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SUBSTITUTION ON HEXAFLUOROBENZENE WITH ANILIDES

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SUMMARY

The difference in reactivity of lithium anilides towards hexafluorobenzene in different solvents has been described.

In tetrahydrofuran lithium *N*-methylanilide gave a 1,4-disubstituted compound, while lithium anilide rendered a monosubstituted compound. In a mixture of tetrahydrofuran and hexamethylphosphoric triamide lithium *N*-methylanilide gave a 1,2,4,5-tetrasubstituted compound, while lithium anilide gave a 1,2-disubstituted compound.

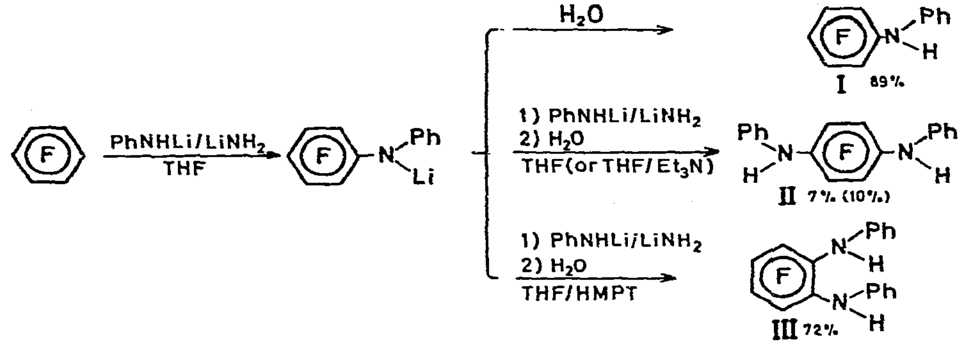
The anilides have been prepared in tetrahydrofuran at 0–10° by treating the anilines with lithium amide.

INTRODUCTION

A large number of displacement reactions on hexafluorobenzene with amines are known[1–9]. Only three papers have dealt with aromatic amines as the nucleophile[4,8,9]. Sodium anilide gave a monosubstituted compound (I), and traces of a *para*-substituted compound (II)[4]. A higher yield of the latter compound has been obtained under more severe conditions (190–200°)[4]. Contrary to this the lithium *N*-methylanilide gave the *para*-substituted compound (VI) in good yield[9]. In this paper the difference in reactivity of lithium anilides towards hexafluorobenzene under different conditions will be described.

RESULTS AND DISCUSSION

Reactions between the lithium anilide and hexafluorobenzene in tetrahydrofuran gave the monosubstituted compound (I), and under more severe conditions a low yield of the *para*-substituted compound (II). The addition of triethylamine had little influence on the product composition. On the other hand a reaction carried out in a mixture of tetrahydrofuran and hexamethylphosphoric triamide resulted in *ortho*-substitution in higher yield than 70%[8].

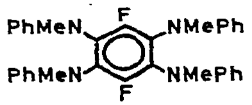
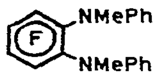
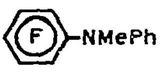
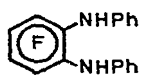
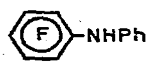


Scheme 1. Reactions between hexafluorobenzene, lithium anilide and lithium amide in different solvent systems.

The ^{19}F NMR spectrum in chloroform-*d* of the *ortho*-substituted compound (III) showed two different multiplets. In each multiplet two peaks were very strong compared with the others. Coupling constant for these peaks was J 23 Hz (Table 1), which agrees with the observation that J_{ortho} has a value of about 20 Hz[12].

TABLE 1

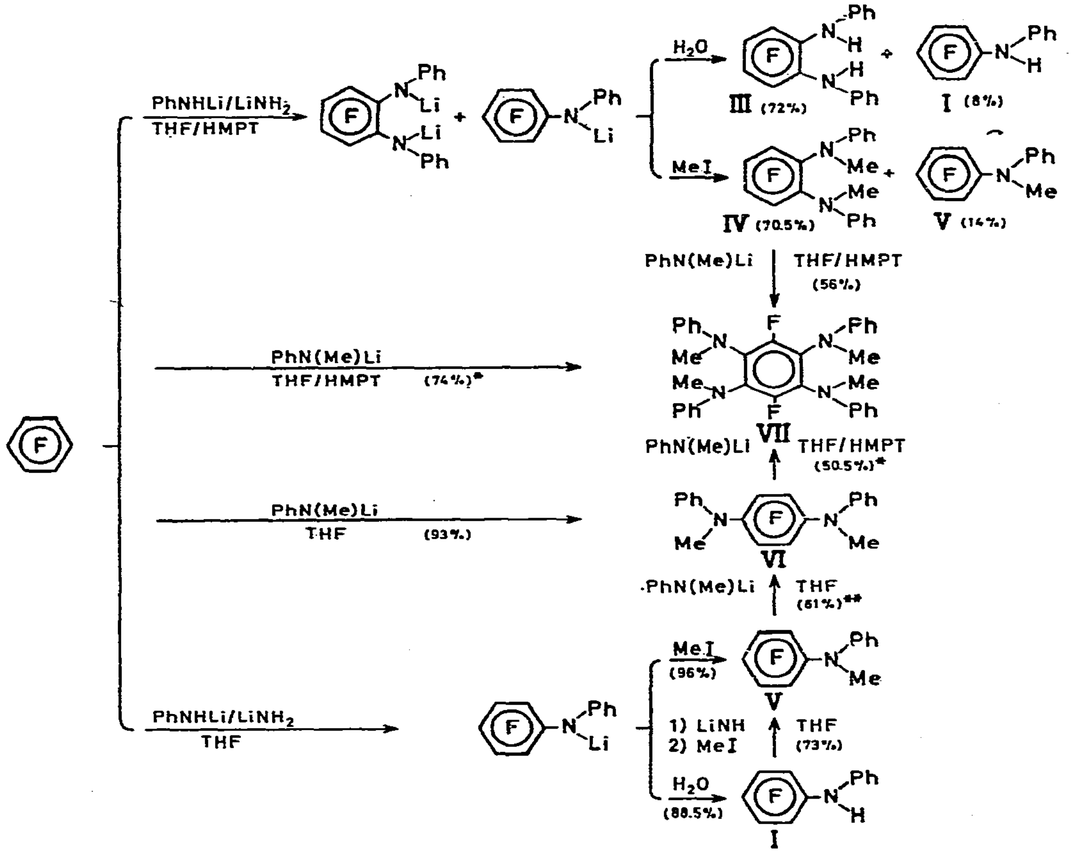
^{19}F CHEMICAL SHIFTS IN CHLOROFORM-*d* WITH C_6F_6 AS INTERNAL STANDARD AT 94.1 MHz

Compound	*^{19}F chemical shift (ppm)*	*Remarks*
	15.9	Singlet
	16.0	Singlet
	17.4	Multiplet (two highest peaks at 17.46 and 17.26 ppm).
	2.7	Multiplet (two highest peaks at 2.76 and 2.54 ppm)
	16.9	Multiplet (two highest peaks at 16.98 and 16.82 ppm)
	3.8	Triplet (peaks at 4.01, 3.80 and 3.59 ppm)
	−0.3	Multiplet (highest peaks at −0.11, −0.27, −0.34, −0.50 ppm)
	12.0	Singlet
	15.2	Multiplet (two highest peaks at 15.35 and 15.11 ppm)
	−1.0	Multiplet (two highest peaks at −0.90 and −1.14 ppm)
	13.0–12.6	Region of bands. Multiplet (highest peaks at 12.87 and 12.67 ppm)
	−0.7 to −1.3	Region of bands. Multiplet (highest peaks at −1.03 and −1.20 ppm)
	−1.8	"Triplet of triplets" (peaks at −1.62, −1.83, and −2.04 ppm)

No reaction resulted between lithium bis(pentafluorophenyl)amide and lithium pentafluoroanilide. When hexafluorobenzene was reacted with lithium anilide in dimethylformamide, an insoluble polymer-like material was formed.

The *ortho*-substituted compound (IV) was prepared in good yield by the reaction steps visualized in Schemes 1 and 2. ^{19}F NMR showed two different multiplets. The coupling constant was *J* 20 Hz (Table 1).

Reaction between equimolecular quantities of lithium *N*-methylanilide and hexafluorobenzene in tetrahydrofuran gave the mono- and the *para*-substituted compounds (V) and (VI) respectively[9]. A convenient way to the monosubstituted compound (V) was obtained by treating the lithium *N*-phenyl pentafluoroanilide prepared *in situ*, with methyl iodide (see Scheme 2). The *para*-substituted compound (VI) was obtained in high yield when lithium *N*-methylanilide was treated with hexafluorobenzene in tetrahydrofuran in 2/1 molar ratio.



Scheme 2. Performed reactions.

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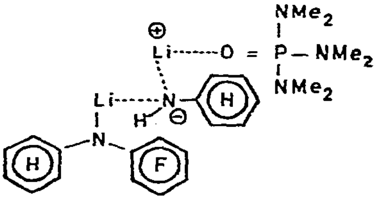
*Calculated with respect to consumed *N*-methylaniline.

**Unpublished work by R. Koppang and H. Gilman. Reagents: PhN(Me)H/BuLi.

If the same reaction was run in a mixture of tetrahydrofuran and hexamethylphosphoric triamide, a tetrasubstituted compound (VII) was isolated in good yield[8], further some of the monosubstituted compound (V) was obtained. The proton NMR spectrum of the tetrasubstituted compound showed only one peak at δ 2.96 ppm for the methyl protons; this peak broadened only by expansion when the spectrum was run in different solvents[8]. These results seem to indicate a compound in which all methyl groups are identical, *viz.* 1,4-difluorotetrakis(*N*-methylanilino)benzene. Previously it has been shown by Tatlow *et al.* that the potassium thiophenoxide in pyridine with hexafluorobenzene gives the disubstituted compound, 1,2,4,5-tetrafluorobis(phenylthio)benzene, and the tetrasubstituted compound, 1,4-difluorotetrakis(thiophenyl)benzene[10]. A tetrakis compound has also recently been formed by treating trichloro-2-thienyllithium with hexafluorobenzene[13].

1,4-Difluorotetrakis(*N*-methylanilino)benzene (VII) could also be obtained from the disubstituted compounds (IV) and (VI) when reactions with lithium *N*-methylanilide were performed in a mixture of tetrahydrofuran and hexamethylphosphoric triamide.

The *ortho*-substituted compound (III) has most probably been formed through an intermediate complex (A) between the lithium *N*-phenylpentafluoroanilide, lithium anilide and hexamethylphosphoric triamide. This complex may activate the *ortho*-fluorine or direct the oncoming anilide towards the *ortho*-position.



A

It has previously been shown that hexamethylphosphoric triamide added to geminal organomagnesium compounds stabilizes the ionized form[11]. A similar condition is also believed to exist for (A).

Wali *et al.*[2] and later Burdon[5] discussed the directional effect of various substituents to hexafluorobenzene at the site of the next substitution. Wall suggested that the nucleophile plays a dominating role in determining the orientation, while Burdon discussed the problem with respect to the relative stability of the transition state. In both discussions the *para*-quinoid structure was used for the explanation of the *para*-substitution. The question is then why lithium *N*-methylanilide reacts with hexafluorobenzene so readily compared with other amines or amides. Already when equimolecular quantities of lithium *N*-methylanilide and hexafluorobenzene were mixed together at −76°, and the temperature raised slowly to room temperature, a yield of 49%* of the *para*-substituted compound (VI) was formed[9]. It is believed

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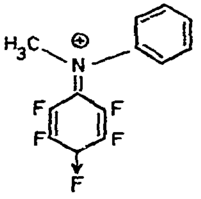
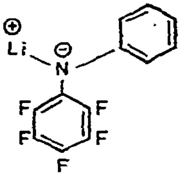
*Calculated with respect to consumed *N*-methylaniline.

that the phenyl group in the mono-substituted compound (V) may stabilize a resonance structure as (B) with a conjugated system.



B



C

Contrary to the lithium in (C), the methyl group will also stabilize the conjugated system. Wall *et al.* suggested that the induced charge in a *para*-quinoid structure as compound (B) would "prefer" to reside closer to the fluorine atom than to the carbon atom, as indicated in the figure, and this would favour a separation of the fluoride ion. It is therefore believed that the increased reactivity of compound (B) towards a nucleophile is caused by the conjugated system and the fluorine atoms, which "withdraws" the electrons from the *para*-position in (B) and "prepares" this site for a nucleophilic attack.

Lithium amide has proved favourable for a fast metalation of anilines in tetrahydrofuran at 0–10°, and was therefore used throughout this work as a metalation compound. The liberation of ammonia showed that a reaction took place.

EXPERIMENTAL

All reactions were carried out under an atmosphere of dry, highly purified nitrogen. Tetrahydrofuran (THF) was dried and distilled prior to use from sodium benzophenone ketyl. Hexamethylphosphoric triamide (HMPT) was first stored on 5 Å molecular sieves and then on calcium hydride. All melting and boiling points are uncorrected. The ^{19}F chemical shifts are gathered in Table 1. IR, NMR, and MS spectra were determined employing Perkin–Elmer 457-IR, Varian 100 MHz, NMR, and AEI-MS 902 spectrometers, respectively.

Reactions with lithium anilide

To a lithium anilide suspension prepared in THF at 10° from aniline (9.3 g, 0.1 mole) and lithium amide [2.6 g, compounds (I) and (Va), and 5.1 g, compounds (II) and (IV)] hexafluorobenzene (9.3 g, 0.05 mole) was added during 20 min.

The reactions described were worked up by cooling, hydrolyzing with 5% HCl, and extracting with ether. The ethers were washed with water, dried on anhydrous sodium sulphate, and concentrated by distillation. When methyl iodide was employed, the ether extract was also treated with a sodium thiosulphate solution.

N-Phenylpentafluoroaniline

After 2 h at 0° the reaction mixture, described above, in THF (100 ml) was stirred for an additional hour at ambient temperature, cooled, and worked up to give a red oil. The oil was chromatographed on neutral Al_2O_3 (Woelm) with petroleum ether (40–65°). This gave 11.45 g (88.5%) *N*-phenylpentafluoroaniline, m.p. 69.5–71.5° (lit.[4] m.p. 71–73°); NH stretch 3400 cm^{-1} (lit.[4] 3400 cm^{-1}); mol. wt. 259 (calcd. mol. wt. 259.2). NMR spectrum in $CDCl_3$ showed one broad peak for the amine proton at δ 5.19 ppm.

2,3,5,6-Tetrafluoro-N,N'-diphenyl-1,4-phenylenediamine (II)

(*a*). *Prepared in tetrahydrofuran (30 ml).* The reaction mixture, already described, was stirred over night at 90°. The ordinary work-up gave a black oil which was chromatographed on neutral Al_2O_3 (Woelm). Elution with petroleum ether (40–65°) gave 1.1 g (8.5%) *N*-phenylpentafluoroaniline, m.p. 69–71°.

Elution with ether/petroleum ether (40–65°)* and subsequent sublimation gave 1.2 g (7.2%) 2,3,5,6-tetrafluoro-*N*,*N'*-diphenyl-1,4-phenylenediamine, m.p. 147–150° (lit.[4] m.p. 149–152°); NH stretch at 3390 cm^{-1} (lit.[4] 3400 cm^{-1}); mol.wt. 332 (calcd. mol.wt. 332.3). NMR spectrum in $CDCl_3$ showed one peak for the amine protons at δ 5.40 ppm.

(*b*) *Prepared in tetrahydrofuran (50 ml)/triethylamine (28 ml).* To the reaction mixture, already described, triethylamine (28 ml) was added, whereupon the temperature of the mixture was raised to 78° during 1 h. The next morning the mixture solidified when cooled, and undried ether (100 ml) was added. The usual work-up, as already described, gave a black oil.

A slow distillation on to a "cold-finger" gave, after recrystallization from petroleum ether (40–65°), 4.7 g (36.3%) *N*-phenylpentafluoroaniline, m.p. 68–70°. On addition of some petroleum ether (40–65°) to the remaining material, a precipitate was formed. This gave, after sublimation and recrystallization from ether/petroleum ether (40–65°), 1.7 g (10.2%) 2,3,5,6-tetrafluoro-*N*,*N'*-diphenyl-1,4-phenylenediamine, m.p. 147–149°.

3,4,5,6-Tetrafluoro-N,N'-dimethyl-N,N'-diphenyl-1,2-penylenediamine (IV)

To the reaction mixture, prepared as already described in THF (50 ml), HMPT (25 ml) was added all at once. The brown mixture was stirred at 65° over night. The resulting blood-red mixture was cooled to 0° and methyl iodide (17.0 g, 0.12 mole) was added over 20 min as an exothermic reaction took place. The mixture was stirred at ambient temperature for 1 h, and at 60° for 2 h, cooled and worked up to give a black oil which was vacuum distilled into two fractions; 1.9 g (13.9%) *N*-phenyl-*N*-methylpentafluoroaniline (V) and a pale yellow oil which crystallized (m.p. 84.5–87°). The crystallized material was chromatographed on neutral Al_2O_3 (Woelm) with petroleum ether (40–65°). This gave 12.72 g (70.5%) 3,4,5,6-tetrafluoro-*N*,*N'*-dimethyl-*N*,*N'*-diphenyl-1,2-phenylenediamine, m.p. 91–92°. Characteristic infrared

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*A sample analyzed by Dr. Tatlow gave an IR spectrum which agreed with the IR of an authentic sample[4]. The sample was assumed by Dr. Tatlow to be contaminated by *N*-phenylpentafluoroaniline.

absorption bands in Nujol were 1495 (s), 1100 (s), 1050 (m), 1030 (m), 996 (m), 980 (s), 950 (s). NMR spectrum in $CDCl_3$ showed one peak for the methyl protons at δ 2.91 ppm. (Found: C, 66.86; H, 4.53; mol. wt., 360. $C_{20}H_{16}F_4N_2$ calcd.: C, 66.67; H, 4.48%; mol. wt., 360.3.)

N-Phenyl-N-methylpentafluoroaniline (V)

(*a*). *Prepared from hexafluorobenzene.* The previously described reaction mixture prepared in THF (50 ml), was warmed to 75° during 1 h and then cooled to 0°. Methyl iodide (7.1 g, 0.05 mole) was added during 10 min. The mixture was stirred over night at ambient temperature. Work-up afforded a black oil which was vacuum distilled. The pale yellow distillate (b.p. 114°/6 mm) crystallized and was chromatographed on neutral Al_2O_3 (Woelm) with petroleum ether (40–65°). This gave 13.1 g (96%) *N*-phenyl-*N*-methylpentafluoroaniline, m.p. 28–29.5°. Characteristic infrared, absorption bands were 1520 (s), 1504 (s), 1093 (m), 1075 (m), 1045 (w), 995 (s), 968 (m). NMR spectrum in $CDCl_3$ showed one peak for the methyl protons at δ 3.22 ppm (Found: C, 57.20; H, 3.29; N, 4.73; mol.wt., 273. $C_{13}F_5H_8N$, calcd.: C, 57.15; H, 2.95; N, 5.13%; mol.wt., 273.2.)

(*b*). *Prepared from N-phenylpentafluoroaniline.* To a mixture of *N*-phenylpentafluoroaniline (3.89 g, 0.015 mole) and lithium amide (0.39 g) THF (15 ml) was added. After stirring for 20 min, the mixture was refluxed for 30 min, cooled to 0° and methyl iodide (2.7 g, 0.019 mole) was added. The mixture was stirred at room temperature over night, and worked up as previously described. This gave a reddish black oil which was vacuum distilled. The distillate was chromatographed on neutral Al_2O_3 (Woelm) with petroleum ether (40–65°), this gave 3.0 g (73.1%) *N*-phenyl-*N*-methylpentafluoroaniline, m.p. 27–29°. Further eluation with petroleum ether (40–65°)/ether gave only traces of recovered *N*-phenylpentafluoroaniline.

2,3,5,6-Tetrafluoro-N,N'-dimethyl-N,N'-diphenyl-1,4-phenylenediamine (VI)

To a lithium *N*-methylanilide suspension prepared at −10° in THF (50 ml), from lithium amide (2.1 g) and *N*-methylaniline (8.56 g, 0.08 mole), hexafluorobenzene (7.44 g, 0.04 mole) in THF (120 ml) was added during 20 min. The mixture was warmed slowly to room temperature at which it was stirred for another hour. The ordinary work-up resulted in a solid which was chromatographed on neutral Al_2O_3 (Woelm) with $CHCl_3$/petroleum ether (40–65°). Recrystallization from $CHCl_3$/ petroleum ether (40–65°) gave 13.4 g (93.2%) 2,3,5,6-tetrafluoro-*N*,*N'*-dimethyl-*N*,*N'*diphenyl-1,4-phenylenediamine, m.p. 160–162°. Characteristic infrared absorption bands in Nujol were 1508 (s), 1490 (s), 1108 (s), 1030 (w), 985 (s), 949 (m). NMR spectrum in $CDCl_3$ showed one peak for the methyl protons at δ 3.28 ppm. (Found: C, 66.96; H, 4.80; mol.wt., 360. $C_{20}H_{16}F_4N_2$ calcd.: C, 66.67; H, 4.48%; mol.wt., 360.3.)

1,4-Difluorotetrakis(N-methylanilino)benzene (VII)

(*a*). *Prepared from 3,4,5,6-tetrafluoro-N-N'-dimethyl-N,N'-diphenyl-1,2-phenylenediamine.* To a lithium amide (0.51 g) suspension in THF (20 ml) at 0° *N*-methylaniline (2.14 g, 0.02 mole) was added. After 25 min 3,4,5,6-tetrafluoro-*N*,*N'*-dimethyl-*N*,*N'*-diphenyl-1,2-phenylenediamine (3.6 g, 0.01 mole) and after another 10 min HMPT (12 ml) were added. The mixture was warmed to 80° over 1 h. The colour had turned from yellow to grey. The next morning the mixture was cooled and worked up as previously described to give dark solid crystals. The crystals were treated twice with 30 ml hot petroleum ether (40–65°) and then sublimed. Recrystallization from $CHCl_3$/petroleum ether (40–65°) gave 3.0 g (56.2%) 1,4-difluorotetrakis(*N*-methylanilino)benzene, m.p. 181–184°, which was identified by comparison with an authentic sample[8]. Only traces of the starting material were recovered from the petroleum ether.

(*b*). *Prepared from 2,3,5,6-tetrafluoro-N,N'-dimethyl-N,N'-diphenyl-1,4-phenylenediamine.* To the suspension of lithium *N*-methylanilide, prepared as under (*a*), HMPT (12 ml) and then 2,3,5,6-tetrafluoro-*N*,*N'*-dimethyl-*N*,*N'*-diphenyl-1,4-phenylenediamine (7.2 g, 0.02 mole) were added. The mixture was warmed to 75° over 1 h and stirred at this temperature over night, cooled, and worked up to give a solid which was washed five times with 20 ml hot petroleum ether (40–65°). Concentration of the petroleum ether gave a sediment which consisted of the starting material and the tetrasubstituted compound (TLC). These were separated by sublimation, which gave 1.9 g of the starting material. The precipitate and the remnant from the sublimation were recrystallized from $CHCl_3$/petroleum ether (40–65°); this gave 2.7 g (50.5%)* 1,4-difluorotetrakis(*N*-methylanilino)benzene, m.p. 181–183°, which was identified by comparison with an authentic sample[8].

ACKNOWLEDGEMENTS

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*Calculated with respect to consumed *N*-methylaniline.