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AROMATIC FLUORINE CHEMISTRY. PART 5. PREPARATION OF 2,6-DIFLUOROANILINE AND 1,2-DIFLUOROBENZENE

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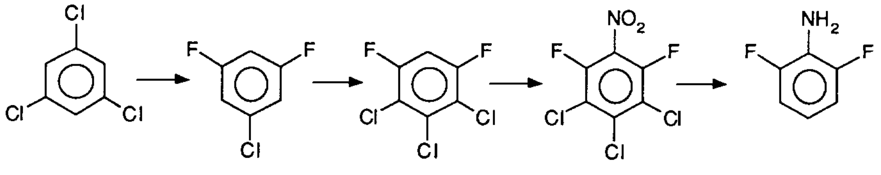
SUMMARY

The preparation of 2,6-difluoroaniline and 1,2-difluorobenzene from 1,2,3-trichlorobenzene is described. An isomeric mixture of 1-chloro-2,3-difluorobenzene and 2-chloro-1,3-difluorobenzene is obtained from KF exchange on 1,2,3-trichlorobenzene. Selective dechlorination of 1-chloro-2,3-difluorobenzene with H_2 and Pd/C catalyst gives 1,2-difluorobenzene. 2,6-Difluoroaniline is obtained via ammonolysis of 2-chloro-1,3-difluorobenzene.

INTRODUCTION

Recently, we described the synthesis of 2,6-difluoroaniline from 1,3,5-trichlorobenzene [1]. The multistep reaction sequence involved (a) KF exchange on 1,3,5-trichlorobenzene, 1, to 1-chloro-3,5-difluorobenzene, 2; (b) chlorination to the trichloro derivative 1,2,3-trichloro-4,6-difluorobenzene, 3; (c) nitration to 3,4,5-trichloro-2,6-difluoronitrobenzene, 4; and (d) reduction to 2,6-difluoroaniline, 5. This procedure, although more efficient than present commercial technology based on 2,6-



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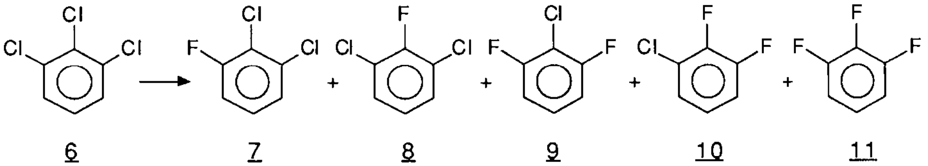
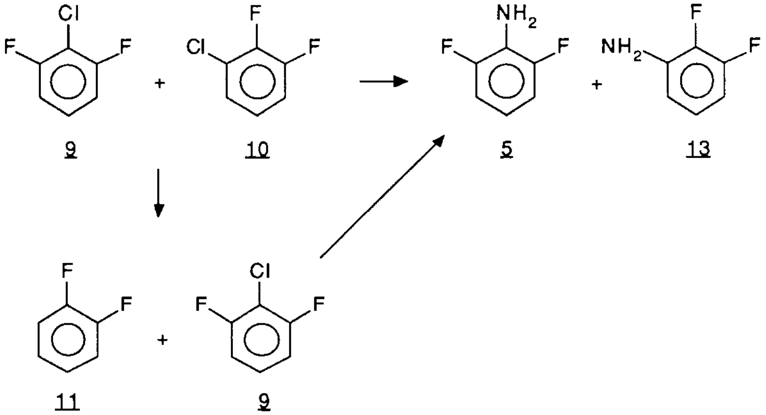
dichlorotoluene [1], suffers from both the cost and availability of 1,3,5-trichlorobenzene. We now describe a facile synthesis of 2,6-difluoroaniline from 1,2,3-trichlorobenzene.

RESULTS AND DISCUSSION

The substitution pattern of 1,2,3-trichlorobenzene, 6, provided a potential precursor for the synthesis of 2,6-difluoroaniline. The KF exchange on 6 had been reported by Finger and coworkers [2] to give a mixture of dichlorofluorobenzene, 7 and 8, chlorodifluorobenzene, 9 and 10, as well as 1,2,3-trifluorobenzene, 11, and smaller amounts of dehalogenated products. As noted by Finger, 9 and 10 are not separable



by distillation. However, successful ammonolysis of the isomeric chlorodifluorobenzenes 9 and 10, would provide the desired 2,6-difluoroaniline and by-product 2,3-difluoroaniline. The latter could be converted to 1,2-difluorobenzene via known diazotization chemistry. The alternative separation would involve a potential selective dechlorination of 10 in the isomeric mixture as illustrated in Scheme 1.



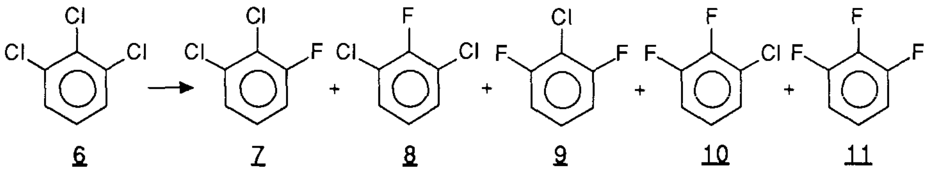
Scheme 1

The KF exchange reactions on 6 are summarized in Table 1 utilizing three different dipolar aprotic solvents, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMI), and 1-methyl-2-pyrrolidinone (NMP). In DMPU, at 270°C and 280°C and 24 and 12 hour reaction times, approximately 1:1 mixtures of the chlorodifluoro:dichlorofluoro isomers are obtained. Increasing the temperature to 290°C, as expected, produces a higher ratio of the difluoro materials but at the expense of a lower mass balance. Comparable results were obtained with DMI. At 290°C and a reaction time of 30 hours, a substantially lower mass balance results. The results with NMP are also comparable to the above-mentioned solvents with a small decrease in the exchange rate. The last two entries in Table 1 show the remarkable effect that cesium fluoride has on the exchange reactions. At 250°C, the exchange reaction is more facile than at 290°C with KF. In addition, the mass balance is improved significantly. The chlorodifluoro isomer mix from the runs described in Table 1 was isolated and purified by distillation for the ammonolysis and reduction reactions. It is noteworthy that very little 1,2,3-trifluorobenzene is formed in the exchange. The amount is significantly less than in the 1,3,5-isomer of trichlorobenzene [1].

The boiling points of 1-chloro-2,3-difluorobenzene and 2-chloro-1,3-difluorobenzene are similar and prohibit their separation via distillation. The selective chemical reduction of 1-chloro-2,3-difluorobenzene to 1,2-difluorobenzene would provide a source of pure 2-chloro-1,3-difluorobenzene for the ammonolysis reaction. With hydrogen and Pd/C catalyst in ethylene glycol as solvent and diethanolamine as the HCl scavenger, the reduction occurs selectively; and when complete, high purity 1,2-difluorobenzene and 2-chloro-1,3-difluorobenzene can be distilled from the reaction mixture.

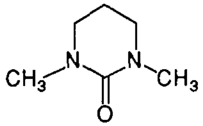
The results of the ammonolysis reactions (1-chloro-2,3-difluoro and 2-chloro-1,3-difluorobenzene mixture) are summarized in Table 2. The solvent and reactant

TABLE 1 KF Exchange on 1,2,3-Trichlorobenzene

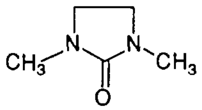


	mol				mol %				
Solvent	6	KF	T (°C)	T (Hr)	6	7 & 8	9 & 10	11	Mass Balance (Runs)
A	0.25	1.0	270	24	4	40	32	<1	77 (1)
A	0.25	1.0	280	12	4-8	40-46	28-38	~1	77-55 (3)
A	0.25	1.0	290	12	1	22	40	~1	70 (1)
B	0.25	1.0	270	24	4	42	34	<1	81 (1)
B	0.25	1.0	280	18	2	34	42	2	80 (1)
B	0.25	1.0	280	30	1	18	34	2	56 (1)
C	0.25	1.0	270	24	10	48	22	<1	82 (1)
C	0.25	1.0	280	18	6	40	27	~1	74 (1)
C	0.25	1.0	290	12	4	38	30	1.5	72 (1)
B	0.50	1.0	290	12	3-4	39-40	35-38	1	81-82 (4)
B	0.50	*1.0	250	12	<1	34	58	~3	95 (1)
B	0.50	*1.0	250	12	<1	32	62	~3	98 (1)

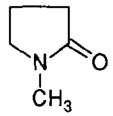
*CsF



A



B



C

A = 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (N,N'-dimethylpropyleneurea, DMPU)
B = 1,3-Dimethyl-2-imidazolidinone (N,N'-dimethylethyleneurea, DMI)
C = 1-Methyl-2-pyrrolidinone (NMP)

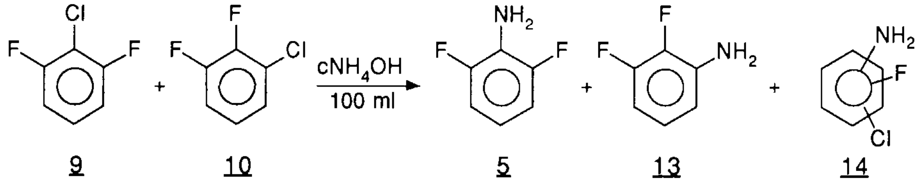
was concentrated NH_4OH (28%). Initial results with the soluble copper salt, $CuSO_4 \cdot 5H_2O$ at 170°C gave poor conversions to the desired difluoroaniline mixture. Cupric oxide was considerably better than the cupric sulfate, but at high conversions, the mass balances decreased significantly. From the studies to date, cuprous oxide appears to be the catalyst of choice. From the data summarized in Table 2, the reaction can be run at 160°C with cuprous oxide with good conversions and mass balances. Doubling the substrate concentration, as expected, decreases the conversion but does not appreciably effect the mass balances. The utilization of cuprous oxide also reduces the level of the product precursor, chlorofluoroaniline, 14 in the product mixture. The overall ratio of the desired 2,6-difluoroaniline to 2,3-difluoroaniline is ~3:2.

EXPERIMENTAL

KF Exchange Reaction

The KF exchange reactions described in Table 1 were carried out in a 600 ml Hastelloy C bomb equipped with a magnetic drive stirrer. Drying the solvents via distillation from CaH_2 appeared to have little beneficial effect. The reaction mixture was analyzed by addition of the 1,2,4-trichlorobenzene as the internal standard followed by GC analysis on a Hewlett Packard 5870 equipped with the following capillary column: 20 meter DB wax 0.18 mm ID, 0.03 μm film. The aromatics were flash distilled from the mixture and the distillate redistilled on a Nester Faust spinning band column. The chlorodifluorobenzene fraction had bp 134-138°C. The dichlorofluorobenzene fraction had bp 172-178°C consistent with the work of Finger [2].

TABLE 2
Ammonolysis of Chlorodifluorobenzene



ClF$_2$B (Mol)	Catalyst (Mol %)	T (°C)	T (Hr)	Mol % 5	13	9 + 10	14	Mass Balance
0.093	A (2%)	170	24	7	3	54	22	85
0.093	A (5%)	170	24	14	9	53	9	85
0.093	B (5%)	170	24	19	11	43	17	90
0.093	B (10%)	170	24	32	25	3	3	63
0.093	C (2%)	170	24	30	18	26	9	83
0.093	C (5%)	170	24	33	24	7	71	
0.093	C (10%)	170	24	37	30	1	5	72
0.096	C (10%)	160	24	39	27	10	4	80
0.192	C (10%)	160	24	27	18	35	3	83
0.096	C (10%)	150	24	19	10	59	2	91
0.096	C (10%)	150	48	37	26	12	3	78
0.096	C (10%)	140	24	10	6	72	2	91

A = $CuSO_4 \cdot 5H_2O$ B = CuO C = Cu_2O

Ammonolysis Reaction

The ammonolysis reactions described in Table 2 were carried out in a 300 ml Hastelloy C bomb equipped with a magnetic drive stirrer. After cooling, the contents of the bomb were filtered to remove solid catalyst and the product isolated by continuous extraction (overnight) with dichloromethane. The internal standard, 1,2,4-trichlorobenzene, was added to the dichloromethane solution for the GC analysis on the above-mentioned column.

Reduction of 1-Chloro-2,3-Difluorobenzene

The isomeric mixture of chlorodifluorobenzenes, 9 and 10 (50 g, 0.34 mol), N-ethyldiethanolamine (45 g, 0.34 mol), ethylene glycol (125 ml), and palladium catalyst (1.5 g, 10% Pd/C) were placed in a 300 ml Hastelloy C Parr reactor equipped with a magnetic drive stirrer. The reactor was closed, pressure tested with N_2, and then pressurized to 200 psi with H_2. The reaction was heated at 100°C, and additional H_2 was added periodically until the reaction no longer consumed H_2. After cooling, the catalyst was filtered and the reaction mixture distilled on a Nester Faust spinning band distillation column. 1,2-Difluorobenzene was obtained, bp 90-92°C, and 2-chloro-1,3-difluorobenzene, bp 132-134°C.

Ammonolysis of 2-Chloro-1,3-Difluorobenzene, 9

2-Chloro-1,3-difluorobenzene (28.5 g, 0.19 mol), cuprous oxide (2.9 g, 0.02 mol), and concentrated ammonium hydroxide (150 ml) were heated in a 300 ml Hastelloy C Parr reactor at 160°C for 24 hours. The solution was neutralized with concentrated HCl to pH 7 and the product isolated by continuous extraction with dichloromethane. GC analysis (area %) gave the following composition: 1,2-

difluorobenzene, 2%; 9, 15%; 5, 71%; fluorodiaminobenzene, 6%; unknowns, 6%. Distillation on the Nester Faust spinning band column gave 2,6-difluoroaniline bp 152-154°C.

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