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The Lithium-arene (cat.) System: New Applications to Organic Transformations

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Abstract: Epoxide **1** and benzamides **4** can be transformed, by means of an excess of lithium and a catalytic amount of an arene (naphthalene or DTBB) upon reaction of intermediates **2** and **5** with different electrophiles, into the D-glucose **3** and cyclohexadiene derivatives **6**, respectively. The same couple lithium-arene in the presence of nickel chloride dihydrate can also be used in the reduction of halogenated compounds **7** to yield products **8**.

Keywords: Functionalized organolithiums, arene-catalyzed lithiation, reduction of benzamides, reduction of halogenated compounds.

Introduction

Arene-catalyzed lithiation has emerged in the last few years as a powerful method to prepare unstable functionalized organolithium compounds [1]. This methodology found application, among many others, in the reductive opening of heterocycles [2]. The lithium-arene (cat.) system was also applied to the hydrogenation of different organic substrates [3]. The most recent advances on these two topics together with the new application to the synthesis of cyclohexa-1,5-diene carboxamides are reported in this communication.

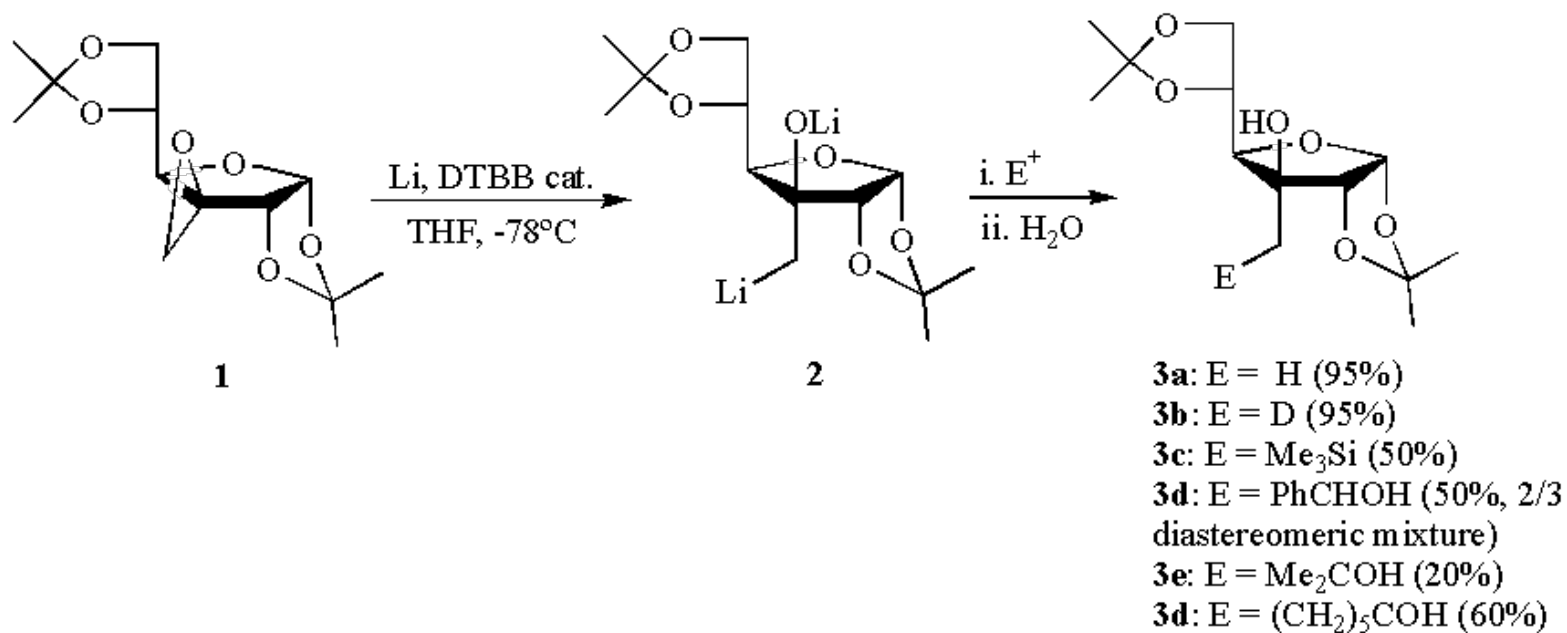
Results and Discussion

The reaction of epoxide **1** with an excess of lithium and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB) in THF at -78deg.C led to the formation of the functionalized organolithium compound **2** which by reaction with several electrophiles yielded after hydrolysis with water the expected D-glucose derivatives **3**. A diastereomeric mixture **3d** (2/3) was obtained when a prochiral carbonyl compound, such as benzaldehyde, was used as electrophile. This mixture was easily separated by flash chromatography so, both diastereoisomers were obtained in enantiomerically pure form (Scheme 1).

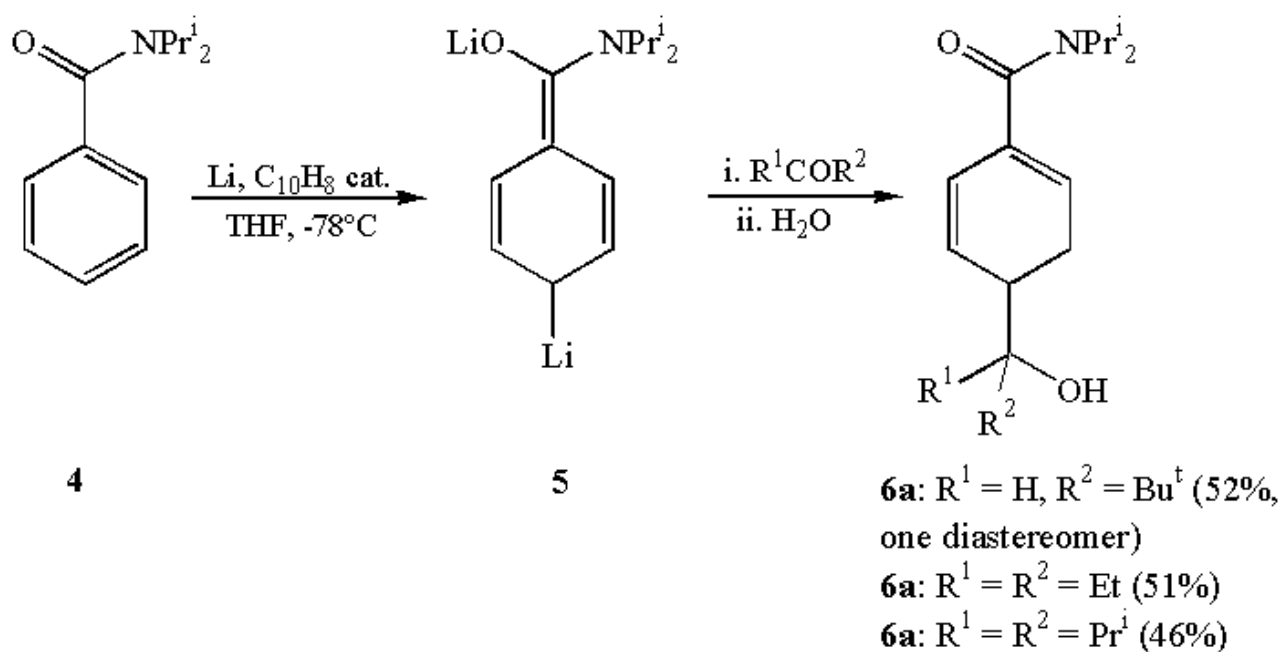
The reaction of benzamide **4** with an excess of lithium powder and a catalytic amount of naphthalene, in the presence of a carbonyl compound (Barbier-type reaction), in THF at -78deg.C gave after hydrolysis with water the corresponding cyclohexadiene derivative **6**, through the dianion **5** (Scheme 2).

The reaction of different halogenated substrates **7** with a mixture of nickel chloride dihydrate, an excess of lithium powder, and a catalytic amount of DTBB in THF at room temperature, led to the corresponding reduced products **8**. When deuterium oxide was used as the ligand in the nickel salt (NiCl₂.2D₂O), a series of deuterated

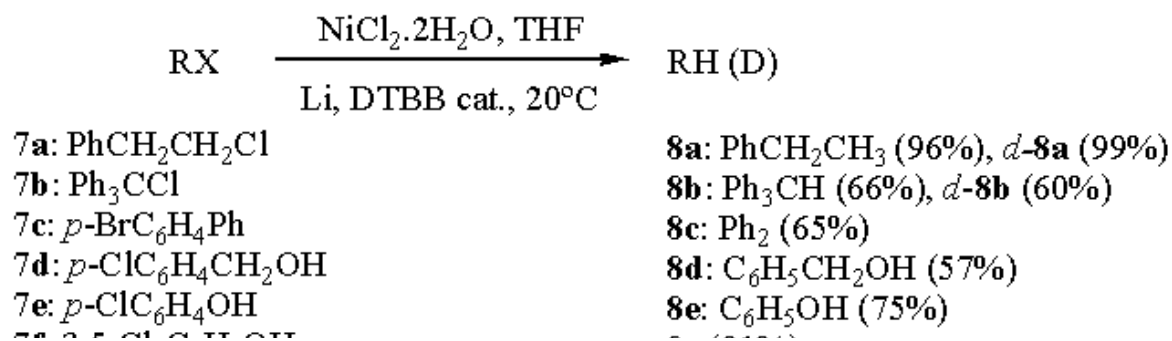
hydrocarbons were obtained (Scheme 3).



Scheme 1



Scheme 2



7f: 3,5-Cl₂C₆H₃OH
7g: *p*-ClC₆H₄NH₂
7h: CH₃(CH₂)₉Cl
7i: Cl(CH₂)₆OH

8e (91%)
8g: C₆H₅NH₂ (70%)
8h: C₁₀H₂₂ (54%), *d*-**8h** (53%)
8i: CH₃(CH₂)₅OH (74%)

Scheme 3

Conclusion

Reactions involving the lithium-arene (cat.) system, allowed the one-pot synthesis of different D-glucose derivatives by reductive opening of the corresponding epoxides, the Birch-type reduction of several benzamides with incorporation of various electrophiles, and the transformation of a series of organic halides into the corresponding alkanes in the presence of a transition metal salt, thus demonstrating its versatility in organic transformations.

Experimental Part

Preparation of 1-{(2*R*,3*S*,5*R*,6*S*)-5-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-6-hydroxy-2,2-dimethyl-perhydrofuro[2,3-*d*]dioxol-6-yl}-2-methyl-2-propenol (**3e**).

Typical Procedure.

To a green suspension of lithium powder (0.120 g, 17 mmol) and DTBB (0.027 g, 0.10 mmol) in THF (10 ml) was added a THF (1 ml) solution of epoxide **1** (0.272 g, 1.0 mmol) at -78deg.C. Stirring was continued for 2 h at the same temperature and then, acetone (0.087 g, 1.5 mmol) was added. The reaction mixture was hydrolyzed with water (5 ml) after 10 min and extracted with ethyl acetate (3x10 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated (15Torr). The residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to afford the corresponding title product (0.066 g, 20%).

TLC (hexane/ethyl acetate 4:1): R_f 0.27

IR (film): 3670-3074 (OH), 1165, 1069 (C-O).

¹H-NMR (CDCl₃): 1.32 (s, 3H), 1.35 (s, 3H), 1.37 (s, 3H), 1.44 (s, 3H), 1.47 (s, 3H), 1.49 (s, 3H), 1.95 (d, 1H), 2.16 (d, 1H), 2.37 (br s, 1H), 3.77 (d, 1H), 4.03-4.13 (m, 2H), 4.34-4.41 (m, 1H), 4.50 (d, 1H), 5.11 (br s, 1H), 5.87 (d, 1H).

¹³C-NMR (CDCl₃): 25.45, 26.5, 26.7, 27.2, 28.9, 33.7, 40.0, 67.4, 73.1, 77.2, 81.5, 84.2, 86.2, 105.0, 109.1, 112.0.

MS (EI): 299 [M⁺-(Me+HO), 1.6%], 43 (100).

Preparation of *N,N*-diisopropyl-4-(1-ethyl-1-hydroxypropyl)-1,5-cyclohexadiene-1-carboxamide (**6b**). Typical Procedure.

To a green suspension of lithium powder (0.1 g, 14 mmol) and naphthalene (0.01 g, 0.08 mmol) in THF (5 ml) was slowly added (*ca.* 10 min) a solution of benzamide **4** (1 mmol) and the carbonyl compound (1.2 mmol) in THF (2 ml) at -78deg.C. Stirring was continued for 2 h and then, the reaction mixture was hydrolysed with water (5 ml) and extracted with ethyl acetate (3x10 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated (15 Torr). The residue was purified by column chromatography (aluminium oxide, hexane/EtOAc) to afford the corresponding title product (0.15 g, 51%).

M.p. 87-88deg.C.

IR (melted): 3323 (OH), 3042, 1442 (HC=C), 1614 (C=O).

¹H-NMR (CDCl₃): 0.89, 0.90 (2t, 6H), 1.00-1.70 (m, 16H), 2.25-2.30, 2.55-2.65 (2m, 3H), 3.20-3.80 (m, 2H), 5.75-6.05 (m, 3H).

¹³C-NMR (CDCl₃): 7.5, 7.6, 20.8, 23.05, 28.4, 28.5, 39.55, 46.0, 48.5, 76.0, 123.85, 124.2, 127.85, 134.65, 170.5.

MS (EI): 275 (M⁺-18, 1%), 105 (100).

Preparation of 1-deuterio-2-phenylethane (*d*-**8a**).

Typical Procedure.

To a mixture of NiCl₂·2D₂O (170 mg, 1.0 mmol), lithium powder (56 mg, 8.0 mmol) and DTBB (27 mg, 0.1 mmol), was added a solution of 2-phenyl-1-chloroethane (141mg, 1.0 mmol) in THF at room temperature under an argon atmosphere. The reaction mixture, which was initially dark green, changed to black indicating the formation of nickel(0). After total conversion of the starting material (GLC), the resulting suspension was diluted with ether (20 ml) and filtered off through a pad containing silica gel and celite (*ca.* 3:1). After drying the filtrate with anhydrous sodium sulfate, it was evaporated (760 Torr) and the resulting residue (99% GLC) distilled in a Kugelrohr apparatus to give *d*-**8a** (0.064 g, 60%).

¹H-NMR (CDCl₃): 1.20-1.28 (m, 2H), 2.63-2.70 (t, 2H), 7.15-7.32 (m, 5H).

¹³C-NMR (CDCl₃): 15.3, 28.8, 125.6, 127.9, 128.3, 144.3.

References and Notes

1. For reviews, see: a) Yus, M. Arene-catalyzed lithiation reactions. *Chem. Soc. Rev.* **1996**, 155-161. b) Nájera, C.; Yus, M. Recent developments in the chemistry of functionalised organolithium compounds. *Recent Res. Devel. Org. Chem.* **1997**, *1*, 67-96.
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3. Alonso, F.; Yus, M. *Tetrahedron* **1998**, *54*, 1921-1928, and references cited therein.

Miguel Yus

Miguel Yus was born in Zaragoza in 1947, and received BSc (1969), MSc (1971) and PhD (1973) degrees from the University of Zaragoza. After spending two years as a postdoctoral fellow at the Max Planck Institut für Kohlenforschung in Mülheim a.d. Ruhr he returned to Spain to the University of Oviedo where he became assistant professor in 1977, being promoted to full professor in 1987 at the same university. In 1988 he moved to a chair in organic chemistry at the University of Alicante where he is currently the head of the Organic Chemistry Department. Professor Yus has been visiting professor at different institutions such as ETH-Zürich and the universities of Oxford, Harvard, Uppsala, Marseille and Tucson. He is a member or fellow of the chemical societies of Argentina, UK, Germany, Japan, Spain, Switzerland and USA. He is coauthor of about 200 papers mainly in the field of development of new methodologies involving organometallic intermediates. His current research interest is focused on the preparation of very reactive functionalised organolithium compounds and their use in synthetic organic chemistry.

Comments

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