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## Functionalized Organolithium Compounds Through an Arene-Catalyzed Lithiation

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**Abstract:** Naphthalene- or DTBB-catalyzed lithiation of chloroimines **1**, deprotonated chlorobenzyl alcohols, mercaptanes or amines **4**, and 3-phenylthiopropylamine **7** in THF at -78deg.C leads to the formation of the corresponding intermediates **2**, **5** and **8**, which by reaction with carbonyl compounds as electrophiles afford the expected bifunctionalized compounds **3**, **6** and **9**, respectively.

**Keywords:** Functionalized organolithiums, arene-catalyzed lithiation

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### Introduction

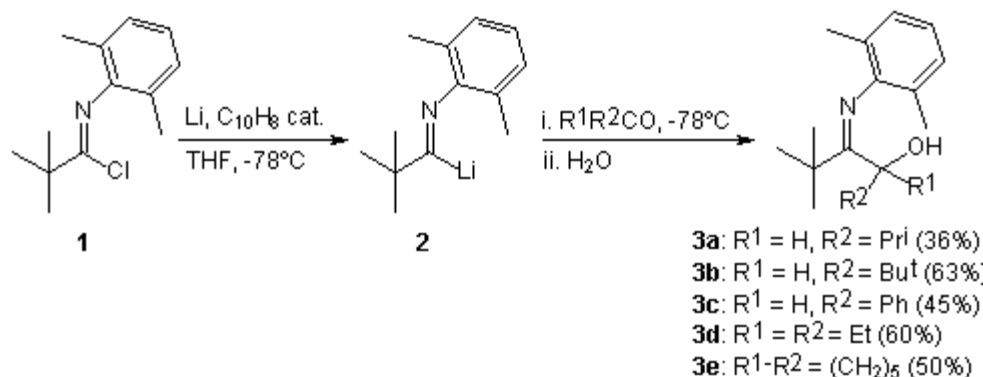
Functionalized organolithium compounds [1] are versatile intermediates in synthetic organic chemistry due to their ability to transfer their own functionality to electrophilic reagents, so making possible to prepare polyfunctionalized molecules in only one reaction step. In this communication we report our last findings in this field.

### Results and Discussion

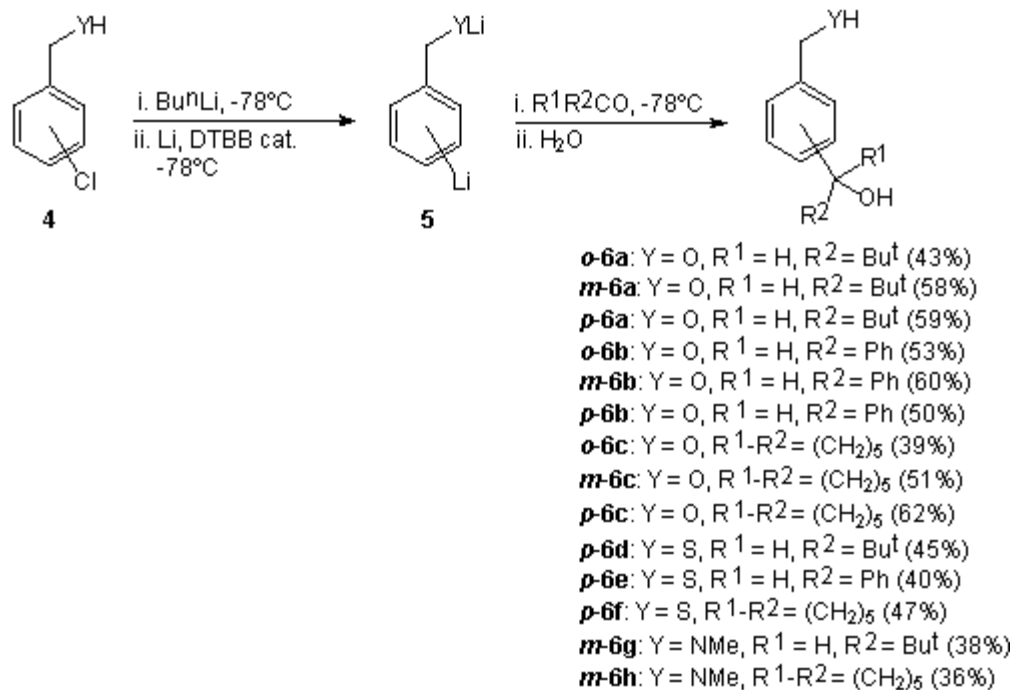
Chloroimine **1** was lithiated under naphthalene catalysis (4 mol%) [2] in THF at -78[integral]C leading to the formation of the acyllithium-type intermediate [3] **2**, which by reaction with different electrophiles [Pr<sup>i</sup>CHO, Bu<sup>t</sup>CHO, PhCHO, Et<sub>2</sub>CO, (CH<sub>2</sub>)<sub>5</sub>CO at the same temperature, followed by final hydrolysis with water, afforded the corresponding functionalized imines **3** (Scheme 1).

The successive reaction of chlorinated benzylic derivatives **4** with *n*-butyllithium and lithium in the presence of a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB, 4 mol %) in THF at -78deg.C led to a solution of the corresponding dianion **5**, which by treatment with different electrophiles [Bu<sup>t</sup>CHO, PhCHO, (CH<sub>2</sub>)<sub>5</sub>CO yielded, after hydrolysis with water at the same temperature, the expected products **6** (Scheme 2).

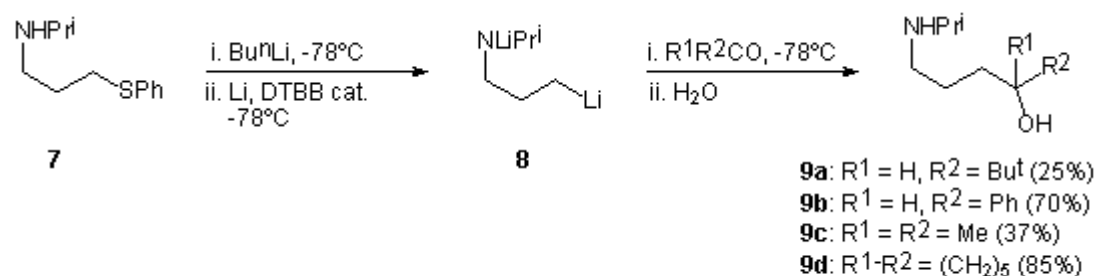
Deprotonation of amine **7** with *n*-butyllithium in THF at -78[integral]C followed by lithiation in the presence of a catalytic amount (2.5 mmol%) of DTBB led to the dianionic intermediate **8**, which reacted with carbonyl compounds [Bu<sup>t</sup>CHO, PhCHO, Me<sub>2</sub>CO, (CH<sub>2</sub>)<sub>5</sub>CO at the same temperature giving, after hydrolysis with water, the expected aminoalcohols **9** (Scheme 3).



**Scheme 1**



**Scheme 2**



**Scheme 3**

## Conclusion

The here described methodology (arene-catalyzed lithiation) allows the preparation under very mild reaction conditions of different functionalized organolithium intermediates, which are versatile reagents for the condensation with carbonyl compounds as electrophiles, yielding polyfunctionalized organic structures.

## Experimental Part

For general information, see reference [4].

Preparation of 2,5,5-Trimethyl-4-(2,6-dimethylphenyl)imino-3-hexanol (**3a**). Typical Procedure.

To a green suspension of lithium powder (0.1g, 14mmol) and naphthalene (0.01g, 0.08mmol) in THF (5ml) was slowly added (ca. 10 min) a solution of chloroimine **1** (1mmol) in THF (2ml) at -78deg.C. Stirring was continued for 2 hr and then, the excess of lithium was filtered off at -78deg.C. Isobutyraldehyde (0.11ml, 1.2mmol) was added to the filtered solution and the mixture was stirred during 12 hr allowing the temperature to rise to 20deg.C. The reaction mixture was hydrolyzed with water (5ml) and extracted with ethyl acetate (3x10ml). The organic layer was dried over anhydrous sodium sulfate and evaporated (15Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to afford the corresponding title product (0.075g, 36%).

TLC (Hexane/EtOAc 9:1):  $R_f$  0.35

IR (film): 3560 (OH), 3060, 1592 (HC=C), 1669 (C=N).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 0.96 (d, 3H), 1.15 (m, 13H), 2.05, 2.1 (2s, 6H), 4.25 (s, 1H), 6.83 (t, 1H), 6.96 (d, 2H).

$^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ): 18.65, 19.15, 21.2, 28.35, 32.35, 40.95, 75.7, 122.0, 127.7, 127.85, 177.55.

MS (EI): 261 ( $\text{M}^+$ , 1%), 132 (100).

Preparation of 2-(2,2-Dimethyl-1-hydroxypropyl)benzyl Alcohol (*o*-**6a**). Typical Procedure.

To a solution of 2-chlorobenzyl alcohol (0.29g, 2mmol) in THF (3ml) was added a solution of *n*-butyllithium in hexane (1.25ml, 2mmol) at -78deg.C for 10 min. The resulting mixture was transferred via cannula to a suspension of lithium powder (0.15g, 20mmol) and DTBB (0.03g, 0.1mmol) in THF (5ml) at -78deg.C, being it then stirred for ca. 45 min at the same temperature. Then, pivaldehyde (0.22ml, 2mmol) was added and the mixture was stirred at -78deg.C for 30 min, when the green colour was recovered. The resulting mixture was then hydrolyzed with water (5ml) at -78 to 20deg.C, extracted with ethyl acetate (3x10ml), the organic layer was dried over anhydrous sodium sulfate and evaporated (15Torr) to give a residue, which was purified by column chromatography (silica gel, hexane/EtOAc) affording the pure title compound (0.123g, 43%).

M.p. 125-127deg.C.

IR (film): 3353 (OH), 3066, 3060, 1635, 1603 (HC=C).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 0.89 (s, 9H), 3.20, 3.28 (2br s, 2H), 4.40 (d, 1H), 4.61 (m, 2H), 7.24, 7.41 (2m, 4H).

$^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ): 26.2, 36.4, 63.0, 72.2, 127.25, 127.3, 128.5, 138.1, 140.3.

MS (EI): 161 ( $\text{M}^+$ -33, 3%), 119 (100).

Preparation of 4-(Isopropylamino)-1-phenyl-1-butanol (**9b**). Typical Procedure.

To a solution of amine **7** (0.21g, 2mmol) in THF (2ml) was added a solution of *n*-butyllithium in hexane (1.25ml, 2mmol) at -78deg.C for 10 min. The resulting mixture was transferred via cannula to a suspension of lithium powder (0.1g, 14mmol) and DTBB (0.03g, 0.1mmol) in THF (5ml) at -78deg.C, being it then stirred for 1 hr at the same temperature. Then, benzaldehyde (0.2ml, 2mmol) was added and the mixture was stirred overnight, allowing the temperature to rise to 20deg.C. The resulting mixture was then hydrolyzed with water (5ml), followed by addition of HCl 3M (50ml) and extracted with ethyl acetate (3x10ml). To the acid aqueous layer was added  $\text{Na}_2\text{CO}_3$  until basic pH and then, the mixture was extracted

with ethyl acetate (3x10ml), this organic layer was dried over anhydrous sodium sulfate and evaporated (15Torr) to give the pure title compound (0.29g, 70%).

IR (film): 3372 (OH, NH), 3084, 3061, 1657 (HC=C).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): 1.11 (d, 6H), 1.6 (m, 4H), 2.6 (m, 1H), 2.85 (m, 2H), 3.75 (br s, 2H), 4.65 (dd, 1H), 7.30 (m, 5H).

<sup>13</sup>C-NMR (CDCl<sub>3</sub>): 22.35, 22.55, 27.45, 39.6, 46.9, 48.65, 73.45, 125.7, 126.6, 128.05, 145.75.

MS (EI): 207 (M<sup>+</sup>, 7%), 72 (100).

## References and Notes

1. For reviews, see: a) N.jera, C.; Yus, M. Functionalized organolithium compounds in synthetic organic chemistry. *Trends Org. Chem.* **1991**, *2*, 155-181. b) N.jera, C.; Yus, M. Recent developments in the chemistry of functionalized organolithium compounds. *Recent Res. Devel. Org. Chem.* **1997**, *1*, 67-96.
2. For a review, see: Yus, M. Arene-catalyzed lithiation reactions. *Chem. Soc. Rev.* **1996**, 155-161.
3. For a review, see: N.jera, C.; Yus, M. Acyl main group metal and metalloid derivatives in organic synthesis. A review. *Org. Prep. Proced. Int.* **1995**, *27*, 383-456.
4. Almena, J.; Foubelo, F.; Yus, M. Reductive opening of phenyl substituted thiacycloalkanes: New way for sulphur-containing organolithium compounds. *Tetrahedron* **1997**, *53*, 5563-5572.

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## 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 fuer Kohlenforschung in Mulheim 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-Zurich 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 functionalized organolithium compounds and their use in synthetic organic chemistry.

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## Comments

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