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DTBB-catalysed lithiation of 6-chloro-1-hexene and related systems: synthetically useful temperature-dependent behaviour[†]

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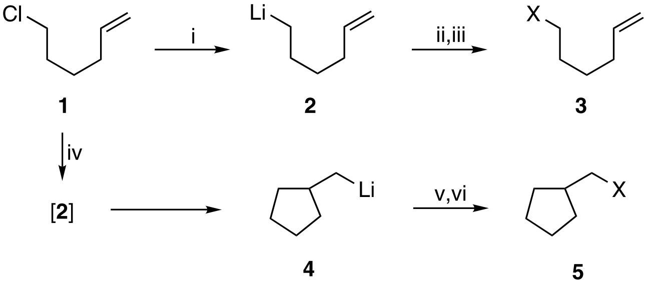
Abstract—The reaction of 6-chloro-1-hexene **1** with lithium powder and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB, 5% molar) in THF at −78°C gives the corresponding organolithium intermediate **2**, which by reaction with different electrophiles [Bu^{t}CHO, PhCHO, Et_2CO, $(CH_2)_5CO$, PhCOMe] affords, after hydrolysis with water, the expected products **3**. The same reaction performed at −30°C gives cyclopentyl derivatives **5**, probably by cyclisation of the open-chain intermediate **2** to give the cyclic organolithium compound **4**. For the tertiary derivative **6**, only the cyclic compound **10** could be isolated at −30°C due to the great instability of the corresponding tertiary organolithium intermediate **7**, which undergoes a proton abstraction even at −78°C. From allyl 2-chloro-phenyl ether **11** only the corresponding cyclic compound **14** was isolated either at −78°C or at −30°C. In all cases a carbanionic cyclisation, better than a radical one, is postulated to occur. © 2002 Elsevier Science Ltd. All rights reserved.

Carbometallation reactions are important from a methodological point of view because together with the formation of a new carbon–carbon bond, a carbon–metal bond is also generated. It means that a second organometallic reagent is formed which, in principle, is able to continue reacting, so in only one reaction step profound structural changes are introduced.[1] Due to the high reactivity of organolithium compounds,[2] carbolithiation reactions are particularly interesting processes, which can take place in both inter- and intramolecular fashions.[3] This last reaction has an additional interest because a cyclic structure is formed, this reaction being a useful methodology in order to prepare functionalised carbocyclic compounds, by final trapping the newly cyclic organolithium intermediate with electrophilic reagents. Different procedures to generate the necessary starting material for the intramolecular cyclisation include: (a) bromine or iodine–lithium exchange using an alkyllithium reagent;[4] (b) sulfur–lithium exchange[5] starting from phenylthioethers and using a lithium–arene;[6] (c) tin–lithium transmetallation from unsaturated tri-*n*-butylstannanes and butyllithium;[7] and (d) cyano-lithium exchange using a lithium–arene in special cases.[8] To the best of our knowledge, the most classical way (a) has never been applied to the corresponding more accessible and stable chlorinated precursors due to the difficulty in carrying out the lithiation step at low temperatures using typical lithiation methodologies. For this purpose, in the last few years we have been developing a lithiation procedure, which consists of using lithium powder and a catalytic amount of an arene,[9–13] naphthalene and 4,4′-di-*tert*-butylbiphenyl (DTBB) being the electron carrier agents most commonly used.[14] We have been using this methodology for, (a) the generation of organolithium compounds from non-halogenated materials,[15] (b) the preparation of functionalised organolithium compounds,[16,17] (c) the



Scheme 1. *Reagents and conditions*: (i) Li powder, DTBB (5% molar), THF −78°C, 45 min; (ii) E = Bu^{t}CHO, PhCHO, Et_2CO, $(CH_2)_5CO$, PhCOMe, −78°C; (iii) H_2O, −78°C to rt; (iv) Li powder, DTBB (5% molar), THF, −30°C; (v) E = Bu^{t}CHO, PhCHO, Et_2CO, $(CH_2)_5CO$, PhCOMe, −30°C; (vi) H_2O, −30°C to rt.

Keywords: chlorine–lithium exchange; intramolecular carbolithiation; DTBB-catalysed lithiation; cyclisation.

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[†] Dedicated to Professor Marcial Moreno-Mañas on the occasion of his 60th birthday.

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generation of polylithium synthons,[18] and (d) the activation of other metals[19] especially nickel.[20] In this paper we apply the above-mentioned arene-catalysed lithiation to the generation of unsaturated organolithium compounds by chlorine–lithium exchange in order to study their possible intramolecular carbolithiation reaction.

The reaction of 6-chloro-1-hexene **1** with an excess of lithium powder[21] (1:2.8 molar ratio; theoretical amount 1:2 molar ratio) and a catalytic amount of DTBB (5 mol%) in THF at −78°C led to a solution of the corresponding organolithium intermediate **2**, which by treatment with different electrophiles [Bu^tCHO, PhCHO, Et_2CO, $(CH_2)_5CO$, PhCOMe] and final hydrolysis with water, both at the same temperature, gave the expected products **3** (Scheme 1 and Table 1, entries 1–9). Some interesting aspects of the process are: (a) both arenes, naphthalene and DTBB, can be used in the reaction with comparable results (Table 1, entries 1, 4 and 6–9); (b) the reaction can also be performed under Barbier-type conditions (in the presence of the electrophile)[22] (Table 1, entries 1 and 2, and footnote f); (c) when lithium–naphthalene was used (the stoichiometric version of the arene-catalysed lithiation) the yield was lower than for the catalytic reaction (Table 1, entries 4 and 5); (d) the reaction can also be carried out starting from the corresponding brominated materials with comparable results (Table 1, entry 2 and footnote g); (e) longer lithiation and S_E reaction times did not improve the yield of the reaction (Table 1, entries 1 and 3).

When the above-mentioned reaction was carried out at −30°C, the cyclic intermediate **4** was the only one generated (probably through the open-chain organolithium compound **2**, via a carbolithiation process) and after reaction with the same electrophiles as for the intermediate **2**, the corresponding products **5** were obtained after hydrolysis, both steps having been carried out at the same temperature (Scheme 1 and Table 1, entries 10–21). In this case the following comments are pertinent: (a) the reaction can be carried out at temperatures ranging between −78 and 0°C, giving the best results at −30°C, so this temperature was chosen as the standard one (Table 1, entries 10–12); (b) the amount of the catalyst can be decreased until about 1%, the reaction working in all cases nicely (Table 1, entries 14 and 15). Even without DTBB the reaction worked well (Table 1, entry 16): actually, we knew[9] that at −30°C the lithiation can be carried out in absence of the electron carrier, but in this case the process needed longer reaction time and the process is not clean being necessary a more careful final purification; (c) also in this reaction the corresponding brominated starting material can be used (Table 1, entry 17 and footnote g).

Table 1. Preparation of compounds **3** and **5**

Entry	Reaction conditions			Electrophile	Product[a]		
	T (°C)[b]	*T* (min)[c]	Catalyst (%)[d]	E	No.	X	Yield (%)[e]
1	−78	45+15	DTBB (5)	Et_2CO	**3a**	Et_2COH	95
2	−78	30+45	DTBB (5)	Et_2CO	**3a**	Et_2COH	90[f] (85)[g]
3	−78	70+30	DTBB (5)	Et_2CO	**3a**	Et_2COH	64
4	−78	30+15	N (5)	Et_2CO	**3a**	Et_2COH	89
5	−78	60+30	N (100)	Et_2CO	**3a**	Et_2COH	33
6	−78	45+15	DTBB (5)	Bu^tCHO	**3b**	Bu^tCHOH	91
7	−78	45+15	DTBB (5)	PhCHO	**3c**	PhCHOH	97
8	−78	45+15	DTBB (5)	$(CH_2)_5CO$	**3d**	$(CH_2)_5COH$	90
9	−78	45+15	DTBB (5)	PhCOMe	**3e**	PhC(OH)Me	77
10	−78 to 0	90+15	DTBB (5)	Et_2CO	**5a**	Et_2COH	53
11	0	60+30	DTBB (5)	Et_2CO	**5a**	Et_2COH	80
12	−30	60+30	DTBB (5)	Et_2CO	**5a**	Et_2COH	92
13	−30	45+20	DTBB (5)	Et_2CO	**5a**	Et_2COH	78
14	−30	45+15	DTBB (2.5)	Et_2CO	**5a**	Et_2COH	83
15	−30	45+15	DTBB (1)	Et_2CO	**5a**	Et_2COH	93
16	−30	50+30	–	Et_2CO	**5a**	Et_2COH	83
17	−30	45+15	DTBB (5)	Et_2CO	**5a**	Et_2COH	95 (74)[g]
18	−30	45+15	DTBB (5)	Bu^tCHO	**5b**	Bu^tCHOH	75
19	−30	45+15	DTBB (5)	PhCHO	**5c**	PhCHOH	87
20	−30	45+15	DTBB (5)	$(CH_2)_5CO$	**5d**	$(CH_2)_5COH$	95
21	−30	45+15	DTBB (5)	PhCOMe	**5e**	Et_2COH	81

[a] All compounds **3** and **5** were ≥95% pure (300 MHz ^{1}H NMR and/or GLC) and were fully characterised by spectroscopic means (IR, ^{1}H and ^{13}C NMR, and MS).

[b] Temperature corresponding to the whole process (lithiation, S_E reaction and hydrolysis).

[c] Reaction time corresponding to the two steps: lithiation+S_E reaction.

[d] DTBB: 4,4′-di-*tert*-butylbiphenyl; N: naphthalene; in parentheses the corresponding amount used (mol%).

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

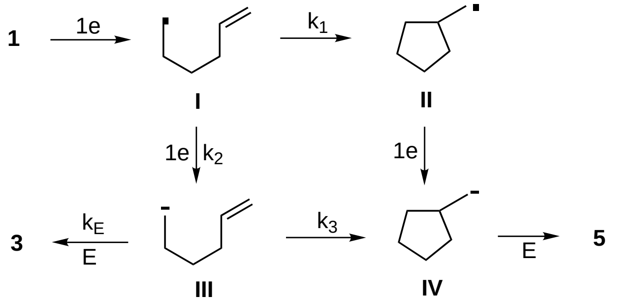
[f] The reaction was performed in the presence of the electrophile (Barbier-type conditions).

[g] Yield corresponding to the reaction starting from 6-bromo-1-hexene instead of compound **1**.

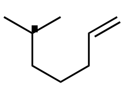
When the reaction shown in Scheme 1 was applied to the tertiary derivative **6** we found that at −78°C the corresponding intermediate **7** initially formed is very unstable and abstracts a proton from the reaction medium (probably from THF[23]), so after adding 3-pentanone as electrophile the only reaction product detected (GLC–MS) was the 'reduced' compound **8**, resulting from a lithium–hydrogen exchange [two-step reaction/−78°C: 61% (GLC); Barbier conditions/−78°C: 60% (GLC)]. It is worth noting that even working under Barbier conditions, only compound **8** was obtained at −30°C [53% (GLC)]. However, at 0°C under Barbier conditions (76%) or at −30°C in a two-step process (75%), the expected cyclic product **10** was the only one isolated after reaction with 3-pentanone and final hydrolysis at the same temperature (Scheme 2).

Finally, we studied the DTBB-catalysed lithiation of compound **11** finding that either at −78°C (ca. 45%) or at −30°C (56%) the only compound isolated, after reaction with 3-pentanone and final hydrolysis, was the alcohol **14**, intermediates **12** and **13** being probably involved in the process (Scheme 3). In this case, no compound resulting from the reaction of intermediate **12** with the electrophile was obtained. The moderate yield obtained is probably due to by-reactions such as partial deallylation[24] or intramolecular deprotonation at the allylic position[25] followed by a Wittig rearrangement.[26]

Concerning the possible mechanism of the reaction, we think that radical of type **I** is initially formed, which could either cyclise to **II** or take a second electron giving the carbanion **III**. Since the cyclisation of the radical is much more rapid than that of the carbanion,[27] we think that once the radical **I** is formed at −78°C it is converted rapidly to the anion **III** ($k_2 \gg k_1$) whereas at −30°C cyclisation of intermediate **III** to the cyclic carbanion **IV** probably occurs. Actually, the other possible pathway at −30°C, through intermediate **II** cannot be completely ruled out. However, we observed that performing the reaction in the presence of cumene as an effective radical scavenger,[4a] the obtained results were not altered significantly, so we deduce that the half-life of radicals **I** and **II** should be very short. On the other hand, since the reaction under Barbier-type conditions gives similar results as in the two-step process, we conclude that the cyclisation **III**→ **IV** is faster than the S_E reaction of carbanion **III** ($k_3 \gg k_E$).



In the case of the tertiary derivative **6**, the radical **V** evolves rapidly at −78°C to the carbanion **VI**, which is very unstable and takes a proton from the reaction medium. At −30°C intermediate **VI** probably gives the most stable primary cyclic carbanion **VIII**. As it was mentioned above, radical **VII**, resulting from the radical **V** by cyclisation, probably does not take part in the reaction.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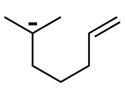
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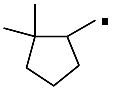
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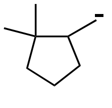
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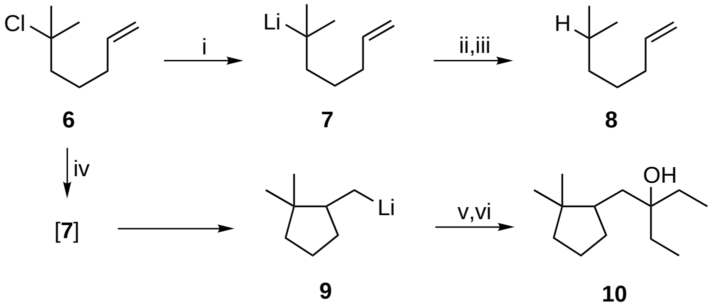
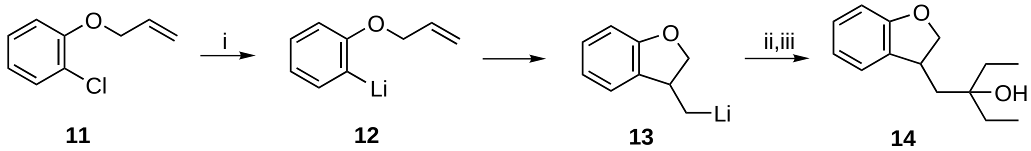


Scheme 2. *Reagents and conditions*: (i) Li powder, DTBB (5% molar), THF −78°C, 45 min; (ii) Et_2CO, −78°C; (iii) H_2O, −78°C to rt; (iv) Li powder, DTBB (5% molar), THF, −30°C; (v) Et_2CO, −30°C; (vi) H_2O, −30°C to rt.



Scheme 3. *Reagents and conditions*: (i) Li powder, DTBB (5% molar), THF, −78 or −30°C; (ii) Et_2CO, same temperature as step i; (iii) H_2O, −78 or −30°C to rt.

In conclusion, we report in this paper the DTBB-catalysed lithiation of 6-chloro-1-hexene and related systems, which can be controlled either giving the corresponding open-chain compounds at −78°C or the cyclic derivatives at −30°C. We believe that in the second case an intramolecular carbolithiation takes place transforming the initially formed organolithium intermediate into the corresponding cyclic one.[28]

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28. *Typical procedure for compounds* **3** *and* **5**: Chlorinated compound **1** (0.138 mL, 1 mmol) was directly added over a green suspension of Li powder (50 mg, 7 mmol) and DTBB (26.6 mg, 0.1 mmol) in THF (3 mL) at the corresponding temperature (−78 or −30°C). The reaction was stirred at the same temperature for 45 min, the corresponding electrophile (1.1 mmol) was then added and after 15 min stirring the reaction crude was hydrolysed with 2 M HCl (10 mL). The mixture was allowed to reach room temperature and extracted with diethyl ether (3×10 mL). The organic phase was dried over anhydrous magnesium sulphate and evaporated at reduced pressure to yield the title compound. Purification by column chromatography (silica gel, hexane/ethyl acetate) gave pure compounds **3** and **5**.