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AROMATIC FLUORINE CHEMISTRY. PART 4. PREPARATION OF 2,6-DIFLUOROANILINE

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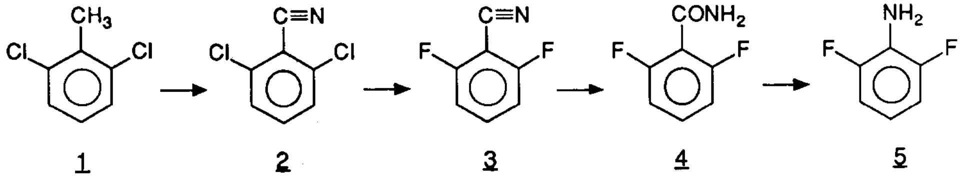
SUMMARY

The preparation of 2,6-difluoroaniline from 1,3,5-trichlorobenzene is described. 1-Chloro-3,5-difluorobenzene prepared via KF exchange on 1,3,5-trichlorobenzene is dichlorinated and nitrated in a single reactor to a mixture of trichlorodifluoronitrobenzenes. The latter are reduced to ~4:1 isomeric mixture of 2,6-difluoroaniline and 2,4-difluoroaniline.

INTRODUCTION

2,6-Difluoroaniline, 5, and 2,6-difluorobenzamide, 4, are valuable intermediates for the preparation of agricultural chemicals [1]. The present technology for the manufacture of 2,6-difluoroaniline is a multistep process that involves (a) ammoxidation of 2,6-dichlorotoluene, 1, to 2,6-dichlorobenzonitrile, 2; (b) conversion of 2 to the fluoro derivative, 2,6-difluorobenzonitrile, 3; (c) hydration of 3 to 2,6-difluorobenzamide, 4; and (d) Hoffmann rearrangement of 4 to 2,6-difluoroaniline, 5. Furthermore, 2,6-dichlorotoluene is not readily available. Separation from other isomers requires the use of zeolites. The alternative is sulfonation, chlorination and desulfonation of



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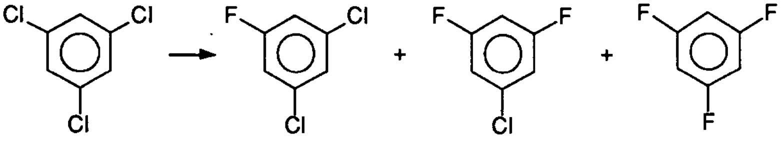
toluene. 2,6-Difluoroaniline has also been prepared by the lithiation of 1,3-difluorobenzene, carbonation to the 2,6-difluorocarboxylic acid and conversion of the acid moiety to the amine with hydrazoic acid (Schmidt reaction) [3].

RESULTS AND DISCUSSION

The meta fluorine substitution pattern of 1-chloro-3,5-difluorobenzene, 8, provided a potential precursor for the synthesis of 2,6-difluoroaniline. 1-Chloro-3,5-difluorobenzene has been prepared by Finger and coworkers by KF exchange on 1,3,5-trichlorobenzene. The synthesis described by Finger [4] utilized dimethyl sulfone as the solvent for the KF exchange reaction. In the present work, 1,3-dimethyl-2-imidazolidinone ("dimethyl ethylene urea") was found to provide a significant improvement over dimethyl sulfone. The results of the KF exchange reaction utilizing a Parr reactor are summarized in Table 1. The results demonstrate that 1-chloro-3,5-difluorobenzene can be prepared in good yield with minimum formation of 1,3,5-trifluorobenzene, 9, by carrying out the exchange reaction at 270-280°C and recycling the monofluorodichlorobenzene intermediate 7.

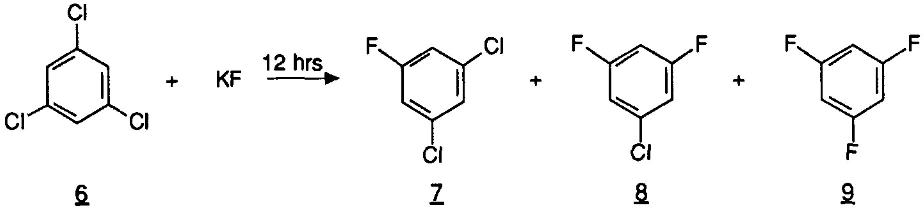


6 7 8 9

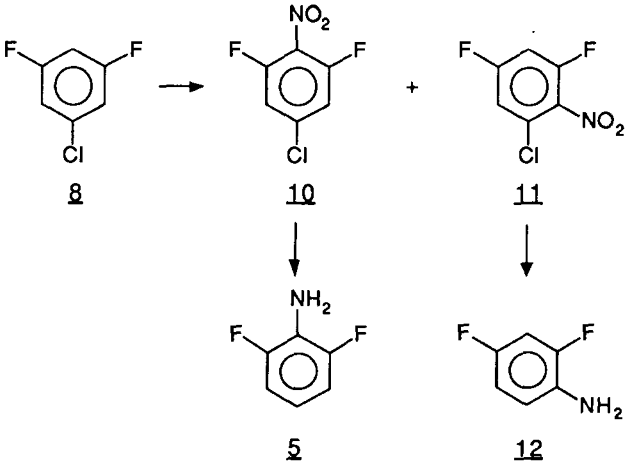
The reaction sequence for the conversion of 8 → 5 is illustrated in Scheme 1. Nitration of 8 gave a 4:1 isomer mixture of chlorodifluoronitrobenzenes, 10 and 11. Reduction of the chlorodifluoronitrobenzenes gave the corresponding difluoroanilines 5 and 12. GC-MS analysis of the difluoroaniline mixture and comparison with authentic materials showed that the major isomer was 12 and the minor component was the desired 2,6-difluoroaniline. The ratio of 12 to 5 was ~4. The isomers are readily separated by distillation (4 bp ~20°C). Although this represented a reasonable synthesis of 12, the latter is more readily prepared by the facile KF exchange on 2,4-dichloronitrobenzene followed by reduction to 12.

TABLE 1

Fluorination of 1.3.5-Trichlorobenzene



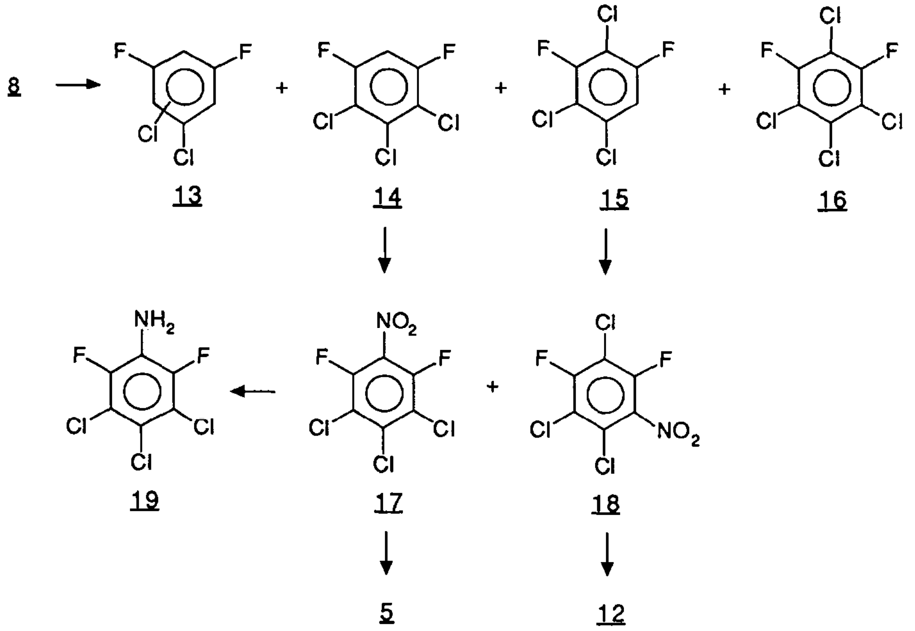
		Reactants (Mol)		GC Analysis (Mol-Area %)				Mass
Run	Temp, °C	KF	6	6	7	8	9	Balance
1	230	0.22	0.10	0.051	0.050	0.008	0.001	110
2	250	0.22	0.10	0.002	0.025	0.045	0.006	78
3	250	0.22	0.10	0.008	0.049	0.037	0.004	98
4	260	0.22	0.10	0.002	0.031	0.055	0.010	98
5	270	0.22	0.10	0.000	0.015	0.060	0.019	94
6	280	0.22	0.10	0.000	0.019	0.054	0.013	87
7	300	0.66	0.10	0.000	0.000	0.019	0.062	81
8	300	0.60	0.10	0.000	0.000	0.004	0.075	79



Scheme 1.

From the preliminary studies on the nitration and subsequent reduction of 8, it was apparent that the resonance effects of the two fluorine atoms far outweighed any steric considerations in the electrophilic substitution of 8. Hence, it seemed reasonable that dichlorination of 8 followed by nitration and reduction should reverse the final isomer distribution of the difluoroanilines 5 and 12. The reaction sequence is illustrated in Scheme 2.

The results of the chlorination studies are summarized in Table 2. The product mix was characterized by GC-MS analysis in conjunction with further derivatization. The yield of the desired 1,2,3-trichloro-4,6-difluorobenzene, 14, is quite good, but as expected, some under and over chlorination to the dichloro and tetrachloro derivatives is observed. Aluminum chloride, antimony trichloride, and ferric chloride were all found to be efficient chlorination catalysts. Results of the nitration and subsequent reduction are summarized in Table 3. The data in Table 3 correlate with Table 2 in that the chlorination and nitration were carried out in the same reactor without isolation (see experimental). The results show that a favorable isomer ratio of ~4 is obtained for the 2,6- and 2,4-difluoroaniline. Overall yields of 2,6-difluoroaniline from 1-chloro-3,5-difluorobenzene were ~55-70%.



Scheme 2.

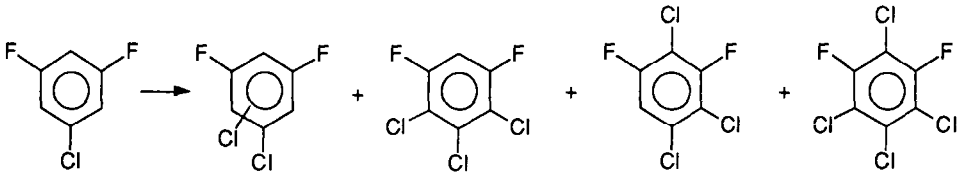
EXPERIMENTAL

1-Chloro-3,5-Difluorobenzene (8)

1,3,5-Trichlorobenzene, 6 (18.2 g, 0.1 mol), 1,3-dimethyl-2-imidazolidinone (100 ml), 1,3-diethylbenzene (5.0 g, internal standard), and potassium fluoride (12.76 g, 0.22 mol) were charged to a 300 ml Parr reactor equipped with a mechanical stirrer. The potassium fluoride was dried under vacuum at 150°C for a minimum of 24 hours. The reactor was sealed, pressure tested and heated at the desired temperature for 12 hours. The reactor was cooled and the contents analyzed by gas chromatographic analysis (see Table 1). The product was isolated by removal of the inorganics by

TABLE 2

Chlorination of 1-Chloro-3.5-Difluorobenzene

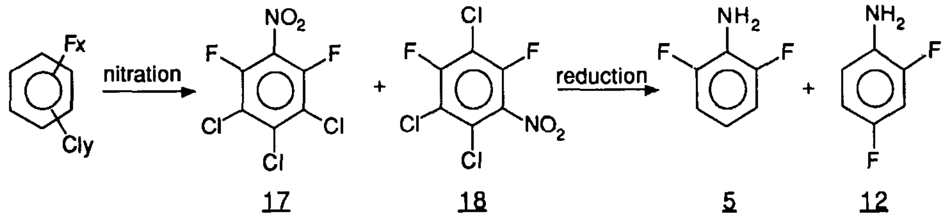


8 13 14 15 16

Run	Catalyst	Solvent	Temp. °C	GC Analysis (Area %)				Yield
				13	14	15	16	
1	$AlCl_3$ (25%)	EDC	24	0	76	17	7	90
2	$AlCl_3$ (10%)	EDC	10	4	74	18	4	91
3	H_2SO_4	H_2SO_4	55	very little reaction				--
4	$AlCl_3$ (5%)	EDC	10	14	66	17	3	--
5	$AlCl_3$ (5%)	CH_2Cl_2	5	7	72	17	4	--
6	$AlCl_3$ (2% + 2%)	CH_2Cl_2	8	5	74	17	4	--
7	$AlCl_3$ (3%)	CH_2Cl_2	3	5	74	17	4	--
8	$FeCl_3$ (5% + 2.5%)	CH_2Cl_2	25	6	76	15	2	--
9	$SbCl_3$ (5%)	CH_2Cl_2	12	4	80	12	2	--
10	$FeCl_3$ (10%)	CH_2Cl_2	10	8	71	13	2	--

TABLE 3

Summary of Nitration and Reduction of Trichlorodifluorobenzene Isomers



Run	Yield (Nitration)[a]	Catalyst Chlorination	GC Analysis (Area %) Ratio, 17:18	GC Analysis (Area %) Ratio, 5:12	Yield[b]
5	78	$AlCl_3$ (5%)	3.47	2.75	--
6	87	$AlCl_3$ (4%)	3.24	5.36	--
7	90	$AlCl_3$ (3%)	3.63	4.53	--
8	85	$FeCl_3$ (7.5%)	3.47	4.25	--
9	74	$SbCl_3$ (5%)	4.22	8.09	--
10	84	$FeCl_3$ (10%)	3.48	2.33	--
11	90	$AlCl_3$ (5%)	4.81	3.34	53
12	91	$AlCl_3$ (5%)	4.29	4.00	72
13	93	$AlCl_3$ (5%)	5.21	3.76	51

[a] Includes trace amounts of under and over chlorination products.
[b] Isolated yield based on 8.

filtration, and the aromatics separated from the solvent via flash distillation. The aromatics were purified by distillation using a concentric tube distillation column to give 1,3,5-trifluorobenzene, 9, bp 76-78°C.

Nitration and Reduction of 1-Chloro-3,5-Difluorobenzene (8)

1-Chloro-3,5-difluorobenzene, 8 (5.0 g, 0.034 mol), was added dropwise to a nitrating solution prepared from 10 g of concentrated nitric acid and 13 g of concentated sulfuric acid at 50°C. The temperature was increased to 80°C for 1 hour. After cooling, the reaction mixture was poured onto ice and the product isolated by extraction with dichloromethane. The GC-MS analysis indicates 2 isomers (ratio 4:1). MS (70 ev) m/z: 193 (M^+ calcd for $C_6H_2F_2ClNO_2$: 193). (When the experiment was repeated to 50°C, the results were identical.)

2.5 g of the above mixture was dissolved in 25 ml of acetic acid and placed in a 200 ml Hastelloy C Parr bomb. Approximately 0.25 g of 10% Pd/C catalyst was added and the bomb sealed, flushed with N_2, pressure tested, and charged with 50 psi of hydrogen. After stirring overnight at room temperature, the reaction mixture was analyzed by GC-MS and found to contain the difluorochloroaniline derivatives. Increasing the temperature to 80°C and the H_2 pressure to 150 psi produced some dechlorination after several hours. Sodium acetate was then added to neutralize the HCl. Under these conditions, the reduction was complete in 2 hours. The final reduced product was analyzed by GC-MS and found to be a mixture of 2,4- and 2,6-difluoroanilines. The retention times and mass spectra were identical with authentic samples. The major component was the 2,4-isomer. The ratio was ~4:1.

Procedure for the Chlorination and Nitration of 1-Chloro-3,5-Difluorobenzene (8)

1-Chloro-3,5-difluorobenzene, 8 (22.8 g, 0.154 mol), aluminum trichloride (0.51 g, 3 mol%) and dichloromethane (200 ml) were charged to a 500 ml flask equipped with condensor, thermometer, magnetic stirrer and gas sparge tube. The condensor was connected to a caustic scrubber. The reaction mixture was cooled to 3°C, and chlorine was added slowly. GC analysis gave the following composition: dichlorodifluorobenzene, 13, 5%; 1,3,4-trichloro-2,6-difluorobenzene, 15, 17%; 1,2,3-trichloro-4,6-difluorobenzene, 14, 75%; and 1,2,3,5-tetrachloro-4,6-

difluorobenzene, 16, 3%. The sparge tube was removed and replaced by an addition funnel, and concentrated sulfuric acid (105.6 g) was added dropwise. The addition funnel was removed and replaced with a distillation head. The dichloromethane was removed by distillation and the reaction mixture cooled to room temperature. After removal of the distillation head and replacement with an addition funnel, concentrated nitric acid (58.6 g, 90%) was added dropwise. The reaction mixture was stirred at room temperature for 1.5 hours and then poured over ice. the organics were extracted with dichloromethane and dried over $MgSO_4$. The solvent was removed on a Büchi evaporator to give 36.0 g (90% based on 17). GC analysis gave the following composition: 1,2,3-trichloro-4,6-difluorobenzene, 14, 2%; 1,2,4-trichloro-3,5-difluoronitrobenzene, 18, 19%; 3,4,5-trichloro-2,6-difluoronitrobenzene, 17, 69%; and 1,2,3,5-tetrachloro-4,6-difluorobenzene, 16, 7%. MS m/z: 216 (M^+, calcd for $C_6HCl_3F_2$: 216); m/z: 261 (M^+, calcd for $C_6Cl_3F_2NO_2$: 261); m/z: 250 (M^+, calcd for $C_6Cl_4F_2$: 250); m/z: 182 (M^+, calcd for $C_6H_2Cl_2F_2$: 182).

Isolation of 3,4,5-Trichloro-2,6-Difluoronitrobenzene, 17 (nc)

The crude nitration product, which contained about 3% 1,2,3,5-tetrachloro-4,6-difluorobenzene, 16; 18% 1,2,4-trichloro-3,5-difluoronitrobenzene, 18; and 76% 3,4,5-trichloro-2,6-difluoronitrobenzene, 17, was subjected to column chromatography utilizing silica gel (Davison Grade 923). The product was eluted with 90:10 hexane-benzene. After removal of solvent on a Büchi evaporator, the residue solidified, mp 33-35°C. ^{13}C NMR ($CDCl_3$, relative Me_4Si) δ 150.75 (C-1), 119.46 (C-2 and C-6), 137.21 (C-3 and C-5), and 147.25(C-4).

Isolation of 3,4,5-Trichloro-2,6-Difluoroaniline, 19 (nc)

3,4,5-Trichloro-2,6-difluoronitrobenzene, 17 (4.5 g, 0.017 mol), 0.9 g 10% Pd/C, and 2-propanol (25 ml) were placed in a 45 ml Hastelloy C Parr bomb. The reactor was purged with N_2, pressure tested, and then pressurized to 130 psi with H_2. After stirring (magnetic stirrer) for 5 hours at room temperature, the reactor was vented. After removal of the catalyst by filtration, the solvent was evaporated on a Büchi evaporator to yield 3.7 g (96%) product, mp 137-140°C. ^{13}C NMR (acetone-d_6, relative Me_4Si) δ 117.43 (C-1), 127.30 (C-2 and C-6), 148.40 (C-3 and C-5), and 145.24 (C-4).

Reduction of Difluorotrichloronitrobenzene Mixture

A mixture (26.3 g) containing 1,2,4-trichloro-3,5-difluoronitrobenzene, 18 (18%); 3,4,5-trichloro-2,6-difluoronitrobenzene, 17 (76%); and 1,2,3,5-tetrachloro-4,6-difluorobenzene, 16, (3%) was charged to a 600 ml Hastelloy C Parr reactor along with 2.63 g of Pd/C catalyst (5 mol% Pd). The reactor was sealed and pressure tested, then pressurized to 150 psi of H_2 and stirred for 16 hours at room temperature. After venting, GC analysis showed that the nitro compounds had been converted to amines. Sodium acetate (33.1 g, 0.4 mol) was added to the reactor and the reactor resealed. The reactor was pressurized to 150 psi of H_2 and heated at 80°C for 6 hours, then cooled and vented. GC analysis showed the reaction was complete. The solids were filtered and the methanol was separated by distillation using a concentric tube column. The residue was diluted with dichloromethane (100 ml) and the organic phase washed with 2x100 ml portions of brine solution to remove residue methanol and acetic acid. The organic phase was dried over $MgSO_4$, filtered, and the solvent evaporated to yield 9.6 g (73%) of difluoroanilines. GC analysis showed the mixture to be 89% 2,6-difluoroaniline, 5, and 11% 2,4-difluoroaniline, 12. MS m/z: 231 (M^+, calcd for $C_6H_2Cl_3F_2N$: 231); m/z: 197 (M^+, calcd for $C_6H_3Cl_2F_2N$: 197); m/z: 163 (M^+, calcd for $C_6H_2ClF_2N$: 163); mz/: 129 (M^+, calcd for $C_6H_5F_2N$: 129).

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