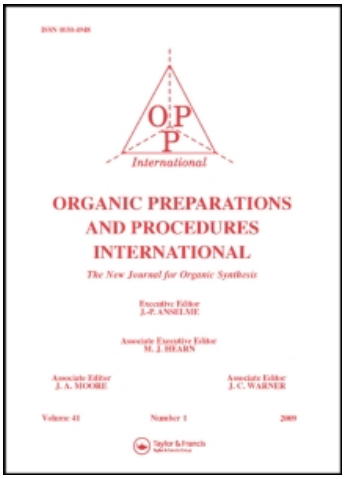

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SYNTHESES OF 2-CHLORO-4,5-DIFLUOROBENZOIC ACID

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SYNTHESES OF 2-CHLORO-4,5-DIFLUOROBENZOIC ACID

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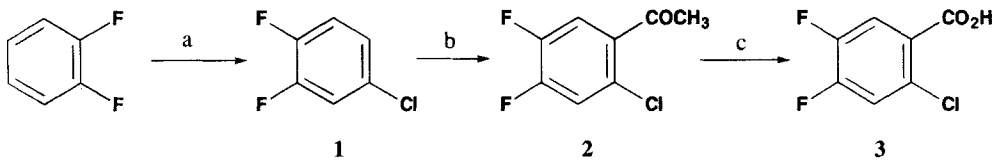
2-Chloro-4,5-difluorobenzoic acid (**3**) is an important intermediate of medicinal products and pesticides. It can be synthesized from dichlorophthalic anhydride,[1] 1,4-dichloro-2-nitrobenzene,[2] dichlorofluorobenzonitrile,[3] 4,5-difluorophthalic acid[4] and 2,4-dichlorofluorobenzene.[5] However, all these methods are either laborious or use expensive reagents. We now report an efficient synthesis of **3** from *o*-difluorobenzene, which is commercially available or which may be easily synthesized from 2-nitrochlorobenzene by halogen-fluorine exchange[6] and by the Balz-Schiemann reaction[7] to introduce the fluorine atoms.

Chlorination of *o*-difluorobenzene in the presence of $FeCl_3$ and Cl_2 provided 3,4-difluorochlorobenzene (**1**) in 90% yield. Friedel-Crafts acylation of **1** with acetyl chloride in the presence of aluminum chloride provided the compound **2** (75%), which upon oxidation with NaOCl provided 2-chloro-4,5-defluorobenzoic acid (**3**) in 80% yield.



1 **2** **3**

a) Cl_2, $FeCl_3$ b) CH_3COCl, $AlCl_3$ c) NaOCl

EXPERIMENTAL SECTION

Mps reported are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ containing TMS as internal reference (chemical shifts in δ, ppm). Microanalyses were performed by our Analytical Department.

3,4-Difluorochlorobenzene (1).- Through a mixture of *o*-difluorobenzene (114g, 1.0 mol) and $FeCl_3$ (2.0g, 12 mmol) was bubbled chlorine gas (56.8g, 0.8 mol) at 50° over 3 hrs; the mixture was washed with water (3 x 200 mL) and dried over $MgSO_4$. and then distilled through a 15 cm column of glass beads to give 134g (90%) of a colorless oil, bp. 118-120°, lit.[2] bp. 118-120°. ^1H NMR ($CDCl_3$): δ 7.14 (m, 1H), 7.07 (m, 2H).

2-Chloro-4,5-difluoroacetophenone (2).- 3,4-Difluorochlorobenzene (149g, 1.0 mol) and aluminum chloride (267g, 2.0 mol) and acetyl chloride (109g, 1.4mol) were mixed and heated to 60° for 9 hrs. The reaction mixture was cooled and quenched with 800g ice and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were steam-distilled to give an oily product, which was distilled

through a 15 cm column of glass beads to give 143.2g (75%) of a colorless oil, bp. 65-67°/5mmHg, lit.[5] bp. 65-67°/4-5mmHg. ^{1}H NMR ($CDCl_3$): δ 7.74 (m, 1H), 7.02 (m, 1H), 2.61 (d, 3H).

2-Chloro-4,5-difluorobenzoic Acid (3).- 2-Chloro-4,5-difluoroacetophenone (95.9g, 0.5mol) and 3.5 L of 5% NaOCl were heated to reflux for 6 hrs. The mixture was cooled and its pH was adjusted to 1 with conc. HCl, and then extracted with 800 mL of CH_2Cl_2 and the extract was dried over $MgSO_4$. Evaporation of the solvent provided 89.7g (93%) of a crude product, which was recrystallized from cyclohexane-water (1:1 v:v) to give 77.2g (80%) of a white solid, mp. 86-88°, lit.[8] mp. 87-89°. ^{1}H NMR ($CDCl_3$): δ 7.87 (m, 1H), 7.01 (m, 1H).

Anal. Calcd for $C_7H_3F_2ClO_2$: C, 43.64; H, 1.56; Cl, 18.44; F, 19.74
Found: C, 43.54; H, 1.54; Cl, 18.56; F, 19.70

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