Journal of Fluorine Chemistry, *66* (1994) 27–30

Disubstitution on hexafluorobenzene with *N*-methylformamides

R. Koppang*

Department of Preclinical Techniques and Material Sciences, Dental Faculty, University of Oslo, Box 1052, Blindern, 0316 Oslo (Norway)

D. Grace

Nycomed Imaging A/S, Box 4220 Torshov, 0401 Oslo (Norway)

(Received February 28, 1992; accepted March 14, 1993)

Abstract

Nucleophilic attack on hexafluorobenzene by *N*-methylformamide, treated with different bases, gave *N*-methyl-2,3,4,5,6-pentafluoroformanilide, *N*-formyl-*N*,*N*′-dimethyl-2,3,5,6-tetrafluorophenylene-1,4-diamine and *N*,*N*′-diformyl-*N*,*N*′-dimethyl-2,3,5,6-tetrafluorophenylene-1,4-diamine. The substituted benzenes could be hydrolyzed to *N*-methyl-2,3,4,5,6-pentafluoroaniline and *N*,*N*′-dimethyl-2,3,5,6-tetrafluorophenylene-1,4-diamine.

Introduction

It has been shown previously that two-stage nucleophilic attack by anilides on hexafluorobenzene causes the replacement of the fluorines in the *para* position [1–3]. By the use of ammonia, methylamine and dimethylamine, a change in disubstitution on hexafluorobenzene from mainly *meta* to *para* can be observed, with a mixture of 60% *meta* and 40% *para* substitution when the nucleophile is methylamine [4]. The disubstitution reactions with *N*-alkyl- or *N*-aryl-anilides proceed very smoothly at low temperatures and give good yields [1–3] compared with reactions with the amines [4–6].

The purpose of the present investigation was to test the hypothesis that *N*-alkylformamides as nucleophiles would provide an easy route to 1,4-disubstitution on hexafluorobenzene with the formation of the corresponding *N*,*N*′-alkyl-2,3,5,6-tetrafluorophenylene-1,4-diamine after hydrolysis of the formamides.

Results and discussion

Since no reaction occurs between *N*-methylformamide and hexafluorobenzene under normal conditions, metallation of the formamide was necessary. Sodium hydride, lithium amide, potassium hydroxide and lithium hydroxide were employed as metallation reagents. The main reaction products obtained with sodium hydride and lithium amide were *N*-formyl-*N*,*N*′-dimethyl-2,3,5,6-tetrafluorophenylene-1,4-diamine (**3**) (41%) and *N*,*N*′-diformyl-*N*,*N*′-dimethyl-2,3,5,6-tetrafluorophenylene-1,4-diamine (**4**) (6%). In some reactions the relative amounts of compounds **3** or **4** varied, but their total amount was approximately the same. When the reaction mixtures were hydrolyzed with potassium hydroxide, *N*-methyl-2,3,4,5,6-pentafluoroaniline (**1**) and *N*,*N*′-dimethyl-2,3,5,6-tetrafluorophenylene-1,4-diamine (**5**) were formed. The same compounds (**1** and **5**) were obtained in a direct reaction between the formamide, potassium hydroxide and hexafluorobenzene but in lower yield. With lithium hydroxide as the base, **1** and **3** were formed with traces of *N*-methyl-2,3,4,5,6-pentafluoroformanilide (**2**). By adding tetrahydrofuran to the reaction mixture with lithium hydroxide, compounds **1**, **2** and **3** could be isolated with traces of **4** present in the reaction mixture. The reactions performed are listed below.

$$\mathrm{CH_3N(H)CHO} \xrightarrow{\text{(i) Base; (ii) } \mathrm{C_6F_6}}$$

$$\underset{\textbf{(1)}}{\mathrm{C_6F_5{-}NHCH_3}} + \underset{\textbf{(2)}}{\mathrm{C_6F_5{-}N(CH_3)CHO}}$$

$$+\underset{\textbf{(3)}}{p\text{-}\mathrm{CH_3(H)N{-}C_6F_4{-}N(CH_3)CHO}}$$

$$+\underset{\textbf{(4)}}{p\text{-}\mathrm{OHC(CH_3)N{-}C_6F_4{-}N(CH_3)CHO}}$$

---

*Author to whom correspondence should be addressed.

SSDI 0022-1139(93)02903-R

$$\xrightarrow{\text{2 N KOH}} C_6F_5{-}NHCH_3$$
(1)

$$+p\text{-}CH_3(H)N{-}C_6F_4{-}N(H)CH_3\text{-}$$
(5)

$$CH_3N(H)CHO \xrightarrow{KOH + C_6F_6} C_6F_5{-}NHCH_3$$
(1)

$$+p\text{-}CH_3(H)N{-}C_6F_4{-}N(H)CH_3$$
(5)

Sodium hydride has been shown to cleave formyl groups, and formanilides react quite rapidly compared with alkyl formamides which require refluxing conditions to give a yield, for example, of 40% of sodium diethylamide [7]. Gas formation was observed during the metallation procedure with sodium hydride and lithium amide and also when hexafluorobenzene was added to the reaction mixture. In these reactions, the total yield based on the amount of hexafluorobenzene employed seems to be *c.* 50%. The results indicate that cleavage of *N*-methylformamide by metallation occurs only to a minor extent, as negligible amounts of *N*-methyl-2,3,4,5,6-pentafluoroaniline were formed. Most probably, unreacted sodium hydride, lithium amide or metallated *N*-methylformamide react with compound **4** as fast as it is formed to give **3**.

The mass spectra of the formanilides concur with the normal pattern [M − CO] for compound **3** and [M − CO] followed by [(M − CO) − CO] for compound **4** [8].

NMR spectra of compounds **2**, **3** and **4** demonstrated the presence of *trans* and *cis* isomers. It has been shown previously that the chemical shifts of formanilides in $CDCl_3$ solution are concentration dependent. However, the differences seem to be small [9–11]. NMR analyses at different concentrations were not performed here, as the ^1H NMR spectra of compounds **3** and **4** gave the same chemical shifts at two arbitrarily chosen concentrations.

The ^1H NMR spectrum of compound **2** in $CDCl_3$ showed two −CHO singlets and two methyl singlets. Based on previous findings [9, 10], the −CHO singlet at the lowest field is due to the *trans* isomer, i.e. when the carbonyl and phenyl groups have a *trans* relationship to each other. From ^1H integration, it may be proposed that the *trans* and *cis* isomers are present in a ratio of 33:67 respectively at ambient temperature. The ^{19}F spectrum contained two sets of three signals (one doublet and two triplets) also compatible with the proposed structures. The ^{13}C spectrum was as expected, apart from the absence of resonances from the carbons at the aromatic 1- and 4-positions, presumably due to an insufficient signal-to-noise ratio.

Compound **3** showed a similar pattern to **2** for the ^1H NMR spectrum (*trans* 20%). The ^{19}F NMR spectrum was in agreement with a *para*-substituted compound with *trans* and *cis* isomers present.

The ^{19}F NMR spectra of **4**, both in $CDCl_3$ and acetone-d_6, gave two multiplets of equal intensity, with a line-shape compatible with an unsymmetrically *para*-disubstituted fluorobenzene, and two singlets compatible with symmetrically *para*-disubstituted fluorobenzenes. This is interpreted as indicating the presence of the *cis–trans*, *trans–trans* and *cis–cis* isomers. From a comparison of the ^{19}F shifts of **4** with those of **2** and integration of the ^{19}F spectrum, it is proposed that the *trans–trans* resonances lie to low field of those of the *cis–cis* isomer and that from ^{19}F integration the ratio of *trans–trans/cis–cis/cis–trans* is 13:39:48 in acetone-d_6 at ambient temperature. The ^{13}C and ^1H spectra are fairly complicated but in reasonable agreement with the proposed structure and isomers.

Experimental

NMR spectra were obtained with Varian XL-300 (300 MHz proton frequency) and Varian Gemini 200 (200 MHz proton frequency) spectrometers. ^1H and ^{13}C chemical shifts are reported with reference to TMS and ^{19}F chemical shifts with respect to C_6F_6, downfield shifts being positive. Mass-spectrometric data were obtained with a VG Micromass 7070F instrument with the data system VG 11-250J. All reactions were performed under N_2. Reaction mixtures were hydrolyzed by the addition of 10% hydrogen chloride to give an acidic medium, extracted with ether, dried with anhydrous magnesium sulfate, concentrated and chromatographed on silica (230–400 mesh) starting with pentane as the elution solvent to which more and more ether was added ending with pure ether. Compounds **3** and **4** were rechromatographed, then recrystallized from a mixture of ether and light petroleum after having been dissolved in ether. The other compounds were recrystallized from light petroleum when necessary.

Reaction of N-*methylformamide with hexafluorobenzene*

(1) In the presence of sodium hydride

Sodium hydride (0.08 mol, 1.92 g in oil) was added during 4 h to a mixture of *N*-methylformamide (5.0 ml) in tetrahydrofuran (40 ml) placed on a 50 °C bath. The mixture was stirred overnight at ambient temperature and for 2 h the next day at 80 °C and then placed on a 0 °C bath. Hexafluorobenzene (0.04 mol, 7.44 g) was added all at once. The temperature was allowed to rise, whereupon an exothermic reaction took place. The viscous, yellowish mixture was refluxed for 1 h, cooled to 0 °C and hydrolyzed after the addition of 30 ml ether. Work-up gave 0.6 g (8%) *N*-methyl-2,3,4,5,6-pentafluoroaniline (**1**) [3, 5], 3.85 g (41%) *N*-formyl-*N,N'*-dimethyl-2,3,5,6-tetrafluorophenylene-1,4-diamine (**3**) (nc) (m.p. 82–83 °C) and 0.66 g (6%) *N,N'*-diformyl-*N,N'*-dimethyl-2,3,5,6-tetrafluorophenylene-1,4-diamine (**4**) (nc) (m.p. 121–123 °C).

Compound **3**: MS (EI, 70 eV) *m/z* (% rel. int.): 236 (64); 208 (20); 207 (25); 205 (11); 195 (12); 194 (12); 193 (100); 192 (93); 191 (7); 179 (5); 178 (6); 166 (5); 165 (6); 137 (6); 103 (6). HRMS: $C_9H_8F_4N_2O$ requires: M, 236.0573. Found, 236.0554. ^{1}H NMR ($CDCl_3$) δ: $(-CH_3)$; 3.27 (s); 3.18 (s); 3.12 (m); 3.09 (m). $(-NH)$: 4.02 (s,br). $(-CHO)$: 8.27 (s, amount 23%); 8.08 (s) ppm. ^{19}F NMR ($CdCl_3$) δ: 12.93 (m) (amount 20%); 10.85 (m); 0.74 (m); 0.39 (m) (amount 19%) ppm. IR (Nujol) (cm^{-1}): 3365 (s); 1704 (s); 1656 (m); 1339 (s); 1312 (m); 1172 (w); 1157 (m); 1065 (s); 995 (s); 965 (s); 788 (m); 738 (w).

Compound **4**: MS (EI, 70 eV) *m/z* (% rel. int.): 264 (69); 236 (16); 208 (18); 207 (24); 205 (8); 195 (13); 194 (12); 193 (100); 192 (11); 191 (7); 179 (5); 178 (7); 166 (4); 165 (7); 137 (5); 103 (4). HRMS: $C_{10}H_8F_4N_2O_2$ requires: M, 264.0522. Found, 264.0510. ^{1}H NMR ($CDCl_3$) δ: $(-CH_3)$: 3.37 (s); 3.34 (s); 3.28 (s); 3.26 (s). $(-CHO)$: 8.30 (s); 8.19 (s) ppm. ^{13}C NMR ($CDCl_3$) δ: $(-CH_3)$: 35.71; 32.70. $(-CHO)$: 162.04; 161.89; 161.54 ppm.^{1}H NMR (acetone-d_6) δ: $(-CH_3)$: 3.42 (m); 3.26 (m); 3.24 (m). $(-CHO)$: 8.41 (m); 8.33 (m); 8.27 (m) ppm. ^{13}C NMR (acetone-d_6) δ: $(-CH_3)$: 35.82; 32.54; 32.48. $(-CHO)$: 163.15; 163.07; 162.96 ppm. ^{19}F NMR (acetone-d_6) δ: 18.1–18.3 (m); 14.25–14.45 (m) (amount 48%); 17.53 (s, amount 13%); 15.07 (s, amount 39%) ppm. IR (Nujol) (cm^{-1}) 1674 (s); 1498 (s); 1171 (s); 1075 (s); 1010 (m); 982 (s); 8.77 (s); 715 (m).

(2) In the presence of lithium amide

Lithium amide (0.08 mol, 1.84 g) was added to a mixture of *N*-methylformamide (5.0 ml) in tetrahydrofuran (50 ml) and dimethylformamide (15 ml). The mixture was refluxed for 9 h, placed on a 0 °C bath and flushed with nitrogen, whereupon hexafluorobenzene (0.04 mol, 7.44 g) was added all at once. The temperature was allowed to rise whereupon an exothermic reaction took place. The viscous, yellowish mixture was refluxed for 1 h, cooled to 0 °C and hydrolyzed after the addition of ether (30 ml). A GC analysis of the crude mixture showed the presence of *N*-methyl-2,3,4,5,6-pentafluoroaniline (**1**), *N*-formyl-*N,N'*-dimethyl-2,3,5,6-tetrafluorophenylene-1,4-diamine (**3**) and *N,N'*-diformyl-*N,N'*-dimethyl-2,3,5,6-tetrafluorophenylene-1,4-diamine (**4**). The mixture was treated with 2 N KOH (50 ml) for 8 h at 95 °C, cooled and extracted with ether. Besides *N*-methyl-2,3,4,5,6-pentafluoroaniline (**1**) [3, 5], work-up also gave 3.5 g (42%) *N,N'*-dimethyl-2,3,5,6-tetrafluorophenylene-1,4-diamine (**5**), m.p. 96–98 °C (lit. value, 92.5–94 °C [5] and 94 °C [6]).

Compound **5**: MS (EI, 70 eV) *m/z* (% rel. int.): 208 (61); 207 (12); 205 (11); 194 (12); 193 (100); 192 (7); 191 (7); 179 (8); 166 (10); 103 (12). ^{1}H NMR ($CDCl_3$) δ: $(-CH_3)$: 2.96. $(-NH)$: 3.27 (disappeared with D_2O treatment) ppm. ^{19}F NMR ($CDCl_3$) δ: 1.50 (s) (lit. 84.2 (s) in acetone from trifluoroacetic acid [5]) ppm. IR (Nujol) (cm^{-1}) 3285 (s); 1520 (s); 1303 (w); 1268 (w); 1163 (m); 1130 (m); 1092 (m); 980 (s); 913 (w); 735 (w, br). Analysis: $C_8H_8F_4N_2$ requires: C, 46.16; H, 3.87%; M, 208.0624. Found: C, 46.05; H, 4.11%; HRMS: M, 208.0643.

(3) In the presence of potassium hydroxide

Hexafluorobenzene (0.02 mol, 3.72 g) was added to a stirred mixture of potassium hydroxide (4.5 g as pellets) and *N*-methylformamide (12 ml) at ambient temperature. After 4 h more potassium hydroxide (4.5 g) was added. Ordinary work-up the next day gave 2.2 g (56%) *N*-methyl-2,3,4,5,6-pentafluoroaniline (**1**) and 0.85 g (20.5%) *N,N'*-dimethyl-2,3,5,6-tetrafluorophenylene-1,4-diamine (**5**).

(4) In the presence of lithium hydroxide

Lithium hydroxide (2.0 g) was added over a period of 30 min to a stirred mixture of *N*-methylformamide (12 ml) and hexafluorobenzene (0.02 mol, 3.72 g) at ambient temperature. After 4 h, 50 ml ether was added. Work-up gave 1.72 g (43.5%) *N*-methyl-2,3,4,5,6-pentafluoroaniline (**1**), 0.70 g (15%) *N*-formyl-*N,N'*-dimethyl-2,3,5,6-tetrafluorophenylene-1,4-diamine (**3**) and 0.05 g (1%) *N*-methyl-2,3,4,5,6-pentafluoroformanilide (**2**) (see next reaction).

(5) In the presence of lithium hydroxide in tetrahydrofuran

Lithium hydroxide (1.5 g) was added over a period of 30 min to a stirred mixture of *N*-methylformamide (5 ml) and hexafluorobenzene (0.02 mol, 3.72 g) in tetrahydrofuran (10 ml) at ambient temperature. Next morning, 20 ml ether was added. Ordinary work-up gave a crude mixture (2.6 g) which by chromatography was separated into 0.80 g (20.5%) *N*-methyl-2,3,4,5,6-pentafluoroaniline (**1**), 0.50 g (11%) *N*-methyl-2,3,4,5,6-pentafluoroformanilide (**2**) (nc, an oil), and 0.96 g (20.5%) *N*-formyl-*N,N'*-dimethyl-2,3,5,6-tetrafluorophenylene-1,4-diamine (**3**) contaminated by traces (4%) of *N,N'*-diformyl-*N,N'*-dimethyl-2,3,5,6-tetrafluorophenylene-1,4-diamine (**4**).

Compound **2**: NMR ($CDCl_3$) δ: $(-CH_3)$: 3.31 (s, amount 33%); 3.21 (s). $(-CHO)$: 8.26 (s, amount 33%); 8.10 (s) ppm. ^{13}C NMR ($CDCl_3$) δ: $(-CH_3)$: 35.71; 32.71. $(-CHO)$: 162.18; 161.92 ppm. ^{19}F NMR ($CDCl_3$) δ: 17.47 (d, amount 33%); 7.85 (t, amount 33%); 0.32

(t, amount 33%); 14.88 (d); 8.33 (t); 1.42 (t) ppm. IR (neat) (cm^{-1}) 1703 (s); 1655 (w); 1515 (s); 1400 (w); 1236 (m); 1338 (m); 1316 (s); 1232 (m); 1206 (w); 1100 (m); 1067 (m); 1035 (s); 995 (s); 926 (s); 880 (w); 756 (s). HRMS: $C_8H_4F_5NO$ requires: M, 225.0213. Found, 225.0214.

References

1 R. Koppang, *J. Organomet. Chem.*, *46* (1972) 193.
2 R. Koppang, *J. Fluorine Chem.*, *8* (1976) 389.
3 R. Koppang, *J. Polym,. Sci., Polym. Chem. Ed.*, *14* (1976) 2225.
4 J.G. Allen, J. Burdon and J.C. Tatlow, *J. Chem. Soc.*, (1965) 6329.
5 G.M. Brooke, J. Burdon, M. Stacey and J.C. Tatlow, *J. Chem. Soc.*, (1960) 1768.
6 L.A. Wall, W.J. Pummer, J.E. Fearn and J.M. Antonucci, *J. Res. Nat. Bur. Stand.*, *67A* (1963) 481.
7 J.C. Powers, R. Seidner and T.G. Parsons, *Tetrahedron Lett.*, (1965) 1713.
8 S. Hammerum and P. Wolkoff, *Adv. Mass Spectrom.*, *7B* (1978) 1318.
9 A.J.R. Bourn, D.G. Gillies and E.W. Randall, *Tetrahedron*, *20* (1964) 1811.
10 A.J.R. Bourn, D.G. Gillies and E.W. Randall, *Tetrahedron*, *22* (1966) 1825.
11 R. Koppang and K. Schaumburg, *J. Fluorine Chem.*, *12* (1978) 169.