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AROMATIC POLYFLUORO-COMPOUNDS. PART LVIII. THE REACTION OF n-BUTYLLITHIUM WITH METHYL-, FLUOROMETHYL-, AND DIFLUOROMETHYL-PENTAFLUOROBENZENE.

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SUMMARY

No metallation of the benzylic C-H bonds was detected when n-butyllithium reacted at -78°C with methyl-, fluoromethyl- and difluoromethyl-pentafluorobenzene. The isolated product, in each case, was the para-substituted butyl toluene; respectively, 1-n-butyl-4-methyl-, -4-fluoromethyl-, and -4-difluoromethyl-tetrafluorobenzene.

INTRODUCTION

As part of our earlier synthetic programme in aromatic fluorocarbon chemistry [1], various organometallic intermediates were utilised, including polyfluoroaryl lithium reagents [2,3]. One approach to the synthesis of these [4] was by direct replacement of aryl hydrogen (e.g. in pentafluorobenzene) by lithium from an alkyllithium compound. However, highly fluorinated organolithium species easily lose lithium fluoride, and for maximum synthetic utility, such eliminations must be inhibited, as when the unsaturated fluoro-product produced thereby is not of normal stability. This applies to the benzynes formed from fluoroaryl lithium compounds [3], and to the sterically unfavourable products derived from fluoro-alicyclic lithium species, with bridgehead-type fusions [5]. Organo-lithium compounds with these structures can be formed readily (R_fH + alkyllithium) and have great synthetic utility.

Another aryl type with no easy elimination pathway is a polyfluorobenzyl lithium, such as $C_6F_5.CF_2Li$, possibly derivable directly from $C_6F_5.CHF_2$. However, the $.CHF_2$ group has a relatively low carbon acidity [6],

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and nucleophilic attack on the pentafluorophenyl nucleus by the alkyllithium present could well occur preferentially. Such a reaction resulted when methylpentafluorobenzene [7] and perfluorotoluene [8], were each treated with methyllithium, the product in each case being a fluoro-p-xylene derivative. This paper describes the reaction of n-butyllithium with three polyfluorotoluenes, to determine which type of reaction occurred.

RESULTS AND DISCUSSION

With the polyfluorotoluenes $C_6F_5.CH_3$ (I), $C_6F_5.CH_2F$ (II), and $C_6F_5.CHF_2$ (III), the hydrogens in the benzylic positions should become increasingly acidic with increasing fluorine substitution, but also would the side chain be expected to activate increasingly the aryl fluorines (particularly the para-ones) towards nucleophilic attack. Hence, it is not clear which compound is most likely to undergo metallation, and all three were treated with n-butyllithium, in the presence of reactants which would trap any benzyllithium intermediates formed.

The fluoromethyl (II) and difluoromethyl (III) compounds were unknown when the work was done [9] and were made from the analogous benzylic chlorides [7] by a standard exchange process [10] using potassium fluoride. These compounds have since been reported via reactions of sulphur tetrafluoride, II from pentafluorobenzyl alcohol, and III from pentafluorobenzaldehyde [11]; II has been made also from reactions of carbocations [12].

Methylpentafluorobenzene (I) in tetrahydrofuran was treated with an equimolar amount of n-butyllithium in n-hexane at -78°C and gave a deep orange solution showing a negative Gilman colour test [13] for butyllithium. A stream of carbon dioxide was then passed through, but work-up afforded only 1-n-butyl-4-methyltetrafluorobenzene (IV), with no acidic product. It is known [14] that triethylenediamine can form complexes with some organolithium species, and can sometimes catalyse metallation reactions of the type sought here. However, addition of an equimolar amount of triethylenediamine to the above reaction did not alter the result. Use of diethyl ether as main solvent gave little reaction at -78°C, unless triethylenediamine was present, but the end result was the same as that described above. Using n-hexane as main solvent, there was no reaction at -78°C even in the presence of triethylenediamine. Warming to 15°C gave a reaction, and iodine was added to trap organometallic species, but again compound IV was the only product isolated.

The reaction of the benzyl fluoride (II) with n-butyllithium in tetrahydrofuran as solvent, but with added acetaldehyde, gave a result analogous to the one above, the only product isolated being 1-n-butyl-4-fluoromethyltetrafluorobenzene (V), though the conversion was poorer, and there was much more unreacted starting material (II).

The benzal fluoride (III) was treated with an excess of n-butyllithium in tetrahydrofuran to give a good yield of 1-n-butyl-4-difluoromethyltetrafluorobenzene (VI). Using equimolar proportions, and in the presence of carbon dioxide, and of benzaldehyde, there was only the same product (VI) detected in each case, though significant amounts of starting material (III) were recovered.

Though strict comparisons were difficult, it seemed as though the fluoromethyl derivatives II and III reacted relatively slowly in the nucleophilic aromatic substitutions, to give V and VI respectively. Certainly, the expected activation, relative to the toluene I, did not occur. It is possible there was some association with the n-butyllithium, giving an increased electron density on the aromatic ring, but the absence of any other product at all, besides IV, V and VI, from any reactions, makes the formation of an actual benzyllithium very unlikely.

Deuteration of difluoromethylpentafluorobenzene (III) did not occur with potassium hydroxide in deuterium oxide under quite forcing conditions. The lack of reactivity to strong alkali of both the C_6F_5- and $-CHF_2$ groups was surprising. No bromination of the $-CHF_2$ group of III could be induced by bromine under prolonged exposure to ultraviolet light.

The structures of the butyl-methylbenzenes (IV-VI) followed from their elemental analyses and nmr spectra. The standard ^1H pattern was shown for an n-butyl group, and both compounds II and V showed the characteristic ^1H and ^{19}F peaks for a $-CH_2F$ group: likewise compounds III and VI showed the expected patterns for $-CHF_2$. The para-orientation of IV, V and VI was shown by the presence of ^{19}F peaks at around 146 ppm (relative to CCl_3F); two very close and of equal intensity for IV, and only one (but for four fluorines) for V and VI: this chemical shift is characteristic of aryl F ortho to an alkyl group. The para-orientation was as expected [7, 8].

EXPERIMENTAL

Reaction of Methylpentafluorobenzene with n-Butyllithium

n-Butyllithium (3.2 g) in n-hexane (20 cm^3) was added rapidly to methylpentafluorobenzene (I) (9.0 g) [7] in dry tetrahydrofuran (100 cm^3) stirred at -78°C in an atmosphere of nitrogen. A deep yellow solution resulted, and after 5 min. a Gilman 11A colour test [13] for the presence of butyllithium was negative. After 30 min., a stream of dry carbon dioxide was passed for 4 hours. The solution was then warmed to 15°C, water (20 cm^3) and diethyl ether (150 cm^3) added cautiously, and the ether layer washed with 4M H_2SO_4 (100 cm^3). The ether layer was then washed with aqueous sodium bicarbonate (2 x 100 cm^3), the aqueous solutions extracted again with ether, and the combined ether layers dried ($MgSO_4$), and the ether distilled off through a 6" column packed with glass helices. The residual orange liquid (7.7 g) showed glc peaks from hexane (8%), methylpentafluorobenzene (20%) and product (72%). Further distillation gave the last, 1-n-butyl-4-methyltetrafluorobenzene (IV) nc, b.p. 203°C (Found: C, 60.4; H, 5.3. $C_{11}H_{12}F_4$ requires C, 60.0; H, 5.5%): ^1H nmr; n-Bu, 7.29 (2) t, 8.50 (4) m, 9.04 (3) t; Ar-Me, 7.75 (3) t: ^{19}F nmr; 145.6, 146.6, equal intensity. The sodium bicarbonate washings were acidified and back-extracted, but only a very small amount of an unidentifiable mixture was recovered.

The experiment was repeated, with the tetrahydrofuran solution containing triethylenediamine (6.0 g) as well as I. A deep red reaction mixture was formed, but otherwise the results were very similar.

When diethyl ether was used as main solvent, instead of tetrahydrofuran, reaction was slow, little colour developed, and after 1 hour at -78°C the Gilman test was positive. Triethylenediamine (2.0 g) in ether (80 cm^3) was added. After 1 hour further, the Gilman test was only slightly positive, and continuation as before afforded liquid product (7.5 g) containing I (44%) and IV (55%). The bicarbonate extract gave a yellow liquid (2.0 g) containing n-pentanoic acid.

Addition as before to I (9.0 g) and triethylenediamine (2.0 g) in ether (150 cm^3) gave a yellow solution with a negative Gilman test after 20 min. at -78°C. Continuation as before gave a liquid product (8.0 g) containing I (14%) and III (85%), with no acidic by-products.

Use of n-hexane (150 cm^3) instead of tetrahydrofuran as main solvent gave no evidence of reaction after 2 hours at -78°C. Triethylenediamine (0.5 g) in n-hexane (20 cm^3) was added; after 1 hour, with no signs of reaction, diethyl ether (10 cm^3) was added. Only after the solution had been warmed to 15°C for 2 hours was there a yellow colour, and a negative Gilman test. Iodine (5.0 g) was then added. Work-up gave a product (8.0 g) containing I (11%) and III (81%), and no organic iodides were found.

Fluoromethylpentafluorobenzene (II)

Chloromethylpentafluorobenzene (12.0 g) [7] was added to a vigorously-stirred suspension of anhydrous potassium fluoride (10 g, dried by heating) in dried dimethylformamide (25 cm^3) at 140°C. After 9 hours at 140°C the mixture was cooled to 15°C, water (20 cm^3) added and the mixture steam-distilled. The organic layer was separated and distilled from phosphorus pentoxide to give fluoromethylpentafluorobenzene (II), (4.5 g), b.p. 134°C (cited 132°C [11]) (Found: C, 42.3; H, 1.2. $C_7H_2F_6$ requires C, 42.0; H, 1.0%): uv, λ_{max} 266 mμ (ε, 6.05 x 10^2): ^1H nmr; 4.53 dt: ^{19}F nmr; 143.2 (2), 151.9 (1), 162.2 (2), 212.0 (1) t.

Reaction of Fluoromethylpentafluorobenzene (II) with n-Butyllithium

Addition of a solution of n-butyllithium (0.8 g) in n-hexane (5 cm^3) with stirring to dry tetrahydrofuran (80 cm^3) containing II (2.0 g) at -78°C in an atmosphere of nitrogen, gave a deep orange solution. After ¾ hour, acetaldehyde (2.0 g) was added and the solution was then warmed to 15°C. Work up as before with separation by glc (column 488 x 3.5 cm, packing silicone gum 301 on kieselguhr (1:6), temp. 150°, N_2 15 lh^{-1}) gave recovered II (0.8 g) and 1-n-butyl-4-fluoromethyltetrafluorobenzene (V) (0.3 g) nc (Found: C, 55.7; H, 4.6. $C_{11}H_{11}F_5$ requires C, 55.5; H, 4.7%): ^1H nmr; n-Bu, 7.21 (2) t, 8.50 (4) m, 9.04 (3) t; CH_2F, 4.53 (2) d: ^{19}F nmr; 146.0 (4) s, 212.7 (1) t.

Difluoromethylpentafluorobenzene (III)

As for compound II, dichloromethylpentafluorobenzene (10.5 g) [7], anhydrous potassium fluoride (15.0 g), and dry dimethylformamide (45 cm^3) at 145°C for 6.5 hours afforded difluoromethylpentafluorobenzene (III) (7.8 g), b.p. 125°C (cited 122-124°C [11]) (Found: C, 38.5; H, 0.2. C_7HF_7 requires C, 38.5; H, 0.5%): uv, λ_{max} 267 mμ (ε, 1.3 x 10^3): ^1H nmr; 3.05 t: ^{19}F nmr; 114.5 (2) d, 144.2 (2), 150.2 (1), 161.7 (2).

Reaction of Difluoromethylpentafluorobenzene (III) with n-Butyllithium

To dry tetrahydrofuran (80 cm^3) containing III (2.0 g), stirred at -78°C in a nitrogen atmosphere, was added n-butyllithium (1.6 g) in n-hexane (10 cm^3). After ½ hour the deep orange solution was warmed to 15°C.

Isolation as for IV gave 1-n-butyl-4-difluoromethyltetrafluorobenzene (VI) (70%) nc, b.p. 198-200°C (Found: C, 51.6; H, 3.6. $C_{11}H_{10}F_6$ requires C, 51.6; H, 3.9%): ^1H nmr; n-Bu, 7.18 (2) t, 8.40 (4) m, 9.01 (3) t; $-CHF_2$, 3.09 (1) t: ^{19}F nmr; 114.5 (2) d, 146.0 (4).

b) The above experiment was repeated with only a slight excess of n-butyllithium. When the solution showed a negative Gilman test, a stream of carbon dioxide was passed for ¼ hour and the solution warmed to 15°C after 1 hour. Only n-hexane, III (42%), and VI (40%) could be detected in, and isolated from, the ether extracts. A further experiment in the presence of benzaldehyde also gave only those three components [III (41%), VI (46%)] together with benzaldehyde and a little tetrahydrofuran.

Attempted Reactions of Difluoromethylpentafluorobenzene (III)

III (1.0 g), KOH (10.0 g) and deuterium oxide (10.0 g) were heated together at 80°C for 19 hours. The organic layer (0.9 g) was unchanged III, with no deuterium content detectable by mass spectrometry.

b) III and bromine were irradiated together by UV light for 190 hours. Only unchanged III was recovered.

Spectra

Nmr spectra were measured on a Perkin Elmer R10 machine; ^1H chemical shifts at 60 Mc/s, are given in τ units relative to tetramethylsilane, and ^{19}F at 56.4 Mc/s are relative to trichlorofluoromethane, both internal references; carbon tetrachloride was the solvent.

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