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Generation of allylic and benzylic organolithium compounds by fluorine–lithium exchange: reaction with electrophiles

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This paper is dedicated to Professor Jean F. Normant on the occasion of his 65th birthday

Abstract

The application of the naphthalene-catalysed lithiation methodology to allylic and benzylic fluorides **1** led to the corresponding allylic and benzylic organolithium reagents, which, in the presence of different electrophiles (Barbier-type reaction conditions), afforded the expected products **2** in moderate yields. The procedure was useful for the transformation of primary, secondary and tertiary benzylic fluorides into the corresponding lithium derivatives. When a two-step lithiation process was used (treatment of fluoride **1** with lithium and a catalytic amount of naphthalene, followed by addition of the electrophilic reagent), only Wurtz-type coupling products were formed.

Keywords: Allyllithium; Benzyllithium; Fluoro–lithium exchange; Lithiation

1. Introduction

From a preparative point of view, the generation of allylic and benzylic organolithium reagents cannot be carried out using the general methodology for organolithium compounds, i.e. the lithiation of allylic or benzylic halides (mainly bromides and chlorides), because the almost exclusive formation of Wurtz-type products takes place [1–3]. Alternatives to overcome this problem, including (a) direct deprotonation with an alkyllithium in the presence of a co-reactant (potassium *tert*-butoxide [4,5] or an amine [6]), (b) mercury–lithium or tin–lithium transmetallation [7–9] or (c) reductive cleavage of allyl phenyl ether [10,11] are of limited application.

Concerning lithiation procedures, in the last few years we have been using an arene-catalysed lithiation [12–14] to prepare very reactive organolithium compounds under very mild reaction conditions. Thus, simple organolithium compounds can be generated using non-halogenated materials [15], functionalised organolithium compounds [16] by chlorine–lithium exchange or by ring opening of heterocycles [17], as well as polylithiated synthons [18] starting from polychlorinated materials under Barbier-type reaction conditions [19].

Recently, we have applied the above-mentioned arene-catalysed lithiation to the generation of allylic and benzylic organolithium compounds starting from the corresponding mesylates [20], phosphates [21], alcohols or their *O*-silylated derivatives [22] and carboxylic acid derivatives (esters, amides, carbonates, carbamates and ureas) [23]. In addition, when the same reaction is quenched with water, this methodology is a useful procedure for deallylation or debenzylation of oxygen- or nitrogen-containing derivatives [24].

On the other hand, from a lithium chemistry point of view, fluorinated materials are not adequate precursors for the generation of organolithium compounds due to the difficulty in cleaving the carbon–fluorine bond, which is the strongest one that carbon can form [25]. Recently, we were able to generate aryllithium reagents by a fluorine–lithium exchange using an arene as the catalyst for the lithiation process [26]. In this paper, we apply the methodology to the generation of allylic and benzylic organolithium compounds from the corresponding fluorinated precursors.

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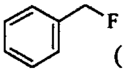
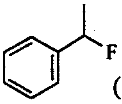
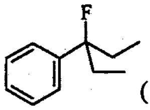
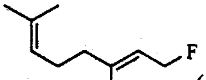
2. Results and discussion

The reaction of benzyl fluoride (**1a**) with an excess of lithium powder (1:10 molar ratio) and a catalytic amount of naphthalene (1:0.16 molar ratio; 8 mol%), in the presence of different electrophiles (Barbier-type conditions; E = Me_3SiCl, ^{i}PrCHO, ^{t}BuCHO, Et_2CO, $(CH_2)_5CO$, Ph_2CO), in THF, at temperatures ranging between − 30 and 0°C, led, after hydrolysis with water, to the expected compounds **2aa**–**2af** (Table 1, entries 1–6) in moderate yields. Other secondary or tertiary starting materials, such as fluorides **1b** and **1c** respectively, gave similar results (Table 1, entries 7 and 8, and 9 and 10 respectively). In the case of using an allylic fluoride, such as the geranyl derivative **1d**, we found a different behaviour depending on the electrophile used. With chlorotrimethylsilane, the expected compound **2da** was isolated (Table 1, entry 11 and table footnote c).

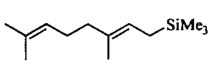
Table 1
Preparation of compounds **2** from fluorocompounds **1**

$$\underset{\mathbf{1}}{\mathrm{RF}} \xrightarrow[\text{ii, H}_2\text{O}]{\text{i, E, Li, C}_{10}\text{H}_8\text{ (8\%), THF, -30 to 0°C}} \underset{\mathbf{2}}{\mathrm{RX}}$$

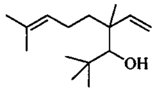
			Product[a]			
Entry	RF (no.)	E	No.	R	X	Yield (%)[b]
1	 **(1a)**	Me_3SiCl	**2aa**	$PhCH_2$	Me_3Si	53
2	**1a**	Pr^iCHO	**2ab**	$PhCH_2$	Pr^iCHOH	25
3	**1a**	Bu^tCHO	**2ac**	$PhCH_2$	Bu^tCHOH	49
4	**1a**	Et_2CO	**2ad**	$PhCH_2$	Et_2COH	38
5	**1a**	$(CH_2)_5CO$	**2ae**	$PhCH_2$	$(CH_2)_5COH$	45
6	**1a**	Ph_2CO	**2af**	$PhCH_2$	Ph_2COH	45
7	 **(1b)**	Me_3SiCl	**2ba**	PhCHMe	Me_3Si	71
8	**1b**	Et_2CO	**2bd**	PhCHMe	Et_2COH	55
9	 **(1c)**	Me_3SiCl	**2ca**	$PhCEt_2$	Me_3Si	43
10	**1c**	Bu^tCHO	**2cc**	$PhCEt_2$	Bu^tCHOH	45
11	 **(1d)**	Me_3SiCl	**2da**	—[c]	Me_3Si	72
12	**1d**	Bu^tCHO	**2'dc**	—[d]	Bu^tCHOH	58[e]
13	**1d**	Et_2CO	**2'dd**	—[d]	Et_2COH	72

[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 fluorinated material **1**. [c] R = geranyl. [d] See structure of compounds **2'dc** and **2'dd** in the text. [e] A *ca.* 1:1 diastereomeric mixture was obtained (300 MHz ^{1}H NMR).

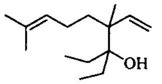
However, with carbonyl compounds, the rearranged products **2′dc** and **2′dd** were obtained (Table 1, entries 12 and 13). These results can be explained by taking into account that the allyllithium derivative **I** initially formed is in equilibrium with the corresponding less stable tertiary one **I′**, and depending on the reactivity of the electrophile gave different regioisomers. Chlorotrimethylsilane (a hard electrophile) is very reactive and reacts rapidly with intermediate **I** before equilibration to **I′**. For less reactive carbonyl compounds (soft electrophiles) the **I** → **I′** equilibration takes place prior to reaction with the electrophile to give compounds **2′**.[1] This behaviour has previously been observed in other similar cases [22,23]. In the case of using pivalaldehyde with the starting material **1d**, the expected mixture of diastereoisomers (ca. 1:1) was obtained (Table 1, entry 12, table footnote e). On the other hand, the reaction shown in Table 1 had to be performed in the presence of the electrophile (Barbier-type conditions) in order to avoid the decomposition of the in situ generated benzylic or allylic organolithium intermediate. When the reaction was carried out in the absence of the electrophile (two-step process), only Wurtz-type coupling products were isolated. Finally, the moderate yields observed in the lithiation of fluorides **1** can be explained due to the formation to some extent of the corresponding 'reduced' products RH as by-products; the separation of these compounds is very easy by column chromatography. Concerning a possible reaction mechanism, an SET process is generally accepted for the halogen–lithium exchange [13].



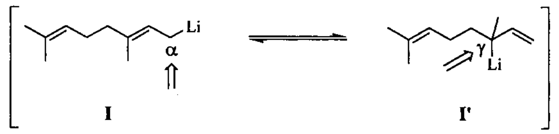
2da



2′dc



2′dd



Starting fluorides **1a**, **1b** and **1d** were prepared from the corresponding bromides via a nucleophilic substitution reaction with hydrated tetrabutylammonium fluoride in acetonitrile. The synthesis of the remaining fluoride **1c** was carried out by treatment of 3-phenyl-3-pentanol (obtained by reaction between 3-pentanone and phenylmagnesium bromide) and bis-(2-methoxyethyl)aminosulfur trifluoride in CH_2Cl_2.

3. Conclusions

From the results described in this paper, we conclude that allylic and benzylic fluorides can be used as starting materials for the generation of the corresponding organolithium derivatives, which are trapped with different electrophiles under Barbier-type reaction conditions.

4. Experimental

4.1. General

For general information, see Ref. [27]. THF was distilled from sodium–benzophenone under N_2 before use. All the commercially available reagents purchased were of the best commercial grade (Aldrich, Acros) and used without any further purification.

*4.2. Preparation of fluorides **1a**, **1b**, and **1d***

Fluorinated starting materials **1a**, **1b** and **1d** were prepared from the corresponding commercially available bromides (10.0 mmol) by reaction with $Bu_4NF{\cdot}3H_2O$ (6.310 g, 20.0 mmol) in acetonitrile (20 ml), according to a literature procedure [28]. When the reaction was complete, water (5 ml) was added, the mixture was extracted with pentane (5 × 10 ml) and the combined organic layers were dried (Na_2SO_4). Compound **1a** was obtained in pure form by distillation of pentane through a 10 cm long Vigreux column at atmospheric pressure, in 76% yield. In the reaction performed to synthesize **1b**, a mixture of the expected fluoride and the elimination product, styrene (ratio **1b**/styrene: 1/0.8, 300 MHz ^{1}H-NMR), was obtained, which could not be separated. However, the presence of the olefin did not interfere in the lithiation process of **1b**. That mixture was separated from pentane as described for fluoride **1a**, giving a 75% combined yield. Geranyl fluoride **1d** was obtained in pure form by evaporation of the solvent at reduced pressure (15 Torr). Physical, spectroscopic and analytical data for the aforementioned fluorides follow.

Benzyl fluoride (**1a**) [28]: R_f (hexane) 0.26; ν_{max}(liquid film) 3091, 3068, 3036, 1599, 1498, 985 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.46–7.30 (5 H, m, ArH), 5.36 (2H, d, $J = 48.2$ Hz, CH_2); δ_C (75 MHz, $CDCl_3$) 136.25 (d, $J = 17.1$ Hz), 128.7 (2C, d, $J = 3.7$ Hz), 128.55, 127.5 (2C, d, $J = 4.9$ Hz), 84.55 (d, $J = 166.0$ Hz); m/z (EI) 112 (< 1, $M^+ + 2$), 111 (4, $M^+ + 1$), 110 (54, M^+), 109 (100), 83 (20), 51 (12); HRMS (EI) M^+, found 110.0537. C_7H_7F requires 110.0532.

(1-Fluoroethyl)benzene (**1b**) [29]: R_f (hexane) 0.24; ν_{max}(liquid film) 3084, 3062, 3032, 1495, 1066 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.46–7.20 (5H, m, ArH), 5.60 (1H,

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[1] Another possible explanation for this different behaviour could be that a chair-like transition state is operative when a carbonyl compound is used as electrophile.

dq, $J = 47.8$, 6.4 Hz, CHF), 1.62 (3H, dd, $J = 23.9$, 6.4 Hz, Me); δ_C (75 MHz, $CDCl_3$) 141.9 (d, $J = 17.5$ Hz), 128.5, 128.15 (2C, d, $J = 2.3$ Hz), 125.15 (2C, d, $J = 6.8$ Hz), 90.9 (d, $J = 167.3$ Hz), 22.9 (d, $J = 25.4$ Hz); *m/z* (EI) 126 (< 1, $M^+ + 2$), 125 (2, $M^+ + 1$), 124 (28, M^+), 123 (10), 109 (100), 104 (21), 103 (14), 83 (11), 78 (16), 77 (14), 51 (29), 50 (16); HRMS (EI) M^+, found 124.0689. C_8H_9F requires 124.0688.

Geranyl fluoride (**1d**) [30]: R_f (hexane) 0.48; ν_{max}(liquid film) 1669, 1650, 976 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.56–5.43, 5.16–5.03 (1H each, 2m, 2 × HC=C), 4.89 (2H, dd, $J = 47.6$, 7.3 Hz, CH_2F), 2.21–1.96 (4H, m, CH_2CH_2), 1.72 (3H, d, $J = 4.9$ Hz, *Me*C=CCH_2F), 1.68, 1.60 (3H each, 2s, Me_2C); δ_C (75 MHz, $CDCl_3$) 144.1 (d, $J = 12.2$ Hz), 131.9, 123.6, 118.95 (d, $J = 17.1$ Hz), 79.35 (d, $J = 156.3$ Hz), 39.55, 26.2 (d, $J = 3.7$ Hz), 25.6, 17.65, 16.4 (d, $J = 2.4$ Hz); *m/z* (EI) 156 (< 1, M^+), 113 (20), 112 (10), 69 (100), 67 (12), 53 (10), 41 (99); HRMS (EI) M^+, found 156.1324. $C_{10}H_{17}F$ requires 156.1314.

4.3. Synthesis of fluoride 1c

3-Pentanone (1.67 ml, 15.0 mmol) was added dropwise to a cooled (0°C) solution of phenylmagnesium bromide (16.0 ml, 1.0 M solution in tetrahydrofuran, 16.0 mmol), under N_2, for ca. 5 min. After 30 min stirring at the same temperature, water (5 ml) was added. The mixture was acidified with 2 M HCl (10 ml) and extracted with ethyl acetate (3 × 20 ml). The combined organic layers were washed with 1.0 M NaOH (2 × 5 ml), water (5 ml) and brine (5 ml) and dried (Na_2SO_4). After evaporation of the solvents (15 Torr), the resulting residue was purified by column chromatography (silica gel, hexane–ethyl acetate), affording 3-phenyl-3-pentanol in 60% yield, whose physical and spectroscopic data were in complete agreement with those reported [31]. The alcohol obtained was transformed into the corresponding fluoride by treatment with bis-(2-methoxyethyl)aminosulfur trifluoride in CH_2Cl_2, following a literature procedure [32]. Fluoride **1c** was isolated by column chromatography (silica gel, hexane) in 64% yield. Physical, spectroscopic and analytical data follow.

3-Fluoro-3-phenylpentane (**1c**): R_f (hexane) 0.40; ν_{max}(liquid film) 3090, 3060, 3029, 1606, 1496, 1031 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.42–7.18 (5H, m, ArH), 2.10–1.75 (4H, m, 2 × CH_2), 0.78 (6H, t, $J = 7.4$ Hz, 2 × Me); δ_C (75 MHz, $CDCl_3$) 142.8 (d, $J = 22.0$ Hz), 128.0 (2C, d, $J = 2.3$ Hz), 126.75 (2C, d, $J = 1.1$ Hz), 124.65, 100.25 (d, $J = 176.3$ Hz), 33.25 (2C, d, $J = 24.3$ Hz), 7.6 (2C, d, $J = 4.5$ Hz); *m/z* (EI) 167 (2, $M^+ + 1$), 166 (17, M^+), 138 (11), 137 (100), 117 (48), 115 (29), 109 (15), 91 (29), 59 (12), 51 (12); HRMS (EI) M^+, found 166.1172. $C_{11}H_{15}F$ requires 166.1158.

4.4. Naphthalene-catalysed lithiation of fluorides 1 in the presence of electrophiles. Isolation of compounds 2. General procedure

To a green suspension of lithium powder (70 mg, 10.0 mmol) and naphthalene (20 mg, 0.16 mmol) in THF (5 ml), under N_2, was dropwise added a solution of fluoride **1** (1.0 mmol) and the corresponding electrophile E (1.5 mmol) in THF (2 ml), at −30°C, for ca. 20 min. The mixture was stirred for ca. 3 h and the temperature allowed to rise to 0°C. The reaction was then hydrolysed with water (10 ml), acidified with 2 M HCl and extracted with ethyl acetate (3 × 20 ml). The combined organic layers were washed successively with a saturated solution of $NaHCO_3$ (5 ml), water (5 ml) and brine (5 ml), and 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** [21], **2ab** [20], **2ac** [23], **2ad**–**af** [20], **2ba**–**bd** [22a], **2da** [22a], **2′dc** [23] and **2′dd** [22a], previously prepared in our laboratory, were fully characterised by comparison of their physical and spectroscopic data with authentic samples. For unknown compounds **2ca** and **2cc**, the corresponding physical, spectroscopic and analytical data follow.

3-Phenyl-3-(trimethylsilyl)pentane (**2ca**): R_f (hexane) 0.45; ν_{max}(liquid film) 3087, 3057, 3030, 3017, 1598, 1497, 1248, 834 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.34–7.01 (5H, m, ArH), 2.12–1.82 (4H, m, 2 × CH_2), 0.90 (6H, t, $J = 7.4$ Hz, 2 × *Me*CH_2), −0.12 (9H, s, Me_3Si); δ_C (75 MHz, $CDCl_3$) 145.8, 127.55, 127.25 (2C), 123.8, 35.25, 23.95 (2C), 9.0 (2C), −2.4 (3C); *m/z* (EI) 222 (< 1, $M^+ + 2$), 221 (< 1, $M^+ + 1$), 220 (4, M^+), 146 (39), 135 (12), 117 (16), 91 (15), 74 (10), 73 (100), 45 (22), 43 (11); HRMS (EI) M^+, found 220.1633. $C_{14}H_{24}Si$ requires 220.1647.

4-Ethyl-2,2-dimethyl-4-phenyl-3-hexanol (**2cc**): R_f (hexane/ethyl acetate: 4/1) 0.45; ν_{max}(liquid film) 3506, 3089, 3057, 1599, 1498 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.48–7.09 (5H, m, ArH), 3.57 (1H, d, $J = 7.1$ Hz, CHO), 2.21–1.85 (4H, m, 2 × CH_2), 1.68 (1H, d, $J = 7.1$ Hz, OH), 0.87, 0.78 (3H each, 2t, $J = 7.4$ Hz each, 2 × *Me*CH_2), 0.70 (9H, s, Me_3C); δ_C (75 MHz, $CDCl_3$) 144.95, 128.05 (2C), 127.7 (2C), 125.65, 83.75, 48.8, 37.55, 28.45 (3C), 26.35, 26.25, 8.65, 8.25; *m/z* (EI) 177 (10, $M^+ - 57$), 148 (59), 119 (87), 117 (14), 105 (42), 91 (100), 87 (13), 69 (12), 57 (40), 45 (11), 43 (18), 41 (60); HRMS (EI) M^+, found 234.2000. $C_{16}H_{26}O$ requires 234.1984.

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References

[1] B. Wakefield, in: D. Barton, W.D. Ollis (Eds.), Comprehensive Organic Chemistry, vol. 3, Pergamon Press, Oxford, 1979, p. 943 part 15.

[2] E.I. Negishi, Organometallics in Organic Synthesis, Wiley, New York, 1980, p. 96.

[3] B. Wakefield, Organolithium Methods, Academic Press, London, 1988, p. 38.

[4] L. Lochmann, J. Pospisil, D. Lim, Tetrahedron Lett. (1966) 257.

[5] M. Schlosser, J. Organomet. Chem. 8 (1967) 9.

[6] S. Akiyama, J. Hooz, Tetrahedron Lett. (1973) 4115.

[7] M. Schlosser, in: M. Schlosser (Ed.), Organometallics in Synthesis, Wiley, Chichester, 1994, p. 53.

[8] W. Schlenk, J. Holtz, Ber. Dtsch. Chem. Ges. 50 (1917) 262.

[9] J.J. Eisch, Organomet. Synth. 2 (1981) 92.

[10] J.J. Eisch, A.M. Jacobs, J. Org. Chem. 28 (1963) 2145.

[11] J.J. Eisch, Organomet. Synth. 2 (1981) 91.

[12] For the first account, see: M. Yus, D.J. Ramón, J. Chem. Soc. Chem. Commun. (1991) 398.

[13] For reviews, see: (a) M. Yus, Chem. Soc. Rev. (1996) 155. (b) D.J. Ramón, M. Yus, Eur. J. Org. Chem. (2000) 225 (microreview).

[14] For a solid-supported version, see: (a) C. Gómez, S. Ruiz, M. Yus, Tetrahedron Lett. 39 (1998) 1397. (b) C. Gómez, S. Ruiz, M. Yus, Tetrahedron 55 (1999) 7017.

[15] For a review, see: D. Guijarro, M. Yus, Recent Res. Dev. Org. Chem. 2 (1998) 713.

[16] For reviews, see: (a) C. Nájera, M. Yus, Trends Org. Chem. 2 (1991) 155. (b) C. Nájera, M. Yus, Recent Res. Dev. Org. Chem. 1 (1997) 67.

[17] For a review, see: M. Yus, F. Foubelo, Rev. Heteroatom. Chem. 17 (1997) 73.

[18] For a review, see: F. Foubelo, M. Yus, Trends Org. Chem. 7 (1998) 1.

[19] For a review, see: F. Alonso, M. Yus, Recent Res. Dev. Org. Chem. 1 (1997) 397.

[20] D. Guijarro, B. Mancheño, M. Yus, Tetrahedron 48 (1992) 4593.

[21] D. Guijarro, B. Mancheño, M. Yus, Tetrahedron 50 (1994) 8551.

[22] (a) E. Alonso, D. Guijarro, M. Yus, Tetrahedron 51 (1995) 11457. (b) E. Alonso, D.J. Ramón, M. Yus, J. Org. Chem. 62 (1997) 417.

[23] E. Alonso, D. Guijarro, P. Martínez, D.J. Ramón, M. Yus, Tetrahedron 55 (1999) 11027.

[24] E. Alonso, D.J. Ramón, M. Yus, Tetrahedron 53 (1997) 14355.

[25] M. Hudlicky, Chemistry of Organic Fluorine Compounds, Prentice-Hall, New York, 1992, p. 175.

[26] D. Guijarro, M. Yus, Tetrahedron 56 (2000) 1135.

[27] P.K. Choudhury, F. Foubelo, M. Yus, Tetrahedron 55 (1999) 10779.

[28] D. Albanese, D. Landini, M. Penso, J. Org. Chem. 63 (1998) 9587.

[29] S. Stavber, I. Kosir, M. Zupan, J. Org. Chem. 62 (1997) 4916.

[30] D.V. Banthorpe, M.J. Ireland, J. Prakt. Chem./Chem.-Ztg. 338 (1996) 279; Chem. Abstr. 125 (1996) 33889.

[31] D. Guijarro, M. Yus, Tetrahedron 50 (1994) 3447.

[32] G.S. Lal, G.P. Pez, R.J. Pesaresi, F.M. Prozonic, H. Cheng, J. Org. Chem. 64 (1999) 7048.