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Chemoselective lithiation of 6-chloro-1-halohex-1-ynes with lithium/naphthalene

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Abstract: The reaction of different 6-chloro-1-halohex-1-ynes (**1**) with lithium naphthalene (1:2 molar ratio) and a carbonyl compound R¹R²CO in THF at -78°C leads, after hydrolysis with water, to the corresponding chlorinated alcohols **2** through a selective lithiation of the sp carbon-halogen bond. The DTBB-catalysed lithiation of 6-chloro-1-halohexynes (**1**) in the presence of an excess of a carbonyl compound R¹R²CO as electrophile in THF at -78 °C led, after hydrolysis with water, to diols **3**.

Keywords: DTBB-catalysed lithiation, lithium-naphthalene, bromine-lithium exchange, chlorine-lithium exchange, electrophilic substitution, diols.

Introduction

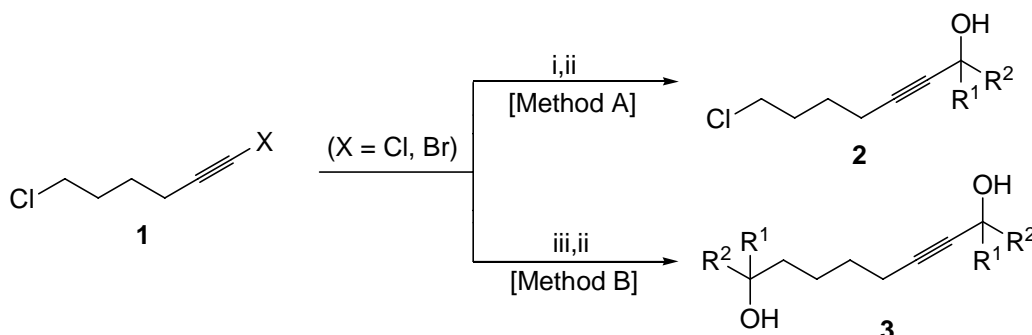
Functionalized organolithium compounds¹ are useful carbanionic intermediates in synthetic organic chemistry because the functionality is transferred to the electrophilic reagent in their reaction with an electrophile, so polyfunctionalized molecules are accessible in only one synthetic operation.² A halogen (chlorine, bromine or iodine) is not particularly compatible with the presence of a carbon-lithium bond in the same molecule,³ because the elimination of lithium halide from the initially generated halogenated organolithium intermediate, especially in intramolecular fashion, would self-destroy it, giving a new, undesirable carbon-carbon bond. The other inherent problem in the preparation of these intermediates is the difficulty of generating carbon-lithium bonds in the presence of a halogen in the same molecule, because the other carbon-halogen bond can be lithiated too (selective monolithiation). There are few examples in the literature of a selective monolithiation of n-chloro-1-iodoalkanes using *t*-BuLi as the lithiating reagent in diethyl ether. Following this methodology, 4-lithio-1-chlorobutane⁴ and 6-lithio-1-chlorohexane⁵ have been prepared. It is also known the selective metallation of 1-bromo-*n*-chloroalkanes (*n* = 4-6)⁶ with magnesium in diethyl ether to give the corresponding chloroalkylmagnesium bromides. Recently, we reported the chemoselective lithiation of a carbon-bromine bond in the presence of a carbon-chlorine one by use of an arene-promoted lithiation of different 1-bromo-*n*-chloroalkanes (*n* = 4-6).⁷ In this communication we report our preliminary results on the selective lithiation of dihalogenated compounds considering the halogen atoms and also the hybridization of the carbon atoms bonded to the halogens.

Results and discussion

The reaction of dihalocompounds **1** with 2 equivalents of lithium naphthalene in the presence of 1.1 equivalents of PhCHO in THF at -78 °C for 45 min yielded, after hydrolysis with water at temperatures ranging between -78°C and room temperature (Method A), the corresponding chlorinated alcohol **2a**

in moderate yields (Scheme 1 and Table 1, entries 1 and 2). Under these reaction conditions, a selective lithiation of the sp carbon-halogen (chlorine or bromine) bond takes place instead of that of the sp³ carbon-chlorine bond.

On the other hand, the reaction of dihalocompounds **1** with an excess of lithium powder (1:10 molar ratio) and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB; 1:0.1 molar ratio; 2.5 mol %) in the presence of different carbonyl compounds [PhCHO, Et₂CO, (CH₂)₅CO] (1:3 molar ratio) in THF at -78 °C for *ca.* 1.5 h, followed by hydrolysis with water at temperatures ranging between -78 °C and room temperature (Method B), led to the expected diols **3** (Scheme 1 and Table 1, entries 3-8).



Scheme 1. Reagents and conditions: (i) 2 LiC₁₀H₈, 1.1 R¹R²CO, THF, -78 °C; (ii) H₂O, -78 to 20 °C; (iii) Li, DTBB (5 mol %), 2.5 R¹R²CO, THF, -78 °C.

Table 1. Lithiation of 6-chloro-1-haloalk-1-ynes (**1**). Preparation of compounds **2** and **3**.

Entry	Starting material			Method	Product	
	No.	X	R ¹ R ² CO		No.	Yield (%) ^a
1	1a	Cl	PhCHO	A	2a	54
2	1b	Br	PhCHO	A	2a	69
3	1a	Cl	PhCHO	B	3a	56
4	1b	Br	PhCHO	B	3a	61
5	1a	Cl	Et ₂ CO	B	3b	32
6	1b	Br	Et ₂ CO	B	3b	36
7	1a	Cl	(CH ₂) ₅ CO	B	3c	59
8	1b	Br	(CH ₂) ₅ CO	B	3c	54

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

Starting materials **1** were prepared from commercially available 6-chlorohex-1-ene by first deprotonation with *n*-BuLi followed by reaction of the resulting lithium acetylide with tosyl chloride in

the case of **1a**⁸ or after treatment with *N*-bromosuccinimide and silver nitrate in acetone for compound **1b**.⁹

Conclusion

In conclusion, we report in this communication the discrimination between *sp* carbon-halogen (chlorine or bromine) bond and *sp*³ carbon-chlorine bond in the lithiation of 6-chloro-1-halohehex-1-ynes, thus making possible either the monolithiation and the introduction of only one electrophile or, the double lithiation and introduction of two electrophilic fragments. Careful choice of lithiation conditions are necessary to perform these processes.

Experimental part

For general experimental information, see reference 7. All reagents used for the synthesis of substrates **1** and DTBB were commercially available (Acros, Aldrich) and were used without further purification. Lithium powder was prepared according to the procedure described in reference 10. Commercially available anhydrous THF (99.9%, water content $\leq 0.006\%$, Acros) were used as solvents in the reactions. All glassware was dried in an oven at 100°C and cooled to room temperature under Ar before use.

*Preparation of the starting 1,6-dichlorohex-1-yne 1a.*⁸

Silver nitrate (0.032 g, 0.2 mmol) and *N*-bromosuccinimide (1.96 g, 11.0 mmol) were added to a stirred solution of 6-chlorohex-1-yne (1.16 g, 10.0 mmol) in dry acetone (30 mL) at room temperature. After stirring for 3 h at the same temperature, hexane (50 mL) was added and the reaction mixture was hydrolyzed with water (20 mL). The reaction mixture was extracted with a 1:1 mixture of ethyl ether and hexane (2 × 20 mL), dried over anhydrous sodium sulfate and evaporated (15 Torr). The resulting residue was the expected product **1a**.

*Preparation of the starting 1-bromo-6-chlorohex-1-yne 1b.*⁹

To a solution of 6-chlorohex-1-yne (1.16 g, 10.0 mmol) in dry acetone (30 mL) was added dropwise a 1.6 M solution of *n*-BuLi in hexane (6.5 mL, 10.4 mmol) at -78 °C. After stirring the reaction mixture for 30 min at the same temperature, a solution of tosyl chloride (1.90 g, 10 mmol) in THF (10 mL) was added dropwise and the reaction mixture was allowed to reach the room temperature overnight. After that, it was hydrolyzed with water (20 mL), extracted with ethyl acetate (2 × 20 mL), dried over anhydrous sodium sulfate and evaporated (15 Torr). The resulting residue was the expected product **1b**.

Selective monolithiation of compounds 1. Preparation of products 2 (Method A). General procedure.

To a stirred THF solution (3 mL) of the corresponding 6-chloro-1-halohehex-1-yne **1** (1.0 mmol) and benzaldehyde (0.16 g, 1.5 mmol) was added dropwise a 0.7 M THF solution of lithium naphthalene (3.0 mL, 2.1 mmol) at -78°C during 45 min. Stirring was continued for 10 additional min and the reaction mixture was carefully hydrolyzed with water (5 mL) and the system was allowed to reach room temperature. The reaction mixture was extracted with ethyl acetate (2 × 20 mL), dried over anhydrous sodium sulfate and evaporated (15 Torr). The resulting residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 40/1) to yield pure product **2a**. Yields are given in table 1.

Double lithiation of compounds 1. Preparation of products 3 (Method B). General procedure.

To a blue suspension of lithium powder (0.070 g, 10 mmol) and a catalytic amount of DTBB (0.027 g, 0.1 mmol) in THF (3 mL) was slowly added a solution of the corresponding 6-chloro-1-halohex-1-yne **1** (1.0 mmol) and a carbonyl compound (R^1R^2CO , 3.0 mmol) in THF (1.2 mL) during *ca.* 1.5 h at -78 °C. After the addition, the reaction mixture was stirred for 15 min at the same temperature. Then, it was hydrolyzed with water (4 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated (15 Torr). The residue was purified by column chromatography (silica gel; hexane/ethyl acetate) to yield pure products **3**. Yields are given in Table 1.

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