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Journal of Fluorine Chemistry 110 (2001) 43–46

JOURNAL OF FLUORINE CHEMISTRY

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A new approach to polyfluoroaromatic amines with an unsubstituted position *ortho* to the amino group

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Received 30 January 2001; accepted 27 April 2001

Abstract

N-acetyl derivatives of polyfluoroaromatic amines have been found to be highly selectively defluorinated by zinc in aqueous ammonia at the position *ortho* to the acetamido group thus affording a new approach to potential building blocks for the synthesis of polyfluorobenzheterocycles. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Reductive defluorination; Hydrodefluorination; Zinc; Aqueous ammonia; Polyfluoroaromatic amines; *N*-acetyl derivatives; Acetamido group

1. Introduction

The reductive defluorination of perfluoroarenes and their functional derivatives is a promising route to partially fluorinated arenes which are valuable starting compounds for synthesis but generally less accessible than their precursors. It has been found that Zn(Cu) in aqueous DMF [1,2] and Zn in aqueous ammonia [3–5] allow the highly selective hydrodefluorination of various polyfluoroarenes, the last reducing system being the simplest and most versatile among those currently known, yielding partially fluorinated arenes highly selectively. However, polyfluoroarenes with an electron donating group, in particular an amino group, have not been involved in these reactions. Nevertheless, the aim of developing the conditions for the selective defluorination of accessible perfluoroaromatic amines at a position *ortho* to the amino group is important since the polyfluorinated amines with an unsubstituted *ortho* position, to be produced, are potentially valuable and versatile building blocks for the synthesis of heterocycles through electrophilic heterocyclizations [6,7]. Thus far, however, there were no methods for these compounds to be easily prepared so they remain difficult to access. In this communication, we focus on the hydrodefluorination of *N*-acetyl derivatives of some polyfluoroaromatic amines, such as pentafluoroacetanilide (**1**), 4-acetamido-2,3,5,6-tetrafluoropyridine (**2**), 4-acetamido-2,3,5,6-tetrafluorobenzotrifluoride (**3**) and 4-acetamido-2,3,5,6-tetrafluorobenzonitrile (**4**), by zinc in aqueous ammonia, which has proved to be an unprecedentedly simple route to target *ortho*-defluorinated amines. At the same time pentafluoroaniline and 4-amino-2,3,5,6-tetrafluorobenzotrifluoride gave no reduced products under typical experimental conditions.

2. Results and discussion

The results of the reduction of *N*-acetyl derivatives of polyfluoroaromatic amines are given in Table 1. According to ^{19}F NMR and GCMS data, the reduction of pentafluoroacetanilide (**1**) by zinc in 30% aqueous ammonia at room temperature gave mainly the product of monodefluorination at a position *ortho* to the acetamido group, 2,3,4,5-tetrafluoroacetanilide (**5**), together with the product of *para*-defluorination, 2,3,5,6-tetrafluoroacetanilide (**6**), and a minor amount of the double defluorination product, 2,4,5-trifluoroacetanilide (**7**) (Scheme 1, Entry 1). The addition of NH_4Cl and $ZnCl_2$ exerted opposite effects on the **5**:**6** ratio: the first salt completely reversed this ratio (Entry 2) whereas the second one made the predominance of *ortho*-defluorination somewhat more pronounced (Entry 3), compound **5** having been isolated after purification in 38% yield (Entry 4).

According to ^{19}F NMR data, the reduction of 4-acetamido-2,3,5,6-tetrafluoropyridine (**2**) and 4-acetamido-2,3,5,6-tetrafluorobenzotrifluoride (**3**) (Scheme 2) gave the

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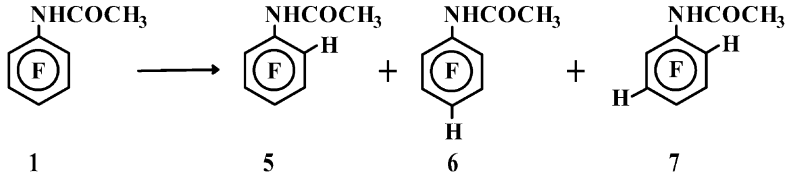
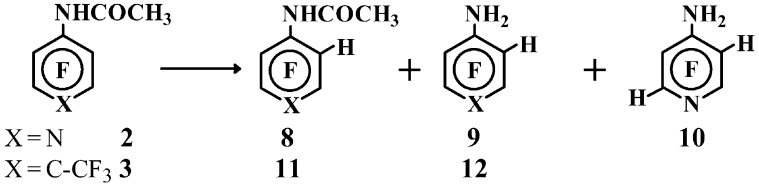
0022-1139/01/$ – see front matter
PII: S0022-1139(01)00404-3

Table 1
Reactions of compounds **1**–**4** with zinc

Entry	Starting compound	Time (h)	**1**–**4**:Zn:salt (mmol)	Product distribution (mol%)		
				Starting compound	Monodefluorination product	Double defluorination product
1	**1**	13	3.5:30	**1** (29)	**5** (51), **6** (16)	**7** (3)
2	**1**	13	3.5:30:20 (NH_4Cl)	**1** (58)	**5** (8), **6** (33)	–
3	**1**	13	3.5:30:10 ($ZnCl_2$)	**1** (13)	**5** (71), **6** (10)	**7** (4)
4	**1**	25	6.2:50:17 ($ZnCl_2$)	**1** (5)	**5** (74), **6** (13)	**7** (6)
5	**2**	12	7.0:60	**2** (10)	**8** (10), **9** (78)	**10** (2)
6	**3**	40	6.2:60	**3** (14)	**11** (50), **12** (36)	–
7	**4**	0.4	5.0:30	**4** (9)	**13** (80)	**14** (6)
8	**4**	3	5.0:50	**4** (0)	**13** (8)	**14** (85)



Scheme 1.

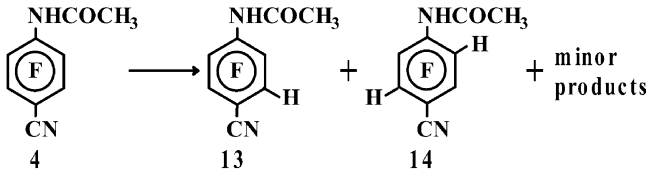


Scheme 2.

products of monodefluorination solely at the position *ortho* to the acetamido group — 4-acetamido-2,3,6-trifluoropyridine (**8**) and 4-acetamido-2,3,6-trifluorobenzotrifluoride (**11**), respectively. The reaction, besides aforementioned *ortho*-defluorinated *N*-acetyl derivatives, gave the products of their hydrolysis — 4-amino-2,3,6-trifluoropyridine (**9**), 4-amino-2,3,6-trifluorobenzotrifluoride (**12**) and, in the case of **2**, also a minor amount of hydrolyzed double defluorination product — 4-amino-2,5-difluoropyridine (**10**) (Entries 5, 6). Compounds **8** and **11** were obtained after treatment of reaction mixtures with acetic anhydride and purification in 42 and 39% yield, respectively.

The reduction of 4-acetamido-2,3,5,6-tetrafluorobenzonitrile (**4**) was remarkably rapid. According to the ^{19}F NMR data, the reaction gave immediately 4-acetamido-2,3,5-trifluorobenzonitrile (**13**), which converted to 4-acetamido-2,5-difluorobenzonitrile (**14**) with increase in reaction time, and minor products likely derived from the conversion of the cyano group (Scheme 3, Entries 7 and 8). Compounds **13** and **14** were isolated in 40 and 45% yield, respectively. Thus, unlike **2** and **3**, in this case the reductive defluorination at the position *ortho* to the acetamido group is not the predominant reaction pathway and the cyano group is evidently the stronger *ortho*-orientating group in the reaction under investigation.

Besides evident synthetic value, the results obtained are of significant interest in the context of the reaction mechanism which is believed to proceed through formation and fragmentation of the radical anion of the polyfluoroarene being hydrodefluorinated [8,9]. The effects of $ZnCl_2$ and NH_4Cl addition upon defluorination of **1** mentioned above elucidate the possible important role of a cation, probably in the stabilization of an incipient fluoride ion. The latter is bound by a zinc cation which is suggested to be involved in coordination with the acetamido group, thus assisting



Scheme 3.

ortho-defluorination. As a factor promoting fluoride ion elimination, ammonium ion has evidently an advantage over a zinc cation but, unlike the latter, its action is probably not associated with coordination thus favoring the fluoride ion elimination from the position *para* to a non-fluorine substituent, this regioselectivity being typical for the defluorination of C_6F_5R compounds [1–5,8,9].

3. Experimental

Melting points were determined in a sealed capillary and are uncorrected. ^{1}H and ^{19}F NMR spectra were recorded in CD_3COCD_3 using a Brucker WP-200 SY spectrometer at 200.1 and 188.3 MHz, respectively. Chemical shifts are reported with respect to TMS and $CFCl_3$. HRMS data were obtained on a Finnigan MAT-8200 high resolution mass spectrometer. The GC–MS analyses were performed with a Hewlett-Packard 5890 apparatus using a 30 m capillary column coated with HP-5 oil. Aqueous ammonia was "Pure" grade, zinc powder was "ZP-2". Solvents and reagents were reagent quality. Pentafluoroaniline was commercially available. 4-amino-2,3,5,6-tetrafluoropyridine, 4-amino-2,3,5,6-tetrafluorobenzotrifluoride and 4-amino-2,3,5,6-tetrafluorobenzonitrile were prepared according to the literature procedures [10].

3.1. Acylation of polyfluoroaromatic amines

The corresponding amine (20 mmol) was refluxed with acetic anhydride (25 mmol) and concentrated $HClO_4$ (0.1 ml) in benzene for 5 min to give the acetyl derivative **1**−**4**. The product was crystallized from aqueous ethanol (yield 80−85%).

Analytical data for **1**: mp 132−133°C (lit. 131−132°C [11]); ^{19}F NMR, δ: 145.3 (2F, F-2,6), 159.0 (1F, F-4), 164.2 (2F, F-3,5). For **2**: mp 133.5−134.5°C; HRMS *m/z*: 208.0246 (M^+), calculated $C_7H_4F_4N_2O$ = 208.0260; ^{1}H NMR, δ: 2.24 (s, 3H, CH_3), 9.80 (s, 1H, NH); ^{19}F NMR, δ: 92.3 (2F, F-2,6), 145.4 (2F, F-3,5). For **3**: mp 152.5–153.5°C; HRMS *m/z*: 275.0178 (M^+), calculated $C_9H_4F_7NO$ = 275.0181; ^{19}F NMR, δ: 55.3 (t, 3F, CF3, J = 21 Hz), 142.7−142.9 (4F). For **4**: mp 160.5−162°C; HRMS *m/z*: 232.0263 (M^+), calculated $C_9H_4F_4N_2O$ = 232.0260; ^{1}H NMR, δ: 2.22 (s, 3H, CH_3), 9.62 (s, 1H, NH); ^{19}F NMR, δ: 135.3 (2F, F-2,6), 142.2 (2F, F-3,5) (the assignment of fluorine resonances is based on ^{19}F NMR data for **1** and the substituent chemical shift value for the cyano group [12]).

3.2. Reaction of pentafluoroacetanilide (*1*) with zinc

Compound **1** (1.40 g, 6.2 mmol), zinc powder (3.25 g, 50 mmol) and $ZnCl_2$ (2.30 g, 17 mmol) were stirred in 30% aqueous ammonia (30 ml) at room temperature for 25 h (Entry 4). Unreacted zinc was separated and washed with water and diethyl ether. The aqueous solution was extracted with diethyl ether (3 × 30 ml). The combined ether extract was dried over $MgSO_4$ and the solvent was removed by distillation. A residue (1.12 g) was crystallized three times from aqueous ethanol (50%) to give 0.49 g of compound **5** (yield 38%), mp 104−105.5°C (lit. 106−107.5°C [13]). HRMS *m/z*: 207.0299 (M^+), calculated $C_8H_5F_4NO$ = 207.0307. ^{1}H NMR, δ: 2.17 (s, 3H, CH_3), 8.11 (m, 1H, H-6), 9.32 (s, 1H, NH). ^{19}F NMR, δ: 140.1 (F-5, J = 21 Hz), 153.4 (F-2, J = 18.5 Hz), 158.2 (F-3, J = 20 and 18.5 Hz), 164.8 (F-4, J = 21 and 20 Hz). The use of ^{19}F NMR data for **1** and substituent chemical shift value for hydrogen atom [12] permit only the structure of **5**, but not the alternative structure — 2,3,4,6-tetrafluoroacetanilide, for which δ values of ∼138 (F-2), 166 (F-3), 136 (F-4), and 122 (F-6) ppm. with no J = 21 Hz in the signals belonging F-4 and F-6 are anticipated.

3.3. Reaction of 4-acetamido-2,3,5,6-tetrafluoropyridine (*2*) with zinc

According to the procedure for **1**, compound **2** (1.45 g, 7.0 mmol) was reduced by zinc powder (3.90 g, 60 mmol) in aqueous ammonia (35 ml) for 12 h (Entry 5) to yield 0.83 g of a mixture which was worked up with acetyl anhydride. The obtained crude product was crystallized from aqueous ethanol to give 0.55 g of compound **8** (yield 42%), mp 76.5−78°C. HRMS *m/z*: 190.0349 (M^+), calculated $C_7H_5F_3N_2O$ = 190.0354. ^{1}H NMR, δ: 2.25 (s, 3H, CH_3), 7.97 (s, 1H, H-5), 9.89 (s, 1H, NH). ^{19}F NMR, δ: 72.3 (F-6, J = 22 and 13 Hz), 90.7 (F-2, J = 21 and 13 Hz), 162.9 (F-3, J = 22 and 21 Hz). The observed fluorine chemical shifts permit structure **8**, but not 4-acetamido-2,3,5-trifluoropyridine, for which δ values of ∼90 (F-2), 122 (F-5) and 138 (F-3) ppm are anticipated [12]. ^{19}F NMR signals of **9** were in accord with literature data [14].

3.4. Reaction of 4-acetamido-2,3,5,6-tetrafluorobenzotrifluoride (*3*) with zinc

According to the procedure for **1**, compound **3** (1.70 g, 6.2 mmol) was reduced by zinc powder (3.90 g, 60 mmol) in aqueous ammonia (40 ml) for 40 h (Entry 6) to give 1.20 g of a mixture which was worked up with acetic anhydride. A crude product was twice crystallized from aqueous ethanol to give 0.62 g of compound **11** (yield 39%), mp 126−128°C. HRMS *m/z*: 257.0251 (M^+), calculated $C_9H_5F_6NO$ = 257.0275. ^{1}H NMR, δ: 2.24 (s, 3H, CH_3), 8.26 (ddd, 1H, H-5, J = 13.5, 6 and 2 Hz), 9.70 (s, 1H, NH). ^{19}F NMR, δ: 54.9 (3F, CF3, J = 21 and 21 Hz), 115.9 (1F, F-6, J = 21, 13.5 and 11 Hz), 137.5 (1F, F-2, J = 21, 19 and 2 Hz), 155.7 (1F, F-3, J = 19, 11 and 6 Hz). The triplet splitting of the CF3 group signal with J_{FF} = 21 Hz due to two *ortho*-located fluorine atoms (δ: 115.9 and 137.5) permit only structure **11**, but not 4-acetamido-2,3,5-trifluorobenzotrifluoride. The similar situation was observed for **12**: ^{19}F NMR, δ: 53.8

(3F, CF3, $J \approx 20$ and 20 Hz), 118.2 (1F, F-6, $J \approx 20$ and 10 Hz), 139.5 (1F, F-2, $J \approx 20$ and 20 Hz), 165.5 (1F, F-3, $J \approx 20$ and 10 Hz).

3.5. Reaction of 4-acetamido-2,3,5,6-tetrafluorobenzonitrile (**4**) with zinc

According to the procedure for **1**, compound **4** (1.16 g, 5.0 mmol) was reduced by zinc powder in aqueous ammonia (27 ml) for 0.4 or 3 h (Entry 7 or 8). A crude product (0.96 g) from Entry 7 was twice crystallized from aqueous ethanol to afford 0.46 g of solid containing 92% of compound **13** (yield 40%), mp 145−148°C. HRMS *m/z*: 214.0353 (M^+), calculated $C_9H_5F_3N_2O = 214.0354$. ^{1}H NMR, δ: 2.19 (s, 3H, CH_3), 7.67 (ddd, 1H, H-6, $J = 9$, 5 and 2 Hz), 9.38 (s, 1H, NH). ^{19}F NMR, δ: 119.3 (F-5, $J = 11$ and 9 Hz), 135.1 (F-3, $J = 20$ Hz), 135.7 (F-2, $J = 20$, 11 and 5 Hz). The observed fluorine chemical shifts are in accord with the predicted [12] for **13**. For the alternative structure 4-acetamido-2,3,6-tetrafluorobenzonitrile, the downfield signal belonging F-6 should be observed at $\delta \sim 110$ ppm in ^{19}F NMR spectrum (see ^{19}F NMR data for **14**). Also for this structure, the signal belonging to H-5 cannot be observed at δ 7.67 ppm. in the ^{1}H NMR spectrum (see ^{1}H NMR data for **11**). A crude product (0.86 g) from Entry 8 was crystallized from aqueous ethanol to afford 0.44 g of compound **14** (yield 45%), mp 202−204°C. HRMS *m/z*: 196.0450 (M^+), calculated $C_9H_6F_2N_2O = 196.0448$. ^{1}H NMR, δ: 2.24 (s, 3H, CH_3), 7.68 (dd, 1H, H-6, $J = 10.3$ and 6 Hz), 8.44 (dd, 1H, H-3, $J = 11.7$ and 6.2 Hz), 9.52 (s, 1H, NH). ^{19}F NMR, δ: 110.5 (F-2, $J = 13$, 11.7 and 6 Hz), 131.3 (F-5, $J = 13$, 10.3 and 6.2 Hz). The observed fluorine chemical shifts are only compatible with the fluorine atom both occupying positions *ortho* to non-fluorine substituents, but not that of 4-acetamido-2,3-difluorobenzonitrile.

Acknowledgements

This work was supported by the Russian Foundation of Basic Research under Grant 99-03-33111, Russian Department of Science and Technology under Grant 9.3.01 and Department of Education of Russian Federation under Grants 015.05.01.13 and 2000.5.90.

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