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Arene-Catalysed Lithiation of Fluoroarenes

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This paper is dedicated to Professor Enrique Meléndez on the occasion of his 65th birthday.

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Abstract—The reaction of different fluoroarenes **1** with lithium and a catalytic amount (7%) of naphthalene in THF at −30°C affords the corresponding aryllithium intermediates which, by reaction with several electrophiles at temperatures ranging between −30 and 0°C, lead to the expected products **2**, after hydrolysis. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

The cleavage of the carbon–fluorine bond is not easy due to its large bond energy, which makes this bond the strongest one that carbon can form, and therefore very resistant to chemical attack.[1] However, this lack of reactivity, which has been successfully used for technological and medical applications, makes the degradation of fluoroderivatives problematic, from an environmental point of view.[2] In the last years, several reports have appeared concerning the activation of the carbon–fluorine bond, mainly using organometallic complexes.[3] The recent communication of Angelici et al. reporting the hydrodefluorination of fluorobenzene using rhodium complexes supported on a palladium–silicon system[4] prompted us to study the lithiation of fluoroarenes. In general, fluorinated hydrocarbons are not active towards different lithiating reagents.[5] In the case of fluorobenzene, its lithiation using non activated lithium works in ether with less than 1% yield, after carbonation.[6] Better yields can be obtained using THF as solvent and by activation of the metal using a stoichiometric amount of an arene, such as naphthalene, being, to the best of our knowledge, the reaction with carbon dioxide the only process studied.[7] In the last few years, we have been developing a new lithiation methodology which uses lithium powder and a catalytic amount of an arene, naphthalene and 4,4′-di-*tert*-butylbiphenyl being the most commonly used.[8–10] This methodology has been shown to be useful in the generation of (a) very reactive organolithium intermediates under very mild reaction conditions starting from non halogenated materials,[11] (b) functionalised organolithium compounds,[12,13] or (c) polylithiated synthons.[14] In this paper we apply the mentioned arene catalysed lithiation to explore the possible synthetic applications of fluoroarenes in a tandem lithiation electrophilic substitution reaction.[15]

Results and Discussion

The reaction of fluorobenzene (**1a**) with an excess of lithium powder (1:10 molar ratio) and a catalytic amount of naphthalene (1:0.14 molar ratio; 7 mol%) in THF at −30°C for 15 min gave a solution of phenyllithium, which upon treatment with different electrophiles [^{i}PrCHO, PhCHO, Et_2CO, $(CH_2)_5CO$, PhCOMe, Me_3SiCl; 1:1.2 molar ratio] at temperatures ranging between −30 and 0°C for ca. 3 h, and final hydrolysis with water and hydrochloric acid, afforded the expected products **2aa**–**af** (see Table 1, entries 1–6). The reaction conditions were optimised using the preparation of compound **2ac** as the model reaction: reactions at −78, −30 and 0°C, as well as processes in the presence of the electrophile (Barbier-type conditions[16]), were carried out, finding the best results working at −30°C and in a two-step reaction. When the process was performed without naphthalene as the electron carrier the yield was substantially lower (see Table 1, entry 3 and footnote c). It is worth noting that it is known that phenyllithium and other organolithiums are able to metallate fluorobenzene to give *o*-fluorophenyllithium,[6,17] so it is important to find the best reaction conditions in order to avoid this *o*-lithiation process.

Other substituted fluoroarenes, such as methyl or methoxy substituted fluorobenzenes, gave similar results to fluorobenzene (see Table 1, entries 7–14). Surprisingly, the reaction did not work for α-fluoronaphthalene: in this case, and using 3-pentanone as the electrophile, only naphthalene (also coming from the arene catalyst) and dihydronaphthalene (1:4 molar ratio) were isolated (tandem GLC/MS) showing that the fluorine/lithium exchange took place under the conditions assayed, but the corresponding

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Keywords: aryl fluorides; lithiation; arene-catalysis; aryllithiums.

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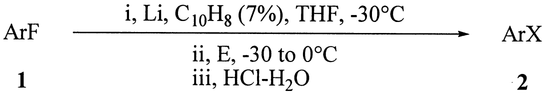
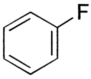
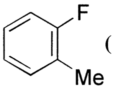
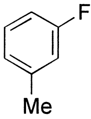
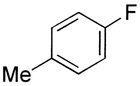
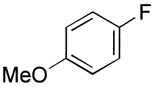
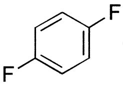
Table 1. Preparation of compounds **2**



$$\underset{\mathbf{1}}{\text{ArF}} \xrightarrow[\text{ii, E, -30 to 0°C; iii, HCl-}H_2O]{\text{i, Li, }C_{10}H_8\text{ (7\%), THF, -30°C}} \underset{\mathbf{2}}{\text{ArX}}$$

			Product[a]			
Entry	ArF (no.)	E	No.	Ar	X	Yield (%)[b]
1	 **(1a)**	^{i}PrCHO	**2aa**	C_6H_5	^{i}PrCHOH	38
2	(**1a**)	PhCHO	**2ab**	C_6H_5	PhCHOH	66
3	(**1a**)	Et_2CO	**2ac**	C_6H_5	Et_2COH	68 (38)[c]
4	(**1a**)	$(CH_2)_5CO$	**2ad**	C_6H_5	$(CH_2)_5COH$	72
5	(**1a**)	PhCOMe	**2ae**	C_6H_5	PhC(OH)Me	52
6	(**1a**)	Me_3SiCl	**2af**	C_6H_5	Me_3Si	50
7	 **(1b)**	PhCHO	**2bb**	$2\text{-}MeC_6H_4$	PhCHOH	63
8	(**1b**)	Et_2CO	**2bc**	$2\text{-}MeC_6H_4$	Et_2COH	43
9	 **(1c)**	PhCHO	**2cb**	$3\text{-}MeC_6H_4$	PhCHOH	57
10	(**1c**)	Et_2CO	**2cc**	$3\text{-}MeC_6H_4$	Et_2COH	52
11	 **(1d)**	PhCHO	**2db**	$4\text{-}MeC_6H_4$	PhCHOH	49
12	(**1d**)	Et_2CO	**2dc**	$4\text{-}MeC_6H_4$	Et_2COH	58
13	 **(1e)**	PhCHO	**2eb**	$4\text{-}MeOC_6H_4$	PhCHOH	61
14	(**1e**)	Et_2CO	**2ec**	$4\text{-}MeOC_6H_4$	Et_2COH	48
15	 **(1f)**	Et_2CO	**2fc**	$4\text{-}FC_6H_4$	Et_2COH	31(37)[d]

[a] All compounds **2** were >95% pure (300 MHz ^{1}H NMR and/or GLC).

[b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting fluoroarene **1**.

[c] In parentheses, yield corresponding to the reaction carried out in absence of naphthalene.

[d] In parentheses, yield of compound **2aa**.

α-lithionaphthalene abstracted a proton from the reaction medium, probably from THF,[18] giving the 'reduced' product. The same result was obtained working under Barbier-type conditions at the three temperatures mentioned above.

When *p*-difluorobenzene was used as starting material and using double the amount of 3-pentanone, a 31% yield was obtained for the 'monosubstitution' product **2fc** together with 37% of compound **2ac**, resulting from a second fluorine/lithium exchange followed by proton abstraction (see Table 1, entry 15 and footnote d). A similar result was obtained performing the reaction in the presence of the electrophile.

Finally, we tried the same reaction using 4-fluorophenol, which was previously deprotonated with *n*-butyllithium. In this case, after 24 h at room temperature, we isolated a ca. 1:1 mixture of phenol and the starting material, indicating that the lithiation worked slowly and the lithium intermediate formed decomposed under the reaction conditions assayed.

In conclusion, we have described here that fluoroarenes can be used as starting materials for the generation of the corresponding lithioarenes using naphthalene as an electron carrier catalyst in the lithiation step.

Experimental

General

For general information see Ref. [19]. Fluorinated starting materials and the electrophilic reagents were purchased of the best commercial grade (Aldrich, Acros) and were used without any further purification.

Naphthalene-catalysed lithiation of fluoroarenes 1 and reaction with electrophiles. Isolation of compounds 2. General procedure

To a green suspension of lithium powder (70 mg, 10.0 mmol) and naphthalene (18 mg, 0.14 mmol) in THF (5 mL), under N_2, was dropwise added a solution of the corresponding fluoroarene **1** (1.0 mmol) in THF (2 mL) over ca. 20 min at −30°C. After 15 min stirring at the same temperature [the starting material was consumed (GLC)], the corresponding electrophile E (1.2 mmol) was added and the mixture was stirred for ca. 3 h allowing the temperature to rise to 0°C. The resulting mixture was then hydrolysed with water (10 mL), acidified with 2 M hydrochloric acid and extracted with ethyl acetate (3×20 mL). The organic layers were successively washed with a saturated solution of $NaHCO_3$ (5 mL), water (5 mL) and saturated NaCl (5 mL), being then dried (Na_2SO_4). After evaporation of the solvents (15 Torr) the resulting residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to yield the title compounds **2**. Products **2aa**–**af**, previously prepared in our laboratory,[20] and compounds **2bb** and **2db**, commercially available (Aldrich), were fully characterised by comparison of their physical and spectroscopic data with authentic samples. For the other known compounds **2cb**,[21] **2dc**,[22] **2eb**,[23] **2ec**,[24] and **2fc**,[25] partially described in the literature, as well as for unknown compounds **2bc** and **2cc**, the corresponding physical, spectroscopic and analytical data follow.

3-(2-Methylphenyl)-3-pentanol (2bc). R_f (hexane/ethyl acetate: 4:1) 0.38; ν_{max} (liquid film) 3472, 3059, 3016, 1601, 1485 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.47–7.44, 7.21–7.12 (1 H and 3 H, respectively, 2 m, ArH), 2.51 (3 H, s, *Me* Ar), 2.14–1.98, 1.94–1.79 (2 H each, 2 m, 2×CH_2), 1.71 (1 H, s, OH), 0.79 (6 H, t, *J*=7.3 Hz, 2× *Me* CH_2); δ_C (75 MHz, $CDCl_3$) 142.75, 135.0, 132.4, 127.3, 126.55, 125.4, 78.75, 33.25 (2 C), 22.45, 8.0 (2 C); *m/z* (EI) 178 (<1, M$^+$), 150 (13), 149 (100), 119 (10), 91 (32), 65 (20), 57 (93), 43 (25%); HRMS (EI) M$^+$−H_2O, found 160.1251. $C_{12}H_{16}$ requires 160.1252.

(3-Methylphenyl)phenylmethanol (2cb).[21] R_f (hexane/ethyl acetate: 7:3) 0.38; ν_{max} (liquid film) 3383, 3085, 3060, 3028, 1606, 1590, 1493 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.44–7.05 (9 H, m, ArH), 5.80 (1 H, s, CHO), 2.36 (3 H, s, Me), 2.30 (1 H, br s, OH); δ_C (75 MHz, $CDCl_3$) 143.8, 143.7, 138.1, 128.4 (2 C), 128.35, 128.25, 127.45, 127.15 (2 C), 126.45, 123.6, 76.2, 21.4; *m/z* (EI) 200 (<1, M$^+$+2), 199 (7, M$^+$+1), 198 (49, M$^+$), 197 (14), 183 (19), 165 (17), 120 (12), 119 (71), 105 (100), 93 (46), 92 (70), 91 (62), 89 (13), 79 (23), 78 (18), 77 (69), 76 (11), 65 (23), 63 (11), 51 (28%); HRMS (EI) M$^+$, found 198.1027. $C_{14}H_{14}O$ requires 198.1045.

3-(3-Methylphenyl)-3-pentanol (2cc). R_f (hexane/ethyl acetate: 4:1) 0.39; ν_{max} (liquid film) 3471, 3026, 1606, 1485 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.29–7.11, 7.09–7.00 (3 H and 1 H, respectively, 2 m, ArH), 2.37 (3 H, s, *Me* Ar), 1.95–1.73 (4 H, m, 2×CH_2), 1.69 (1 H, s, OH), 0.77 (6 H, t, *J*=7.6 Hz, 2×*Me*CH_2); δ_C (75 MHz, $CDCl_3$) 145.7, 137.4, 127.8, 126.95, 126.15, 122.5, 77.35, 34.9 (2 C), 21.65, 7.8 (2 C); *m/z* (EI) 179 (<1, M$^+$+1), 178 (<1, M$^+$), 150 (10), 149 (96), 91 (25), 65 (16), 57 (100), 43 (15%); HRMS (EI) M$^+$, found 178.1363. $C_{12}H_{18}O$ requires 178.1358.

3-(4-Methylphenyl)-3-pentanol (2dc).[22] R_f (hexane/ethyl acetate: 4:1) 0.34; ν_{max} (liquid film) 3450, 3092, 3053, 3023, 1613, 1512 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.25,7.13 (2 H each, 2 d, *J*=7.9 Hz each, ArH), 2.33 (3 H, s, *Me*Ar), 1.88–1.72 (4 H, m, 2×CH_2), 1.67 (1 H, s, OH), 0.75 (6 H, t, *J*=7.3 Hz, 2×*Me*CH_2); δ_C (75 MHz, $CDCl_3$) 142.75, 135.65, 128.65 (2 C), 125.35 (2 C), 77.25, 34.8 (2 C), 20.9, 7.8 (2 C); *m/z* (EI) 178 (<1, M$^+$), 149 (78), 91 (19), 65 (11), 57 (100), 43 (13%); HRMS (EI) M$^+$−H_2O, found 160.1245. $C_{12}H_{16}$ requires 160.1252.

(4-Methoxyphenyl)phenylmethanol (2eb).[23] R_f (hexane/ethyl acetate: 7:3) 0.29; ν_{max} (liquid film) 3403, 3084, 3061, 3028, 1611, 1585, 1512, 1494 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.42–7.23, 6.92–6.84 (7 H and 2 H, respectively, 2 m, ArH), 5.79 (1 H, s, CHO), 3.79 (3 H, s, Me), 2.42 (1 H, br s, OH); δ_C (75 MHz, $CDCl_3$) 158.95, 144.0, 136.15, 128.35 (2 C), 127.85, 127.35 (2 C), 126.35 (2 C), 113.8 (2 C), 75.7, 55.2; *m/z* (EI) 215 (12, M$^+$+1), 214 (42, M$^+$), 213 (15), 197 (12), 165 (12), 153 (11), 152 (13), 137 (32), 136 (12), 135 (60), 109 (100), 108 (37), 107 (13), 105 (64), 94 (20), 92 (12), 79 (16), 78 (16), 77 (83), 65 (13), 64 (12), 51 (28), 50 (12), 40 (25%); HRMS (EI) M$^+$, found 214.0967. $C_{14}H_{14}O_2$ requires 214.0994.

3-(4-Methoxyphenyl)-3-pentanol (2ec).[24] R_f (hexane/ethyl acetate: 1:1) 0.57; ν_{max} (liquid film) 3404, 3071, 3059, 3037, 1612, 1511 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.29, 6.87 (2 H each, 2 d, *J*=8.9 Hz each, ArH), 3.80 (3 H, s, MeO), 1.90–1.72 (4 H, m, 2×CH_2), 1.69 (1 H, br s, OH), 0.76 (6 H, t, *J*=7.6 Hz, 2× *Me*CH_2); δ_C (75 MHz, $CDCl_3$) 157.95, 137.85, 126.6 (2 C), 113.25 (2 C), 77.05, 55.15, 34.85 (2 C), 7.8 (2 C); *m/z* (EI) 195 (<1, M$^+$+1), 194 (3, M$^+$), 176 (12), 165 (92), 147 (15), 91 (11), 77 (14), 57 (100), 43 (11%); HRMS (EI) M$^+$, found 194.1284. $C_{12}H_{18}O_2$ requires 194.1307.

3-(4-Fluorophenyl)-3-pentanol (2fc).[25] R_f (hexane/ethyl acetate: 4:1) 0.38; ν_{max} (liquid film) 3462, 3086, 3061, 3029, 1604, 1509 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.40–7.28, 7.05–6.95 (2 H each, 2 m, ArH), 1.92–1.70 (4 H, m, 2×CH_2), 1.69 (1 H, s, OH), 0.75 (6 H, t, *J*=7.3 Hz, 2×Me); δ_C (75 MHz, $CDCl_3$) 161.4 (d, *J*=244 Hz), 141.35 (d, *J*=2 Hz), 127.1 (2 C, d, *J*=7 Hz), 114.6 (2 C, d,

J=21 Hz), 77.1, 35.0 (2 C), 7.7 (2 C); m/z (EI) 164 (3, M^+-18), 153 (81), 135 (21), 57 (100), 43 (62), 40 (12%); HRMS (EI) M^+-H_2O, found 164.1019. $C_{11}H_{13}F$ requires 164.1001.

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