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2-Chloromethyl-3-(2-methoxyethoxy)propene: Naphthalene-catalysed Lithiation and Reaction towards Electrophiles

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Abstract: The reaction of the title compound (1) with an excess of lithium powder and a catalytic amount of naphthalene (2.5%) in the presence of an electrophile $[E_1^+=Bu^{t}CHO, Et_2CO, (CH_2)_5CO, PhCOMe, Me_3SiCI]$ in THF at -78 to -30°C, followed by treatment with a second electrophile $[E_2^+=Bu^{t}CHO, Me_2CO, Et_2CO, (CH_2)_4CO, (CH_2)_5CO, Bu^{t}COMe, Bu^{t}_2CO, PhCH=NPh, Me_3SiCI, D_2O]$ at -30°C to room temperature leads, after hydrolysis, to the expected compounds 2. For carbonyl derivatives, compounds 2 were successively hydroborated (BH₃:THF) and oxidised [33% H₂O₂ and then PCC or RuCl₂(PPh₃)₃] to give directly the corresponding perhydrofurofurans 4.

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The trimethylmethane dianion I has been subject of interest not only from a theoretical point of view, concerning the so-called "Y aromaticity", but also from a synthetic perspective due to its capability to react with electrophiles yielding polyfunctionalised molecules in only one reaction step.¹ The initial preparation of this dianion by double deprotonation (with BuⁿLi/TMEDA² or BuⁿLi/KOBu³) allowed the introduction of two equal electrophilic fragments by reaction with different electrophiles (haloalkanes,^{2a-d,3c} carbonyl compounds,^{3c} epoxides^{3c} and nitriles^{2e}). The use of a chloro/lithium exchange reaction for the preparation of I was not possible due to decomposition of the monolithio derivative initially formed. This problem was overcome recently⁴ using an arene-catalysed lithiation⁵ in the presence of several electrophiles (Barbier-type conditions⁶). One obvious problem using both mentioned strategies (H/Li or Cl/Li exchange) is that it is not possible to introduce two different electrophilic fragments. In order to avoid this inconvenience some strategies using mixed silicon-tin or silicon-heteroatom precursors of type II have been developed and used, in general, under catalytic conditions for the reaction with different electrophiles.⁷ In this paper we report the use of the title compound for the introduction of two different electrophiles in the isobutylene skeleton through a naphthalene-catalysed lithiation.⁸

0040-4039/98/\$19.00 © 1998 Elsevier Science Ltd. All rights reserved. *PII*: S0040-4039(98)00476-6 The reaction of 2-chloro-3-(2-methoxyethoxy)propene (1)⁹ with an excess of lithium powder (1:7 molar ratio) and a catalytic amount of naphthalene (1:0.1 molar ratio; 2.5 mol %) in the presence of different electrophiles [E_1 + = Bu⁴CHO, E_1 ₂CO, (CH₂)₅CO, PhCOMe, Me₃SiCl] in THF at temperatures between -78 and -30°C led to a reaction mixture that was again treated with a second electrophile [E_2 + = Bu⁴CHO, Me₂CO, Et₂CO, (CH₂)₅CO, Bu⁴COMe, Bu⁴₂CO, PhCH=NPh, Me₃SiCl, D₂O] at -30°C to room temperature yielding, after hydrolysis with water, the corresponding products 2, in which two different electrophilic fragments have been introduced in the isobutylene skeleton (Scheme 1 and Table 1).



Scheme 1. Reagents and conditions: i, Li, $C_{10}H_8$ cat. (2.5%), $E_1^+ = Bu^{\circ}CHO$, E_2CO , (CH₂)₅CO, PhCOMe, Me₃SiCl, THF, -78 to -30°C; ii, $E_2^+ = Bu^{\circ}CHO$, Me₂CO, E_2CO , (CH₂)₄CO, (CH₂)₅CO, Bu^{\circ}COMe, Bu^{\circ}₂CO, PhCH=NPh, Me₃SiCl, D₂O, -30 to 20°C; iii, H₂O.

Table 1. Preparation	of Compounds 2
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Entry	Electrophile E ₁ +	Electrophile E ₂ +	Producta				
			No.	E ₁	E ₂	Yield (%)b	
1	ButCHO	Et ₂ CO	2a	ButCHOH	Et ₂ COH	43	
2	Et ₂ CO	ButCHO	2a	Et ₂ COH	Bu ^t CHOH	34	
3	Et ₂ CO	Me ₂ CO	2 b	Et ₂ COH	Me ₂ COH	47	
4	Et ₂ CO	ButCOMe	2c	Et ₂ COH	ButC(OH)Me	44	
5	Et ₂ CO	Bu ¹ ₂ CO	2 d	Et ₂ COH	But ₂ COH	61	
6	Et ₂ CO	PhCH=NPh	2 e	Et ₂ COH	PhCHNHPh	34	
7	Et ₂ CO	Me ₃ SiCl	2 f	Et ₂ COH	Me ₃ Si	12	
8	Et ₂ CO	D_2O	2 g	Et ₂ COH	D	77	
9	(CH ₂) ₅ CO	(CH ₂) ₄ CO	2 h	(CH ₂) ₅ COH	(CH ₂) ₄ COH	57	
10	(CH ₂) ₅ CO	PhCH=NPh	2i	(CH ₂) ₅ COH	PhCHNHPh	25	
11	PhCOMe	(CH ₂) ₅ CO	2ј	PhC(OH)Me	(CH ₂) ₅ COH	38	
12	Me ₃ SiCl	Et ₂ CO	2 f	Me ₃ Si	Et ₂ COH	75	

^a All products 2 were >95% pure (GLC and/or 300 MHz ¹H NMR) and were fully characterised by spectroscopic means (IR, ¹H and ¹³C NMR, and mass spectrometry). ^b Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting chloroether 1.

From a mechanistic point of view, the reaction begins with a chloro/lithium exchange to give a functionalised organolithium compound¹⁰ of type III, which in the presence of the first electrophile (E_1^+) undergoes electrophilic substitution giving the corresponding alkoxide of compounds 3. When the reaction mixture was hydrolysed at this point, the expected products derived from 3-pentanone (3a) and cyclopentanone (3b) were isolated in 97 and 65% yield, respectively. After the reaction of the first electrophile the lithiation was

allowed to continue in the presence of a second electrophile (E_{2}^{+}), the lithiation (to give the intermediate IV)- S_{E} tandem reaction took place to afford products 2.



From the compounds obtained as shown in Scheme 1, we found specially interesting the corresponding derivatives from carbonyl compounds because they can be easily transformed into non-symmetrically substituted perhydrofurofurans,¹¹ which constitute the heterocyclic core of important natural products such as aflatoxins,¹² asteltoxin¹³ and other important potent biologically active products.¹⁴ Thus, compounds **2a-d**, **2h** and **2j** were hydroborated and successively oxidised with hydrogen peroxide and PCC (for ketone derivatives) or RuCl₂(PPh₃)₃ (for aldehyde derivatives) to give the expected perhydrofurofurans **4** (Scheme 2 and Table 2).



Scheme 2. Reagents and conditions: i, BH₃·THF, 0°C; 33% H₂O₂, 3M NaOH, 0°C; iii, PCC, CH₂Cl₂, 0°C or RuCl₂(PPh₃)₃, PhH, 0°C (see text).

Entry	Starting material	Oxidation ^a method	Productb						
			No.	R ¹	R ²	R ³	R4	Yield (%)	
1	2a	A	4a	But	Н	Et	Et	36d	
2	2 b	В	4b	Et	Et	Me	Me	58	
3	2 c	В	4c	Et	Et	But	Me	53d	
4	2d	В	4d	Et	Et	But	But	72	
5	2h	В	4h	(CH ₂) ₅		(CH ₂) ₄		56	
6	2j	В	4j	Ph	Me	(CH	I ₂)5	47d	

Table 2. Preparation of Compounds 4

^a Method A: RuCl₂(PPh₃)₃; Method B: PCC. ^b All products 4 were >95% pure (GLC and/or 300 MHz ¹H NMR) and were fully characterised by spectroscopic means (IR, ¹H and ¹³C NMR, and mass spectrometry). ^c Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting chloroether 1. ^d Obtained as a *ca.* 1:1 diastereoisomeric mixture (300 MHz ¹H NMR).

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