCl solution was added. The product was extracted with 60 ml of *iso*-propyl ether and was purified by adding 10% KOH solution to the ether extracts. Acidification of the aq. layer to pH 2 and extracting the product with 50 ml of isopropylether. The extracts were dried ($MgSO_4$) and evaporated to provide 11.5 g of the solid (M.P. 111-113°C, 95% crude yield and required no purification). NMR($CDCl_3$): 7.93 (dd, 1H), 7.56 (dd, 1H). A small sample was recrystallized from toluene for elemental analysis. Analytical calculated for $C_7H_3BrF_2O_2$: C, 35.48; H, 1.28; Found: C, 35.45; H, 1.33.

Synthesis of intermediate 7:

The difluorophthalic anhydride (2.36 g, 12.8 mmol) was heated in 15 ml of methanol until the reaction turned homogeneous (10 min). The solvent was then evaporated and *in vacuo* and 15 ml of dichloromethane and oxalyl chloride (2.48

mmol, 1.2 ml) were added and the mixture was allowed to stir for 16 h. Evaporation of the solvent *in vacuo* provided 7 in quantitative yield. NMR($CDCl_3$): 7.70 (dd, 1H), 7.58 (dd, 1H), 3.94 (s, 3H).

Synthesis of intermediate 8:

Intermediate 7 (2.5 g, 10.66 mmol) was dissolved in 100 ml of THF and the sodium salt of 2-thio-1-hydroxypyridine (1.67 g, 11.19 mmol) was added. The mixture was allowed to stir for 24 h. The THF was evaporated *in vacuo* and the residual oil was partitioned between 50 ml of water and 75 ml of dichloromethane. The organic layer was washed with 20 ml of water and dried over $MgSO_4$. Evaporation of the solvent provided an oil which crystallized upon the addition of 20 ml of isopropyl alcohol. Ester 8 was isolated as a yellow solid by filtration and air drying. M.P.= 117-118°C. NMR($CDCl_3$): 8.08 (dd, 1H, fluoroaromatic), 7.95 (dd, 1H), 7.88 (dd, 1H, fluoroaromatic), 7.74 (dd, 1H), 7.28 (m, 1H), 6.74 (m, 1H). Analytical calculated for $C_{14}H_9F_2NO_4S$: C, 51.69; H, 2.79; N, 4.31; S, 9.86. Found: C, 51.56; H, 2.61; N, 4.25; S, 9.85.

2-Bromo-4,5-difluorobenzoic acid 1:

Intermediate 8 (400 mg, 1.23 mmol) and bromotrichloromethane (10 ml) were heated to reflux while AIBN (35 mg, 0.25 mmol) in 4 ml of bromotrichloromethane was added via a syringe pump over a period of 10 hours, and reflux was continued for 6 additional hours. The solvent was evaporated and the residual oil was suspended in 5 ml of THF and 10 ml of water and LiOH (1.85 mmol, 77 mg) was added. The mixture was allowed to stir at room temperature for 3 h. Evaporation of the THF in vacuo followed by adding 20 ml of 10% aq. HCl solution allowed for formation of a solid which was filtered and air dried. The solid (62% yield) was identical in all respect to the 2-bromo-4,5-difluorobenzoic acid made from the Sandmeyer procedure reported above.

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