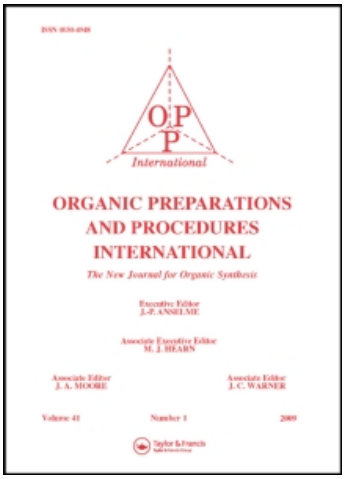

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ISOMER-SELECTIVE SYNTHESES OF 2,6-DICHLORO-4-NITROTOLUENE AND 2,4-DIFLUOROANILINE

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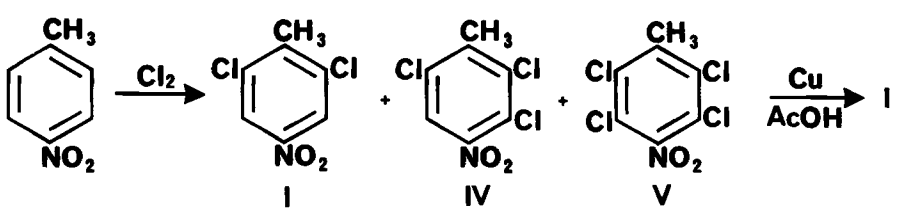
We report herein isomer-selective syntheses of 2,6-dichloro-4-nitrotoluene (**I**) and 2,4-difluoroaniline (**II**), which are important intermediates for the preparation of the coccidiostat 2,6-dichloro-4-nitrobenzamide[1] and the new analgesic drug Diflunisal[2].

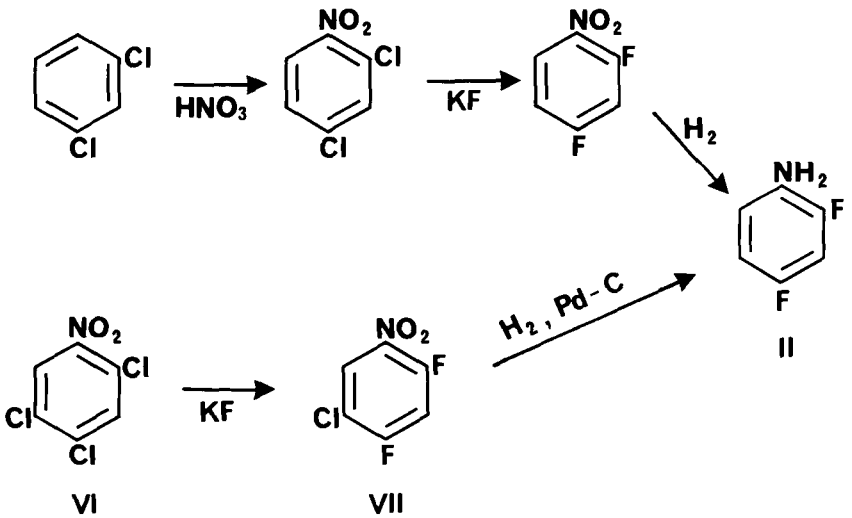
In connection with the synthesis of 2,6-dichloro-4-nitrobenzamide we required large quantities of **I** as an intermediate. The published preparation of **I** *via* dichlorination of *p*-nitrotoluene[3] proceeds in low yield (*ca*. 30 %) as a consequence of a non-selective chlorination leading to a difficultly separable mixture of 2,6-dichloro-4-nitrotoluene (**I**) and 2,5-dichloro-4-nitrotoluene (**III**). Our method for **I** employs overchlorination of **I** and **III** to 2,3,6-trichloro-4-nitrotoluene (**IV**), together with a trace of the tetrachloro-4-nitrotoluene (**V**). Selective dechlorination in **IV** and **V** with copper powder and acetic acid[4] yields **I**, 91 % from *p*-nitrotoluene (Scheme I).



Scheme I

A similar strategy was applied to the preparation of 2,4-difluoroaniline (**II**). The current literature method proceeds from mixed o- and p-dichlorobenzenes which are isomerized[5] by aluminum chloride to m-dichlorobenzene and then converted to 2,4-difluoroaniline as shown in Scheme II.

To circumvent the difficult isomerization step, a new procedure was developed which takes advantage of the fact that both o- and p-dichloro benzenes are chlorinated further to the same 1,2,4-trichlorobenzene. Nitration followed by the halogen exchange of **VI** provides 2,4-difluoro-5-chloronitrobenzene (**VII**). Catalytic hydrogenation results in reduction of the nitro group as well as specific hydrogenolysis of the chlorine atom to give **II** , with no detectable loss of fluoride (Scheme II).



Scheme II

The fluorine displacement step (**VI** to **VII**) is noteworthy. The Swarts reaction[6] usually requires the use of dipolar aprotic solvents (e.g., DMF, DMSO and Sulfolane) and high temperature. By utilizing a solid-liquid phase-transfer catalyst[7] (Aliquat 336)[8] the reaction proceeds in toluene at 110° in 88% yield. 18-Crown-6 has been used for similar aliphatic halide dis-

placements.[9]

Thus, easily obtained polyhalogenated aromatic compounds were used for the isomer-selective preparation of **I** and **II** in high yield.

EXPERIMENTAL

2,6-Dichloro-4-nitrotoluene (**I**)

Chlorination of p-nitrotoluene.- Chlorine was bubbled at a rate of about 1.2 g per minute into a tared 500 mL three-necked flask equipped with a mechanical stirrer, thermometer, gas inlet tube and drying tube, containing a melt of p-nitrotoluene (68.5 g, 0.5 mol) and dry antimony trichloride (11.4 g, 0.05 mol) at 65° . The moderately exothermic reaction was maintained at 65-70° during the chlorination. After a 53 g weight increase was noted, 50 mL of water was added and the mixture was stirred at 70° for 20 min. Benzene (100 mL) was added, the mixture filtered and the precipitate washed with benzene (25 mL). The benzene layer in the filtrate was removed and the aqueous layer was extracted with benzene. The combined benzene extracts were dried ($MgSO_4$) and evaporated in vacuo to dryness to yield 120 g of a mixture of chlorinated nitrotoluenes consisting of **I** (70%), **IV** (25%) and **V** (5%) by vpc analysis.[10]

Reduction of mixed chloronitrotoluenes.- To the chlorinated 4-nitrotoluene mixture (18.8 g) was added 10 mL of chlorobenzene, 5.85 mL of glacial acetic acid and copper-powder (7.3 g). The mixture was then heated at reflux for 21 hrs, during which time the temperature of the reaction mixture gradually rose from 119° to 145°. After cooling, 10 mL of water was added and the chlorobenzene was removed by steam distillation. Benzene (50 mL) was added and the mixture filtered to remove any inorganic material. The insoluble residue was washed with benzene. The combined benzene extracts were shaken with 25 mL of conc. hydrochloric acid to remove any toluidines. The benzene

layer was washed with water and evaporated to dryness in vacuo to yield 15.5 g (91 %) of 2,6-dichloro-4-nitrotoluene, mp. 59-62°, lit.[4] mp. 65° which is 97-99 % pure by vpc analysis.

2,4-Difluoroaniline (II)

Fluorination of 2,4,5-trichloronitrobenzene.- A mixture of 2,4,5-trichloronitrobenzene (5.0 g, 0.022 mol), anhydrous potassium fluoride (3.25 g, 0.056 mol) and Aliquat 336 (3.0 g, 0.006 mol) in 75 mL of toluene was heated at reflux for 140 hrs. The reaction mixture was poured into water (300 mL) and the product separated by steam distillation. Approximately 2 l. of distillate was collected. The distillate was extracted with ether (4 x 70 mL) and washed with water, then 5% sodium hydroxide (35 mL), 50 mL of water and dried over sodium sulfate. Evaporation of the solvent in vacuo gave 3.8 g (88 %) of crude 2,4-difluoro-5-chloronitrobenzene (VII) which is 92% pure[11] by vpc analysis. A pure sample can be obtained by vacuum distillation, bp. 70-72° / 1 mm Hg, lit.[12] bp. 105° / 15 mm Hg.

Hydrogenation of 2,4-difluoro-5-chloronitrobenzene.- A solution of VII (2.0 g, 20.6 mmol) in 30 mL of methanol was hydrogenated over 10 % Pd/C for 20 min at room temperature under 40 psi and then for an additional 4 hrs at 60° under the same hydrogen pressure (Parr apparatus). The catalyst was filtered and washed with methanol (2 x 16 mL). The solvent was evaporated in vacuo, and the residue was extracted with dichloromethane (30 mL). The extract was washed successively with water (15 mL), 5% ammonium hydroxide (70 mL), water (15 mL) and dried (Na_2SO_4). Evaporation of the solvent gave 1.25 g (94 %) of 2,4-difluoroaniline (II) as a pale yellow oil which is 91 % pure[13] by vpc analysis. A pure sample was obtained by distillation, bp. 48-52° / 15 mm Hg, lit.[14] bp. 169.5° /753 mm Hg.

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8. Aliquat 336 ; a mixture of $(\underline{n}\text{-}C_8\text{-}C_{12})_3\overset{+}{N}\text{-}CH_3\ Cl^-$ (from General Mills, Inc.,).
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10. Vpc conditions : column, 10' 20 % QF-1 on GCP ; column temperature, 190^0 ; carrier gas, Helium, 120 mL / min.
11. Partially fluorinated compounds 2-fluoro-4,5-dichloronitrobenzene (**VIII**) and 4-fluoro-2,5-dichloronitrobenzene (**IX**) were isolated from the reaction mixture.

VIII

IX

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13. Partially reduced compounds 2,4-difluoro-5-chloroaniline were isolated from the crude reaction mixture.

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