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3-Chloropropyl Phenyl Ether as a 1,3-Dilithiopropane Source: Sequential Reaction with Carbonyl Compounds

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Abstract

The reaction of 3-chloropropyl phenyl ether (**1**) with lithium powder and a catalytic amount of DTBB (2.5% molar) in THF at -78°C followed by successive treatment with a carbonyl compound [E^1 = Bu^tCHO, Me_2CO, $(CH_2)_5CO$] at -78 to 20°C and, after 1 h at this temperature, a second one [E^2 = Bu^tCHO, PhCHO, $MeCOPr^n$, $(CH_2)_5CO$] at -78°C leads, after hydrolysis with water, to the formation of the corresponding 1,5-diols (**2**), in which two different electrophilic fragments have been introduced.

Keywords: lithiation; catalysis; carbanions; diols.

1,3-Dilithioalkanes [1-3][1] cannot be prepared directly from the corresponding dihalides [4,5] because the 3-chlorolithioalkane initially formed suffers spontaneous γ-elimination, even at very low temperatures, giving the corresponding cyclopropane derivatives [6,7]. Only in special cases [for instance, starting from 3-chloro-2-(chloromethyl)propene] and reaction conditions (combining an arene-catalysed lithiation [8,9] carrying out the lithiation in the presence of the electrophile, under Barbier-type conditions [10,11]) was it possible to introduce as many electrophilic fragments as were chlorine atoms in the starting material [12-14]. Except in the situation mentioned [15],[2] mercury-lithium transmetallation is the only way to generate non-stabilised 1,3-dilithiated intermediates [16-18]. The simplest compound of this series, 1,3-dilithiopropane, is a very unstable species (half-life of 1 h at 20°C [18]) easily loosing lithium hydride to give allyllithium [18-20].[3] In the last few years, we have been studying the use of an arene-catalysed lithiation reaction [8,9] for the preparation

[1] For recent reviews on polylithium compounds, see references [1-3].

[2] For the last paper from our laboratory on the preparation of polylithium synthons, see reference [15].

[3] A doubly lithium bridged structure for 1,3-dilithiopropane has been proposed based on theoretical calculations [19,20].

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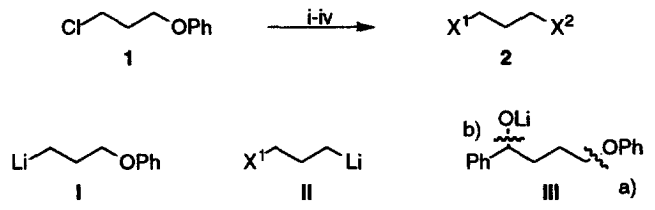
of very unstable functionalised [21,22] organolithium compounds starting from chlorinated materials [23],[4] thioethers [24] or heterocyclic derivatives [25,26].[5] Very recently we discovered that this methodology can be applied to the generation of alkyllithiums from alkyl phenyl ethers [27]. In this paper we report the preparation of a new 1,3-dilithiopropane synthon taking advantage of the different reactivity of carbon-chlorine and carbon-oxygen bonds towards arene-catalysed lithiation.

The reaction of 3-chloropropyl phenyl ether [**1**; prepared by treatment of 1-bromo-3-chloropropane with potassium phenolate in methanol (>90%)] with a blue suspension of an excess of lithium powder (1:10 molar ratio; theoretical amount, 1:4) and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB; 1:0.1 molar ratio; theoretical amount, 1:4; 2.5% molar) in THF at -78°C for 30 min gave a solution of the intermediate of type **I**, which reacted with an electrophile [E^1 = Bu^tCHO, Me_2CO, $(CH_2)_5CO$; 1:1.3 molar ratio] at temperatures ranging between -78 and 20°C. After 1 h stirring at room temperature the second lithiation took place giving a new intermediate of type **II**, which reacted again with a second electrophile [E^2= Bu^tCHO, PhCHO, $MeCOPr^n$, $(CH_2)_5CO$; 1:1.3 molar ratio] at -78°C to give, after hydrolysis with water at -78 to 20°C, the expected 1,5-diols **2** (Scheme 1 and Table 1).

One remark about the reaction shown in Scheme 1 is that benzaldehyde cannot be used as E^1 in the first step because after reaction with the intermediate **I** the resulting compound **III** suffers a benzylic cleavage [28][6] (b) together with the expected ether cleavage (a), giving a mixture of products.



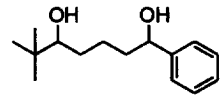
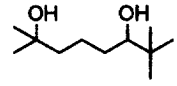
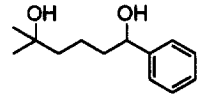
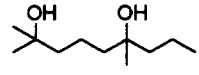
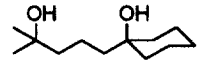
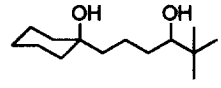
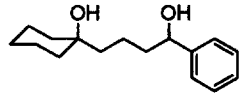
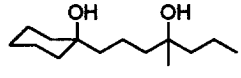
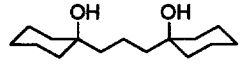
Scheme 1. *Reagents and conditions*: i, Li, DTBB (2.5% molar), THF, -78°C, 30 min; ii, E^1 = Bu^tCHO, Me_2CO, $(CH_2)_5CO$, 20°C, 1 h; iii, E^2 = Bu^tCHO, PhCHO, $MeCOPr^n$, $(CH_2)_5CO$, -78°C, 5 min; iv, H_2O, -78 to 20°C.

[4] For the last paper on this topic from our laboratory, see reference [23].

[5] For the last paper on this topic from our laboratory, see reference [25]. For a recent review, see reference [26].

[6] This behaviour has been observed for instance in the reductive opening of phthalan [28].

Table 1.
Preparation of compounds **2**

Entry	E^1	E^2	Product **2**[a] No.	Structure	Yield[b]	R_f[c]
1	Bu^tCHO	PhCHO	**2a**		68[d]	0.20[d]
2	Me_2CO	Bu^tCHO	**2b**		53	0.16
3	Me_2CO	PhCHO	**2c**		64	0.15
4	Me_2CO	$MeCOPr^n$	**2d**		45	0.10
5	Me_2CO	$(CH_2)_5CO$	**2e**		48	0.12
6	$(CH_2)_5CO$	Bu^tCHO	**2f**		60	0.18
7	$(CH_2)_5CO$	PhCHO	**2g**		52	0.19
8	$(CH_2)_5CO$	$MeCOPr^n$	**2h**		49	0.16
9	$(CH_2)_5CO$	$(CH_2)_5CO$	**2i**		70	0.17[e]

[a] All isolated products **2** were 95% pure (GLC) and were fully characterised by spectroscopic means (IR, ^1H and ^{13}C NMR and MS).
[b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **1**.
[c] Silica gel, hexane/ethyl acetate: 2/1.
[d] *ca.* 1/1 diastereomeric mixture (75 MHz ^{13}C NMR).
[e] Mp 116°C (hexane/ethyl acetate).

Of course, the reaction can be used for the introduction of the same electrophile in both steps as illustrated in Table 1, entry 9 for cyclohexanone.

From a manipulation point of view it is worthy to note that the above mentioned preperation of compounds **2** is very easy to follow by just looking colour changes: during both lithiation steps the initial blue colour disappeared, coming back again when the substrate is consumed, so you can realise perfectly when it is neccessary to add the corresponding electrophile, and the final hydrolysis.

As a conclusion, we describe here a new way to generate the equivalent of the 1,3-dianion of propane and the introduction of two different electrophiles in a sequential process. The reaction is possible because of the different reactivity of the carbon-chlorine and carbon-oxygen bonds towards lithiation: whereas the chlorine/lithium exchange takes place at -78°C the carbon-oxygen bond needs higher temperatures (above -40°C) to occur [28]. In this study we employed carbonyl compounds as electrophiles, so differently substituted 1,5-diols were prepared.

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