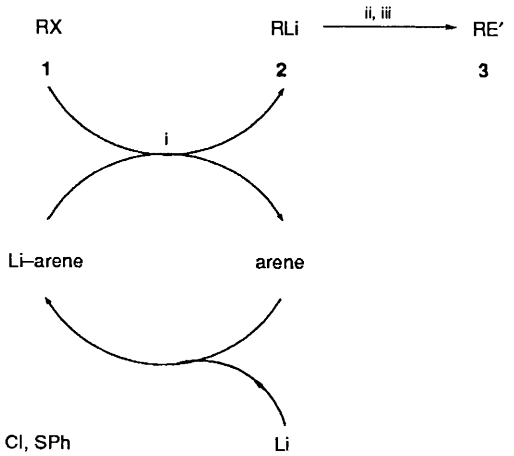
Arene-catalysed Lithiation Reactions with Lithium at Low Temperature

Miguel Yus* and Diego J. Ramón

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, 03690 Alicante, Spain

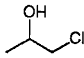
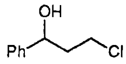
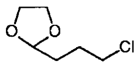
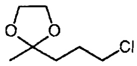
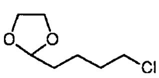
The reaction of functionalized alkyl chlorides or phenyl sulphides with an excess of lithium powder in the presence of a catalytic amount of an arene (1%; naphthalene, biphenyl, 4,4′-di-*tert*-butylbiphenyl) in tetrahydrofuran (THF) at −78 °C gives the corresponding organolithium compounds, which react with electrophiles such as water, *iso*-butyraldehyde, or cyclohexanone to yield the expected reaction products.

The main problem to be solved in the preparation at low temperature of unstable organolithium compounds[1] is the lithiation process, which needs a very active lithiation agent. When the starting material is an alkyl chloride **1** (X = Cl) or phenyl sulphide **1** (X = PhS), the best procedure consists in the use of lithium naphthalenide.[2] Thus, very reactive oxido-[3a] or amido-functionalized[3b] organolithium compounds as well as masked lithium homo-[4a] and bishomo-enolates[4b] have been prepared by a chloro–lithium interchange at −78 °C. However, the lithiation of phenyl sulphides[5a] allows the preparation of unsubstituted[5b] and α-functionalized[5a] organolithium compounds. In general, the lithiating agent most often used is lithium naphthalenide. However, in many cases the separation of naphthalene from the reaction products either by sublimation or chromatography presents problems. This difficulty can be overcome using lithium 1-(dimethylamino)naphthalenide[6] at temperatures below −45 °C, so in the work-up the generated arene can be easily removed by acid extraction. This procedure is not of general application owing to the tendency of this lithium-arene to undergo



Scheme 1 *Reagents and conditions*: i, LiBu for **1a**, **b**, −78 °C; ii, E$^+$ = H$_2$O, Pr^{i}CHO, (CH$_2$)$_5$CO, −78 to 20 °C; iii, H$_2$O

Table 1 Arene-catalysed lithiation of compounds RX and reaction with electrophiles E^+

	RX[a]					Product RE'[b]			
Entry	Formula	No.	Arene[c] (%)	Reaction time[d]/h	E^+	No.	E'	Yield[e] (%)	Lit.
1		**1a**	N (2)	1	$\mathrm{Pr^iCHO}$	**3a**	$\mathrm{Pr^iCHOH}$	68[f]	12
2		**1b**	N (1)	1.5	H_2O	**3b**	H	89	13
3		**1c**	N (1)	1	$\overline{(\mathrm{CH_2})_5\mathrm{C}}\mathrm{O}$	**3c**	$\overline{(\mathrm{CH_2})_5\mathrm{C}}\mathrm{OH}$	62[g]	4[b]
4		**1d**	N (20)	1	$\overline{(\mathrm{CH_2})_5\mathrm{C}}\mathrm{O}$	**3d**	$\overline{(\mathrm{CH_2})_5\mathrm{C}}\mathrm{OH}$	72[h]	4[b]
5		**1d**	N (5)	1		**3d**		65	
6		**1d**	N (1)	1		**3d**		67	
7		**1d**	B (1)	1.5		**3d**		68	
8		**1d**	DBB (1)	2		**3d**		60	
9		**1d**	—	4		—		0[i]	
10		**1e**	N (1)	1	$\overline{(\mathrm{CH_2})_5\mathrm{C}}\mathrm{O}$	**3e**	$\overline{(\mathrm{CH_2})_5\mathrm{C}}\mathrm{OH}$	75	—[j]
11	MeSPh	**1f**	N (1)	2.5	$\overline{(\mathrm{CH_2})_5\mathrm{C}}\mathrm{O}$	**3f**	$\overline{(\mathrm{CH_2})_5\mathrm{C}}\mathrm{OH}$	92	13
12	$CH_2{=}CHCH_2SPh$	**1g**	N (1)	3	H_2O	—[k]	—	95[k]	13

[a] In the case of entries 1 and 2 the starting material was previously treated with LiBu (1.1 molar ratio, −78 °C, 15 min) before adding lithium powder. [b] All isolated products (≥95% pure by GLC) were characterized spectroscopically (IR, ^{1}H and ^{13}C NMR and mass spectrometry) in comparison with the literature data. [c] N = naphthalene; B = biphenyl; DBB = 4,4'-di-*tert*-butylbiphenyl. The % is based on the starting material **1**. [d] For the lithiation step. [e] Isolated yield after flash chromatography (silica gel; hexane–ethyl acetate) based on the starting material **1**. [f] Mixture of diastereoisomers (*syn*:*anti* 1:3.5[12]). [g] The reaction with lithium naphthalenide (1:2.5 molar ratio) at −78 °C needs 7 h and the yield is 62%.[4b] [h] As for *g*, yield 61%. [i] Only starting material **1d** was isolated (>90%). [j] Selected data: R_f = 0.41 (hexane–ethyl acetate 3:2); ν_{OH} = 3440 cm^{-1}; δ_H 3.75–4.05 (m, 4 H, 2 CH_2O), 4.85 (t, *J* 5.05 Hz; 1 H, OCHO); δ_C 64.75 (2 CH_2O), 71.3 (COH), 104.55 (CO_2); *m/z* 228 (M^+). [k] This yield refers to benzenethiol as the only product isolated.

decomposition yielding 1-lithionaphthalene,[6] which interferes in the further reaction with electrophiles. Another problem arising from the use of lithium naphthalenide comes from radical reactions of the intermediate naphthalenide radical anion. This problem can be solved using lithium biphenylide[7] or 4,4-di-*tert*-butylbiphenylide,[8] which are less susceptible to radical attack. However, these reagents can present the same problems of separation as arise with naphthalene. Anyway, in all the mentioned lithiation reactions[3–5] a stoichiometric amount of the corresponding lithiation reagents has been always used. Here we report that lithium powder and a catalytic amount (up to 1%) of an arene (naphthalene, biphenyl, or 4,4'-di-*tert*-butylbiphenyl) is even more effective than the corresponding lithium-arene in the lithiation at low temperature of chloro- or phenylthio-derivatives.†

The successive reaction of chlorohydrins **1a**, **b** with butyllithium and an excess of lithium powder (1 : 10 molar ratio) in the presence of 1–2% of naphthalene, both at −78 °C, yielded a solution of the corresponding organolithium compound **2**, which was trapped by reaction with *iso*-butyraldehyde or water affording the expected products **3a** and **3b**, respectively (Table 1, entries 1 and 2). In the case of the chlorinated dioxolanes **1c–e**, the direct lithiation as above gave the expected organolithium intermediates, which were reacted with cyclohexanone to yield products **3c–e**, respectively (Table 1, entries 3, 6 and 10). In the case of **1d** the influence of the catalytic amount of naphthalene was studied: in general, no important differences were observed using 20, 5 or even 1% of naphthalene (based on the amount of starting material **1**; Table 1, entries 4–6). As a blank reaction, in the absence of naphthalene no reaction took place, the starting material **1d** being recovered unchanged (Table 1, entry 9). On the other hand, the reaction of **1d** was studied using a catalytic amount of biphenyl or 4,4'-di-*tert*-butylbiphenyl (1%), obtaining similar results as for naphthalene (Table 1, entries 7 and 8). When phenyl sulphides such as **1f** or **1g** were used as starting materials the direct lithiation in the presence of naphthalene (1%) afforded the expected breaking of the aliphatic carbon–sulphur bond[5] forming the corresponding methyl- or allyllithium and lithium benzenethiolate, which were trapped with cyclohexanone or water, respectively (in the second case only benzenethiol was isolated; Table 1, footnote *k*; entries 11 and 12) (Scheme 1).‡

From the preliminary results described in this paper we concluded that the method reported here improves greatly the use of lithium-arenes for lithiation reactions because: (*i*) preparation of the lithium-arene compound is not necessary; (*ii*) the reaction is very clean, without by-processes derived from the intermediate anion radical; (*iii*) work-up is simple

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† To our best knowledge only three examples have been recently reported in which lithium and a catalytic amount of an arene has been used in other different lithiation processes: (*a*) reductive preparation of bibenzyl under sonication conditions,[9a] (*b*) reductive scission of cyclopropylacetylenes[9b] and (*c*) reductive opening of oxetanes[9c] by means in each case of lithium and a catalytic amount (10–20%) of 4,4'-di-*tert*-butylbiphenyl.

‡ *General procedure*: To a cooled (−78 °C) suspension of lithium powder (Aldrich 325 mesh, 99.9%; 25 mmol) in THF (5 ml) and the corresponding arene (see Table 1) was added the substrate **1** (2.5 mmol) under argon and the mixture was stirred for 1–3 h (see Table 1). Then the corresponding electrophile (3.0 mmol; 0.5 ml in the case of water) was added and the temperature allowed to rise to 20 °C during *ca*. 3 h. The resulting mixture was hydrolysed with water, neutralized with HCl (2 mol dm^{-3}), extracted with diethyl ether, and the organic layer dried over anhydrous Na_2SO_4. The solvents were evaporated and the residue was chromatographed (silica gel; hexane–ethyl acetate) to yield the corresponding products **3**.

owing to the very small amount of the arene required; (*iv*) the end of the reaction is detected easily because when the starting material is consumed the typical colour of lithium-arene (green, brown, or violet for N, B or DBB, respectively) appears. On the other hand, we think that this procedure can be applied to the preparation of other metal-arenes,[10a] to obtain highly reactive metals,[7] in transmetallation processes,[10b] and, in general, as a substitute for methods that use lithium-arenes.[11]

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