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Aliphatic organolithiums by fluorine–lithium exchange: *n*-octyllithium

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Dedicated to Professor Daniel Uguen on occasion of his 60th birthday

Abstract—The reaction of 1-fluorooctane (**1**) with an excess of lithium powder (4–10 equiv.) and DTBB (2–4 equiv.) in THP at 0°C for 5 min gives a solution of the corresponding 1-octyllithium (**2**), which reacts then with different electrophiles at 0°C (D_2O, MeSiCl, Bu^tCHO, Et_2CO), or −78°C [$ClCO_2Me$, $(PhCH_2S)_2$] or −40°C (CO_2) to room temperature to give, after hydrolysis, the expected products (**3**). The same process applied to 2-fluorooctane gives mainly octane as reaction product, independently on the electrophile used, resulting from a proton abstraction by 2-lithiooctane formed from the reaction medium before addition of the electrophilic reagent. © 2003 Elsevier Science Ltd. All rights reserved.

The carbon–fluorine bond is the strongest that carbon can form and therefore its cleavage is not an easy task.[1] Two important consequences can be drawn from this fact: (a) In recent times, fluorinated (especially perfluorinated) solvents have been introduced mainly in order to perform two-phase catalysis,[2] and (b) the degradation of fluoroderivatives in Nature is problematic from an environmental point of view.[3] The most used methodology in order to perform defluorination processes, excluding elimination reactions giving olefins,[4] involves the use of a metallic catalyst under drastic reaction conditions.[5] Recently we have been studying the lithiation of fluoroderivatives using an arene-catalysed methodology,[6–8] naphthalene and 4,4′-di-*tert*-butylbiphenyl (DTBB) being the electron-transfer agents most commonly used.[9] Thus, arylic[10] and benzylic or allylic[11] fluorides could be converted into the corresponding organolithium intermediates, and after reaction with electrophiles the expected products were obtained; in the second case (benzylic and allylic starting materials) was necessary to work under Barbier-type conditions (lithiation in the presence of the electrophile)[12] in order to avoid Wurtz-type side reactions.[13] However, when the same methodology (arene-catalysed lithiation) was applied to aliphatic fluorides the starting material remained unchanged. Very recently, we could perform the defluorination of fluoroalkanes using the reductive methodology mentioned in the presence of equimolecular amounts of 1,2-bis(trimethylsilyl)benzene as activating agent;[14] this procedure is however not appropriate to introduce an electrophilic fragment (different than hydrogen) in the molecule. In this paper we report for the first time on the direct transformation of an alkyl fluoride into an organolithium intermediate using a modification of the mentioned arene-catalysed methodology.

The reaction of 1-fluorooctane (**1**) with an excess of LiDTBB (4 equiv.) in tetrahydropyran (THP) at 0°C for 5 min led to a solution of the corresponding 1-lithiooctane (**2**), which after reaction with different electrophiles (D_2O, Me_3SiCl, Bu^tCHO, Et_2CO) at the same temperature and final hydrolysis with phosphate buffer yielded the expected products **3** (Method A)

Scheme 1. *Reagents and conditions*: (i) LiDTBB (4 equiv.), THP, 0°C, 5 min (Method A) or Li excess, DTBB (2 equiv.), THP, 0°C, 5 min (Method B); (ii) $E^+ = D_2O$, Me_3SiCl, Bu^tCHO, Et_2CO, $ClCO_2Me$, CO_2, $(PhCH_2S)_2$ (5 equiv.), 0 or −78°C (or −40°C) to 0°C; (iii) H_2O.

Keywords: fluorine–lithium exchange; DTBB-catalysed lithiation; electrophiles; proton abstraction; organolithium compounds.

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(Scheme 1 and Table 1, entries 1, 3, 5 and 7). Alternatively, the lithiation can be performed using an excess of lithium powder (ca. 10 equiv.) and a stoichiometric amount of DTBB (2 equiv.) also in THP at 0°C during 5 min for the same electrophiles as above (Method B) (Table 1, entries 2, 4, 6 and 8). In the case of using methyl chloroformate or dibenzyl disulfide the reaction with the electrophile worked better at temperatures ranging between −78°C and room temperature; for carbon dioxide −40°C to room temperature are the best reaction conditions (Table 1, entries 9–11).

Up to date, the preparation of alkyllithium reagents from alkyl fluorides has been an elusive task.[10,11,14] Several reasons prevented this apparently simple target: (a) The relentless tendency of alkyl fluorides to undergo ET reactions at low temperature, (b) the reactivity towards ethereal solvents of the alkyllithium reagents at higher temperatures,[15] (c) the apparent nucleophilic reactivity displayed by lithium–arene species other than DTBB toward primary alkyl fluorides,[16] and (d) the reactivity toward the solvent of the lithium–arene species themselves.[7b] While alkyl fluorides are not reduced by Li–arenes in any appreciable amount at −78°C, the reduction takes place at room temperature or 0°C at a convenient rate (less than 5 min). Unfortunately, alkyllithium reagents are stable in THF (the most commonly used solvent in lithium chemistry)[13,17] or THP at −78°C, but readily abstract a proton from THF at 0°C or higher temperatures;[15] THP is a better behaving solvent.[7b] Even in THP at 0°C, which proved to be the temperature of choice, short reaction times are mandatory. With substoichiometric DTBB at 0°C, arene catalysed cycles are too slow and long reaction times are required, allowing alkyllithium reagents to react with the solvent. After addition of the electrophile, the main reaction product was the alkane. The use of a substoichiometric amount of arene catalysts other than DTBB is precluded due to their inactivation as electron carrier by reductive alkylation.[16] Differences between Methods A and B lie on the possible participation of a dilithium–arene when an excess of lithium is used (Method B). This has been studied for the case of naphthalene,[7,16] and it is currently under investigation for biphenyl derivatives such as DTBB. We then tried the lithiation of a secondary fluoroalkane such as 2-fluorooctane using Method B, which in general works better than Method A (see Table 1) under the same reaction conditions as shown in Scheme 1. Using the same electrophiles (D_2O, Me_3SiCl, Bu^tCHO, Et_2CO) at 0°C we obtained >94% yield of octane. It seems that the expected 2-lithiooctane is formed, but under the reaction conditions assayed it does not survive long enough to take up a proton from the reaction medium before the reaction with the electrophile.

In conclusion, we report in this paper the preparation for the first time of a primary organolithium compound (1-lithiooctane) by fluorine–lithium exchange and its reaction with different electrophiles.[18] The reaction with a secondary fluoroalkane (2-fluorooctane) gives the corresponding 2-lithiooctane that takes a proton from the reaction medium giving octane; this renders impossible its reaction with other electrophiles.

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Table 1. Preparation of compounds **3**

Entry	Method	Electrophile	Temperature	Product[a]		
		E^+	S_E (°C)	No.	E	Yield (%)[b]
1	A	D_2O	0	**3a**	D	96[c]
2	B	D_2O	0	**3a**	D	98[d]
3	A	Me_3SiCl	0	**3b**	Me_3Si	78
4	B	Me_3SiCl	0	**3b**	Me_3Si	85
5	A	Bu^tCHO	0	**3c**	Bu^tCHOH	63
6	B	Bu^tCHO	0	**3c**	Bu^tCHOH	85
7	A	Et_2CO	0	**3d**	Et_2COH	64
8	B	Et_2CO	0	**3d**	Et_2COH	65
9	B	$ClCO_2Me$	−78→0	**3e**	CO_2Me	59
10	B	CO_2	−40→0	**3f**	CO_2H	60
11	B	$(PhCH_2S)_2$	−78→0	**3g**	$PhCH_2S$	53

[a] All compounds **3** were >95% pure (GLC and/or 300 MHz ^1H NMR) and were fully characterised by spectroscopic means (IR, ^1H and ^{13}C NMR, and MS).

[b] Isolated yield determined by quantitative GLC (using decane as internal standard for compounds **3a**–**d**) or 300 MHz ^1H NMR (using *N*,*N*-diphenylformamide as internal standard for compounds **3e**–**g**) based on the starting 1-fluorooctane (**1**).

[c] >99% deuterium incorporation (mass spectrometry).

[d] 97% deuterium incorporation (mass spectrometry).

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18. ***Typical procedure***: A suspension of lithium powder[19] [Method A: 14 mg (2 mmol); Method B: 70 mg (10 mmol)] and DTBB [Method A: 559 mg (2.1 mmol); Method B: 266 mg (1 mmol) in THP (10 mL) was stirred for 2 h at room temperature. After cooling at 0°C, to the resulting mixture was added dropwise a mixture of 1-fluorooctane [Method A: 33 mg (0.25 mmol); Method B: 66 mg (0.5 mmol)] and decane [Method A: 35.5 mg (0.25 mmol); Method B: 71 mg (0.5 mmol)] as internal standard (for D_2O, Me_3SiCl, Bu^tCHO, Et_2CO as electrophiles. After 5 min stirring [the starting material was consumed (GLC)] the corresponding electrophile (5 mmol) was added at the same temperature and after 20 min the mixture was hydrolysed with phosphate tampon (5 mL), extracted with Et_2O (3×20 mL), dried over Na_2SO_4 and evaporated. For D_2O, Me_3SiCl, Bu^tCHO and Et_2CO yields were determined by quantitative GLC. When $ClCO_2Me$ or $(PhCH_2S)_2$ were used as electrophiles, after lithiation the mixture was cooled at −78°C and pentane (5 mL) was added before adding the electrophile, allowing then the temperature to rise to room temperature with stirring, being then hydrolysed as it was before described. For CO_2, after lithiation through the mixture cooled at −40°C was bubbled CO_2 gas for 5 min allowing then the temperature to rise to room temperature before acidic extraction and work-up as described above. For the last three electrophiles [$ClCO_2Me$, $(PhCH_2S)_2$ and CO_2] yields were determined by quantitative ^1H NMR using *N*,*N*-diphenylformamide as internal standard. Characterisation of compounds **3** was made by spectroscopic means (IR, ^1H and ^{13}C NMR, and MS).
19. Lithium powder was prepared as described before: Yus, M.; Martínez, P.; Guijarro, D. *Tetrahedron* **2001**, *57*, 10119.