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Highly regioselective nickel-catalyzed hydrodefluorination of pentafluoroacetanilide

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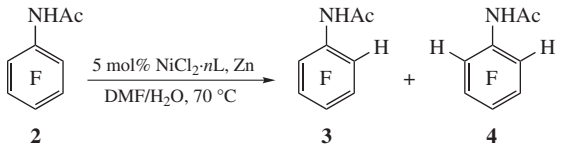
A highly regioselective reaction of pentafluoroacetanilide hydrodefluorination, which proceeds under the action of zinc in the presence of nickel complexes, leading to the formation of 2,3,4,5-tetra- and 3,4,5-trifluoroacetanilide was observed.

The C–F bond activation by transition metal complexes is of both theoretical and practical interest.[1,2] There is a particular interest in the catalytic hydrodefluorination of polyfluorinated organic compounds, which allows one to obtain products with a reduced amount of fluorine atoms. Aisenberg and Milstein[3,4] were the first to report the catalytic hydrodefluorination of C–F bonds in hexafluorobenzene that proceeds under the action of Me_3SiH in the presence of trimethylphosphine rhodium complexes. Kiplinger and Richmond[5,6] described the interaction of perfluorinated aromatic compounds with Cp_2MX_2–$HgCl_2$–Mg or Cp_2MX_2–PMe_3–Mg reductive systems (M = Ti, Zr, Hf; X = Cl, F). We found that the hydrodefluorination of perfluorinated arenes occurs under the action of zinc in the presence of catalytic amounts of nickel complexes.[7] The behaviour of aromatic polyfluorinated compounds containing at least one hydrogen atom or other substituents under the conditions of catalytic hydrogenation is of interest. 1,2,4,5-Tetrafluorobenzene is the only product of pentafluorobenzene hydrodefluorination in the presence of rhodium complexes[3,4] and metallocenes.[5,6] Note that similar results were obtained for non-catalytic hydrodefluorination of pentafluorobenzene.[8–10] In contrast, in the presence of nickel complexes, the activation of C–F bonds to hydrogen occurs predominantly in the *ortho*-position.[7] An analogous orienting effect of the carbonyl group of the pentafluorobenzoic acid derivatives C_6F_5COX (X = OH,[11,12] NH_2,[12] OEt[12]) was observed. Deacon *et al.*[11] suggested a method of 2,3,4,5-tetrafluorobenzoic acid preparation through the reductive defluorination of pentafluorobenzoic acid under $YbCp_2$(dme) catalysis conditions. We found that pentafluorobenzoic acid and its derivatives C_6F_5COX (X = NH_2, OEt) undergo hydrodefluorination to give 2,3,4,5-tetrafluoro- and 3,4,5-trifluorobenzoic acids and their derivatives under the action of zinc in the presence of nickel complexes with 2,2′-bipyridine or 1,10-phenanthroline in aqueous DMF.[12] 3,4,5-Trifluorobenzoic acid can be obtained in a quantitative yield. In this work, we investigated the preparation of 2,3,4,5-tetra- and 3,4,5-trifluoroaniline, which are important intermediate products for biologically active compounds[13] *via* hydrodefluorination of pentafluoroaniline or its derivatives.

Pentafluoroaniline **1** does not react with zinc in aqueous DMF at 70 °C. Analogous results were observed in the presence of nickel chloride and complexes with 2,2′-bipyridine and 1,10-phenanthroline (Scheme 1). The reactivity of pentafluoroacetanilide **2**, readily accessible through the acylation of **1** with acetic anhydride, substantially differs from the reactivity of **1**. The interaction of compound **2** with zinc in the presence of catalytic amounts (5 mol% relative to substrate) of nickel



2 **3** **4**

L = Bpy or Phen, n = 1–3

Scheme 1

Table 1 Hydrodefluorination of pentafluoroacetanilide **2**.

Run	Catalyst	*t*/h	Conversion[a] (%)	Selectivity[a] (%)	
				3	**4**
1	—	5	0	—	—
2	$NiCl_2$	5	0	—	—
3	$NiCl_2$·Bpy	5	28	100	0
4	$NiCl_2$·Phen	5	63	100	0
5	$NiCl_2$·2Bpy	4	100	65	35
6	$NiCl_2$·2Phen	4	97	96	4
7	$NiCl_2$·2Phen	6	98	97	3
8	$NiCl_2$·3Bpy	4	100	26	74
9	$NiCl_2$·3Phen	4	100	69	31
10	$NiCl_2$·3Phen	6	100	62	38

[a]HPLC data.

complexes generated *in situ* from $NiCl_2$ and 2,2′-bipyridine or 1,10-phenanthroline in aqueous DMF at 70 °C leads to the hydrodefluorination of C–F bonds in the *ortho*-positions to the NHCOMe group (Table 1)[†] with formation of a mixture of 2,3,4,5-tetrafluoroacetanilide **3** and 3,4,5-trifluoroacetanilide **4**.[‡] Shteingarts and co-workers[14,15] demonstrated that acetanilide **2** reacts with zinc in aqueous ammonia to form a mixture of **3**, 2,3,5,6-tetrafluoroacetanilide and 2,4,5-trifluoroacetanilide **5** in a molar ratio of 51:16:3. Addition of zinc chloride (3–14 equiv. relative to substrate) increased the selectivity for product **3** up

[†] *General procedure of hydrodefluorination.* A three-bottom flask supplied with a thermometer, a magnetic stirrer bar and a heating bath under an argon atmosphere was charged with $NiCl_2·6H_2O$ (30 mg, 0.125 mmol), 2,2′-bipyridine [20 mg, (0.125 mmol), 40 mg (0.250 mmol) or 60 mg (0.375 mmol) for $NiCl_2$·L, $NiCl_2$·2L or $NiCl_2$·3L, respectively] or 1,10-phenanthroline [25 mg, (0.125 mmol), 50 mg (0.250 mmol) or 75 mg (0.375 mmol) for $NiCl_2$·L, $NiCl_2$·2L or $NiCl_2$·3L, respectively], DMF (2.5 ml) and water (0.5 ml). The resulting mixture was stirred at 70 °C for 1 h. Zinc dust (1635 mg, 25 mmol) was added in one portion. The resulting mixture was additionally stirred for 10 min and **2** (563 mg, 2.5 mmol) was added. The reaction mixture was heated with stirring at 70 °C. Proceeding of the reaction was monitored by HPLC taking analytical samples every hour.

to 80%. Product **5** becomes prevailing (50–73% selectivity) in the presence of copper chloride(II) (2–5 equiv. relative to substrate). Moreover, 2,3,5-trifluoroacetanilide (6–8%) was found in the reaction mixtures. At the same time, the formation of product **4** was not observed.

In our case acetanilide **2** does not react with zinc in aqueous DMF in the absence of a catalyst, as well as in the presence of nickel chloride without nitrogen-containing ligands (Table 1, runs 1, 2).

The conversion of substrate **2**, as well as molar ratios of resulting acetanilides **3** and **4**, depend on the composition of the nickel catalyst. The complexes, which are generated from the equivalent amounts of nickel chloride and ligand (2,2′-bipyridine or 1,10-phenanthroline), demonstrated high efficiency in the homo-coupling reaction of aryl halides proceeding in anhydrous DMF,[7] but did not show high activity in the hydrodefluorination reactions (Table 1, runs 3, 4). In both cases, the complete conversion of **2** was not achieved within 5 h. Acetanilide **3** was the main product of the reaction. The activity of the corresponding 2,2′-bipyridine complex is lower than that of $NiCl_2$–Phen by a factor of ~2. An increase in the number of ligands leads to a remarkable rise of the catalytic activity of the nickel complexes. For instance, the complete consumption of starting compound **2** was detected after 4 h in the presence of $NiCl_2$·2Bpy. In addition to acetanilide **3**, the formation of 3,4,5-trifluoroacetanilide **4**, the hydrodefluorination product of **3**, was observed (Table 1, run 5). Under similar conditions, the $NiCl_2$·2Phen complex demonstrates a lower activity: the conversion of **2** is only 97% for 4 h (Table 1, run 6) and compound **3** is the main product. The extension of the reaction time to 6 h does not practically influence both the conversion of **2** and the ratio of defluorination products (Table 1, run 7).

The highest activity is demonstrated by the complexes with three ligands. The complete conversion of **2** occurs after 4 h for both complexes with 2,2′-bipyridine and 1,10-phenanthroline (Table 1, runs 8, 9). In the first case, the quantity of **4** prevails over that of **3**. Under the same conditions, the $NiCl_2$·3Phen complex shows the activity lower than that of $NiCl_2$·3Bpy: after 4 h, product **3** (69%) still predominates over **4** (31%). Prolongation of the reaction time to 6 h in the presence of $NiCl_2$·3Phen complex does not affect the contribution of **4** in the reaction mixture (Table 1, run 10).

The resulting mixtures of fluorinated acetanilides were hydrolyzed with aqueous alkali and target products were isolated by steam distillation giving mixtures of fluorinated anilines. Taking into account differences between boiling points of pentafluoro- and 2,3,4,5-tetrafluoroaniline [153 °C and 78 °C/13 Torr (200 °C/760 Torr), respectively], we suppose that they can be obtained from the mixtures by rectification and then 3,4,5-trifluoroaniline can be isolated by the steam distillation of the rectification residue.

Thus, we demonstrated the possibility of the preparation of 2,3,4,5-tetrafluoro- and 3,4,5-trifluoroanilines from pentafluoroaniline through the acylation of the latter with acetic anhydride, the further hydrodefluorination of the resulting pentafluoroacetanilide with zinc in the presence of nickel complexes with 2,2′-bipyridine or 1,10-phenanthroline and the final deacylation of the products with aqueous alkali.

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‡ The structures of compounds **3** and **4** were proved by ^{19}F NMR data ($CFCl_3$ as the standard).

2,3,4,5-Tetrafluoroacetanilide **3**: ^{19}F NMR (DMF) δ: –140.3 (m, F-5 $^3J_{FF}$ 22.5 Hz, $^3J_{HF}$ 10 Hz), –152.0 (m, F-2, $^3J_{FF}$ 17.7 Hz), –158.1 (m, F-3, $^3J_{FF}$ 20 Hz, $^3J_{FF}$ 20 Hz), –164.4 (m, F-4, $^3J_{FF}$ 21 Hz, $^3J_{FF}$ 21 Hz) [lit.,[15] δ: –140.1 (*J* 21 Hz), –153.4 (*J* 18.5 Hz), –158.2 (*J* 20 and 18.5 Hz), –164.8 (*J* 21 and 20 Hz)].

3,4,5-Trifluoroacetanilide **4**: ^{19}F NMR (DMF) δ: –135.0 (dd, 2F, F-3, F-5, $^3J_{FF}$ 21.3 Hz, $^3J_{HF}$ 10.5 Hz), –169.2 (tt, 1F, F-4, $^3J_{FF}$ 21.5 Hz, $^4J_{HF}$ 6.5 Hz).

3,4,5-Trifluoroaniline (prepared by alkaline hydrolysis of **4**): ^{19}F NMR (CCl_4) δ: –135.6 (dd, 2F, F-3, F-5, $^3J_{FF}$ 21.5 Hz, $^3J_{HF}$ 9.3 Hz), –175.5 (tt, 1F, F-4, $^3J_{FF}$ 21.5 Hz, $^4J_{HF}$ 5.5 Hz) [lit.,[16] (C_6F_6 as the standard) δ: –27.5, –12.6 J_{FF} 22 Hz].

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