Synthesis and Applications of Tetrahydrofuran-Stable Substituted (3-Lithioxyalkyl)- and (4-Lithioxyalkyl)lithiums, Modified with Magnesium 2-Ethoxyethoxide

Ioannis D. Kostas and Constantinos G. Screttas*

National Hellenic Research Foundation, Institute of Organic and Pharmaceutical Chemistry, 116 35 Athens, Greece

Received February 18, 1997

Substituted hydroxyalkyl phenyl sulfides **3** have been synthesized from the corresponding allylic or homoallylic alcohols **2**. Regiospecific cleavage of the C−SPh bond of the sulfides **3** by lithium dispersion in tetrahydrofuran (THF) led to the synthesis of substituted (3-lithioxyalkyl)- and (4-lithioxyalkyl)lithiums **4**, most of which share the ω carbon with a carbocyclic ring. The organolithiums were modified with magnesium 2-ethoxyethoxide in order to suppress their reactivity toward THF cleavage, thus offering the advantage of preparing storable ethereal solutions of certain types of (lithioxyalkyl)lithiums. This strategy appears to be of rather broad scope. The functionalized organolithiums prepared in this way react normally with electrophilic reagents with yields in the range 35−55%. Thus, carboxylations of **4** yielded lactones **5**, some of which are natural products, while reactions of **4** with benzophenone and cyclic ketones yielded 1,4- and 1,5-diols **6** and **7**, respectively.

Introduction

The synthetic utility of organolithium compounds increases considerably if the lithium reagents bear an additional functionality.[1] Indeed, such reagents can introduce, usually in a regiospecific manner, a hydrocarbyl moiety possessing the additional functionality at a predetermined position, thus permitting further chemical elaboration. A number of such reagents have already been reported.[1] The present report provides information on a methodology for preparing tetrahydrofuran-stable organometallic reagents capable of introducing a 3-mono- or 3,3-disubstituted 3-hydroxypropyl group as well as a 4-mono- or 4,4-disubstituted 4-hydroxybutyl group.

Various syntheses of γ- and δ-lithioalkoxides have been reported. γ-Lithioalkoxides have been prepared by reaction of organolithium reagents with allylic alcohols,[2] lithiation of γ-chloroalkoxides,[3] tin−lithium exchange of a γ-(tributylstannyl)alkoxide,[4] and reductive lithiation of phenyl sulfides[5] or oxetanes[6] by lithium di-*tert*-butylbiphenylide (LDBB). The latter method was extended to the synthesis of δ-lithioalkoxides by reductive lithiation of substituted tetrahydrofurans, where the cleavage of the C−O bond was promoted either *via* complexation at the oxygen atom of THF by a Lewis acid or by appending an alkenyl group to the 2-position of the ring.[7] Syntheses of δ-lithioalkoxides by chlorine-lithium exchange[8] or by reductive lithiation of phenyl sulfides with LDBB[9] are also known. However, the syntheses of these organolithiums according to the above-mentioned procedures require low temperatures and immediate derivatization, as organometallics are not stable at room temperature in ethereal solvents due to metalation of the solvent and further cleavage.[10,11]

In this work, we report on the development of a new method of broad applicability for the synthesis of substituted (3-lithioxyalkyl)- and (4-lithioxyalkyl)metallics **4**, most of which share the ω carbon with a carbocyclic ring. The previously reported[12] preparation of organolithium reagents in THF in the presence of magnesium 2-ethoxyethoxide was also applied to the synthesis of (lithioxyalkyl)lithiums **4**, i.e., to the preparation of storable THF solutions of **4**.

Results and Discussion

The method for the synthesis of the (3-lithioxyalkyl)- and (4-lithioxyalkyl)lithiums **4** involves addition of vinyl- or allylmagnesium chloride to carbonyl compounds **1** followed by the conversion of the resulting allylic or homoallylic alcohols[13] **2** to the corresponding primary alkyl phenyl sulfides **3** by the anti-Markownikow addition of thiophenol (Scheme 1). Finally, regiospecific cleavage of the C−SPh bond of the substituted hydroxyalkyl phenyl sulfides **3** by lithium metal in the presence of magnesium 2-ethoxyethoxide leads to the corresponding organometallic reagents **4** (Scheme 2).

The cleavage of the sulfides **3** was effected by an excess of lithium dispersion in the presence of magnesium

* To whom correspondence should be addressed.

⊗ Abstract published in *Advance ACS Abstracts,* July 15, 1997.

(1) For selected reviews, see: (a) Stowell, J. C. *Chem. Rev.* **1984**, *84*, 409. (b) Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1. (c) Yus, M. *Chem. Soc. Rev.* **1996**, 155.

(2) Crandall, J. K.; Clark, A. C. *J. Org. Chem.* **1972**, *37*, 4236.

(3) (a) Nájera, C.; Yus, M.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 289. (b) Barluenga, J.; Flórez, J.; Yus, M. *Synthesis* **1985**, 846. (c) Yus, M.; Ramón, D. J. *J. Chem. Soc., Chem. Commun.* **1991**, 398.

(4) (a) Meyer, N.; Seebach, D. *Chem. Ber.* **1980**, *113*, 1290. (b) Zidani, A.; Vaultier, M. *Tetrahedron Lett.* **1986**, *27*, 857.

(5) Ahn, Y.; Cohen, T. *J. Org. Chem.* **1994**, *59*, 3142.

(6) Mudryk, B; Cohen, T. *J. Org. Chem.* **1989**, *54*, 5657.

(7) Mudryk, B.; Cohen, T. *J. Am. Chem. Soc.* **1991**, *113*, 1866.

(8) Barluenga, J.; Fernandez, J. R.; Florez, J.; Yus, M. *Synthesis* **1983**, 736.

(9) (a) Mudryk, B.; Shook, C. A.; Cohen, T. *J. Am. Chem. Soc.* **1990**, *112*, 6389. (b) Liu, H.; Cohen, T. *J. Org. Chem.* **1995**, *60*, 2022.

(10) Wakefield, B. J. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979, Vol. 3, pp 943ff.

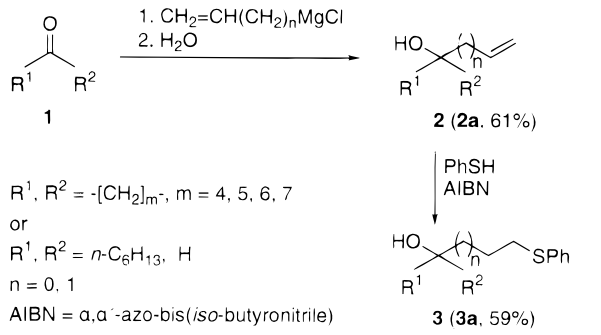
(11) Review: Maercker, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 972.

(12) Screttas, C. G.; Steele, B. R. *J. Org. Chem.* **1989**, *54*, 1013.

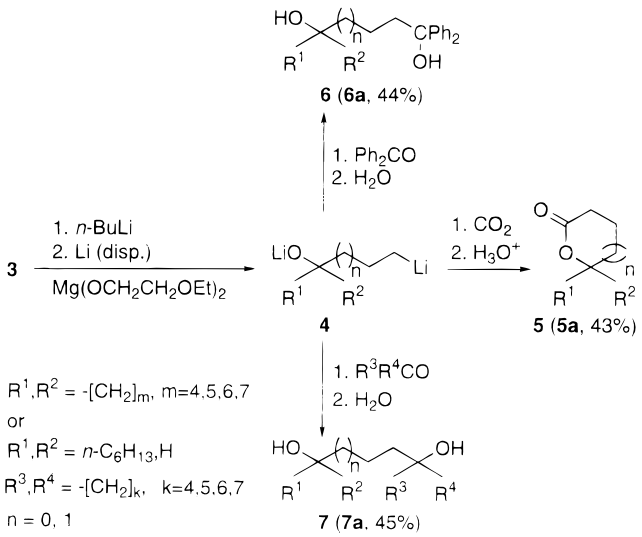
(13) For selected examples of similar methods for synthesis of allylic or homoallylic alcohols, see: (a) Marcou, A.; Normant, H. *Bull. Soc. Chim. Fr.* **1965**, *12*, 3491. (b) Katzenellenbogen, J. A.; Lenox, R. S. *J. Org. Chem.* **1973**, *38*, 326. (c) Masamune, T.; Sato, S.; Abiko, A.; Ono, M.; Murai, A. *Bull. Chem. Soc. Jpn* **1980**, *53*, 2895. (d) Oppolzer, W.; Schneider, P. *Tetrahedron Lett.* **1984**, *25*, 3305.

S0022-3263(97)00301-0 CCC: $14.00

Scheme 1



Scheme 2



2-ethoxyethoxide in THF/methylcyclohexane ca. 10/1 (v/v). Our group has previously reported the preparation of organolithium reagents in THF in the presence of magnesium 2-ethoxyethoxide.[12] The presence of the magnesium alkoxide markedly diminishes the metalating ability of the initially formed organolithium reagents, hence increasing their stability in tetrahydrofuran solutions at room temperature. The reaction temperature for the cleavage of the C−SPh bond was 0−20 °C. The presence of methylcyclohexane in the solvent system results from the butyllithium solution used for the deprotonation of the hydroxy sulfide **3**. The molar ratio (sulfide)/(magnesium alkoxide) was approximately 1:1. The yields of the organolithiums were taken to be the yield of the product after reaction with a given electrophile.

Carboxylation and subsequent acidic hydrolysis of **4** yielded lactones **5** (Scheme 2). This reaction provides simple and efficient one-pot syntheses of substituted γ-butyro-[14] and δ-valerolactones **5** (most of which are spirolactones).[15] The problem of thiophenol in product isolation was confronted by its conversion to thioanisole by reaction with dimethyl sulfate.[16] Synthesis of such lactones is of great interest as lactonic functionality is present in a large variety of natural products and biologically active compounds.[17] 5-Hexyldihydro-2-furanone (**5e**) and 6-hexylterahydro-2-pyranone (**5e′**), for instance, are aroma constituents of various fruits.[18]

The reactivity of **4** with benzophenone and cyclic ketones was also investigated, yielding diols **6** and **7**, respectively (Scheme 2). Carbinols **6** are new compounds, and the synthesis of the symmetric or unsymmetric bis(1-hydroxycycloalkyl)alkanes **7** is more convenient for practical reasons than other methods.[19] It may be of interest to note that, in most cases, there is a consistency between the yields of the lactones and of diols. For example, reagent **4a** on carboxylation afforded the corresponding lactone **5a** in 43% yield, compared to a 44% yield of the diol **6a** and 45% yield of the diol **7a** upon reaction with benzophenone and cyclopentanone, respectively.

In conclusion, a general method has been illustrated for the synthesis of 3-mono- or 3,3-disubstituted (3-lithioxypropyl)lithiums and of 4-mono- or 4,4-disubstituted (4-lithioxybutyl)lithiums **4** , as room temperature-stable THF solutions, by the regiospecific cleavage of the C−SPh bond of the corresponding sulfides **3** with lithium dispersion. The synthetic value of these organolithiums was demonstrated by the synthesis of certain γ- and δ-lactones and spirolactones **5**, some of which are natural products, as well as by the synthesis of symmetric and unsymmetric tetrasubstituted 1,4- and 1,5-diols **7**.

Experimental Section

Preparation of Sulfides 3. Typical Procedure. 1-[2-(Phenylthio)ethyl]cyclopentanol (3a).[20] A solution of the alcohol **2a** (18.2 g, 162.5 mmol) and thiophenol (16.5 mL, 162.0 mmol) in hexane (70 mL) was refluxed under nitrogen for 46 h. During refluxing, a catalytic amount of α,α′-azobis(isobutyronitrile) (1 g) was added in several portions. It was then diluted with toluene and washed with a 50% aqueous solution of NaOH (20 mL). The organic phase was dried, filtered, and evaporated to dryness. Isolation of pure product was carried out by distillation, yielding the sulfide **3a** (21.2 g, 59%). **3a**: bp 140−141 °C (1 mmHg); IR ($CHCl_3$, cm^{-1}) 3610 and 3460 (OH, free and H-bonded); ^{1}H NMR ($CDCl_3$) δ 7.12−7.35 (m, 5H), 3.03−3.08 (m, 2H), 2.09 (brs, 1H), 1.50−1.91 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 136.39, 128.63, 128.47, 125.52, 81.82, 40.44, 39.35, 28.77, 23.38; MS (EI) *m*/*z* (rel intesity) 222 (M^+, 100).

Synthesis of (Lithioxyalkyl)lithiums 4 and Their Carboxylation. Preparation of Lactones 5. Typical Procedure. 1-Oxaspiro[4.4]nonan-2-one (5a).[15b,c] A solution of the sulfide **3a** (2.2 g, 9.9 mmol) in THF (10 mL) was added to a mixture of magnesium 2-ethoxyethoxide (2.5 g, 12.4 mmol

(14) The use of other (3-lithioxypropyl)lithiums in a γ-butyrolactone synthesis has been reported; see refs 2, 3a, and 6.

(15) For selected examples of syntheses of γ- and δ-lactones, see: (a) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5321. (b) Canonne, P.; Foscolos, G. B.; Bélanger, D. *J. Org. Chem.* **1980**, *45*, 1828. (c) Canonne, P.; Bélanger, D.; Lemay, G.; Foscolos, G. B. *J. Org. Chem.* **1981**, *46*, 3091. (d) Schlecht, M. F.; Kim, H.-J. *Tetrahedron Lett.* **1985**, *26*, 127.

(16) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1978**, *43*, 1064.

(17) (a) *Comprehensive Organic Chemistry. The Synthesis and Reactions of Organic Compounds*; Chairman and Deputy Chairman of the Editorial Board Sir Derek Barton, F.R.S. and W. David Ollis, F.R.S.; Sutherland, I. O., Ed.; Pergamon Press: London, 1979; Vol *2*, pp 869−956. (b) Gutman, A. L.; Zuobi, K.; Bravdo, T. *J. Org. Chem.* **1990**, *55*, 3546 and references cited therein.

(18) (a) Engel, K. H.; Ramming, D. W.; Flath, R. A.; Teranishi, R. *J. Agric. Food Chem.* **1988**, *36*, 1003; *Chem Abstr.* **1988**, *109*, 127496r. (b) MacLeod, A. J.; MacLeod, G.; Snyder, C. H. *Phytochemistry* **1988**, *27*, 2189; *Chem. Abstr.* **1988**, *109*, 148205k. (c) Guichard, E.; Souty, M. *Z. Lebensm-Unters. Forsch.* **1988**, *186*, 301; *Chem Abstr.* **1988**, *109*, 109117p. (d) Schreier, P.; Drawert, F. *Chem., Mikrobiol., Technd. Technol. Lebensm.* **1981**, *7*, 23; *Chem. Abstr.* **1981**, *95*, 59882d. (e) Kikuchi, N.; Miki, T. *Microchim. Acta* **1981**, *I*, 249. (f) Georgilopoulos, D. N.; Gallois, A. N. *Z. Lebensm-Unters. Forsch.* **1987**, *184*, 374; *Chem. Abstr.* **1987**, *107*, 114480q. (g) MacLeod, G.; Ames, J. M. *Phytochemistry* **1990**, *29*, 165; *Chem. Abstr.* **1990**, *112*, 137790h.

(19) (a) Pinkney, P. S.; Nesty, G. A.; Pearson, D. E.; Marvel, C. S. *J. Am. Chem. Soc.* **1937**, *59*, 2666. (b) Bailey, A. S.; Diaper, D. G. M.; Schwemin, M. V. H. *Can. J. Chem.* **1961**, *39*, 1147. (c) Achyutha Rao, S.; Periasamy, M. *Tetrahedron Lett.* **1988**, *29*, 1583.

(20) Kutner, A.; Perlman, K. L.; Lago, A.; Sicinski, R. R.; Schnoes, H. K.; DeLuka, H. F. *J. Org. Chem.* **1988**,*53*, 3450.

in 25 mL of THF) and *n*-BuLi (5.3 mL of 1.89 M solution in methylcyclohexane, 10 mmol) at −78 °C under argon, after which it was stirred at room temperature overnight. A suspension of an excess of lithium dispersion (0.4 g, 57 mmol, free from mineral oil) in THF (15 mL) was then added, with ice−water bath cooling, after which the mixture was warmed slowly to room temperature and stirred overnight. The excess lithium was filtered, and the reaction mixture was poured rapidly into a beaker containing a slurry of crushed dry ice and anhydrous diethyl ether. When the carboxylation mixture had reached room temperature, water was added, and the volume was reduced by evaporation. After filtration, the aqueous phase was washed twice with toluene and once with hexane. Then a 50% aqueous solution of NaOH (3.5 mL) and dimethyl sulfate (1.6 mL) was added, and the mixture was refluxed for 2 h. It was washed again with toluene and hexane and evaporated to dryness. After the addition of about 5 mL of water, it was acidified with 20% H_2SO_4, with ice−water bath cooling. The product was extracted with dichloromethane (5 × 20 mL) and dried. After filtration, the solvent was evaporated, yielding **5a** (0.6 g, 43%) as the only component according to analytical GLC chromatography. A sample of **5a** for spectroscopic analysis was isolated by preparative GLC chromatography; the ^{1}H and ^{13}C NMR spectra were in accordance with those previously reported.[15c]

Reaction of (Lithioxyalkyl)lithiums 4 with Ketones. Typical Procedure. 1-(3,3-Diphenyl-3-hydroxypropyl)-cyclopentanol (6a). To a solution of **4a** in THF (50 mL)/methylcyclohexane (5.3 mL), prepared from **3a** (2.2 g, 9.9 mmol) as described above, was added a solution of benzophenone (1.6 g, 8.8 mmol) in THF (10 mL), with ice−water bath cooling, after which it was stirred at room temperature for 1 h. Water was then added, and after filtration, the product was extracted with toluene. The organic phase was washed with a 50% aqueous solution of NaOH (10 mL) and then with water. It was dried and filtered, and the solvent was evaporated, yielding 2.05 g of the crude product, which was recrystallized from hexane/toluene, yielding **6a** (1.3 g, 44%) as a white solid. **6a**: mp 122−124 °C; IR ($CHCl_3$, cm^{-1}): 3620 and 3410 (OH, free and H-bonded); ^{1}H NMR ($CDCl_3$) δ 7.18−7.45 (m, 10H), 2.49 (t, J = 7.4 Hz, 2H), 2.32 (brs, 2H), 1.50−1.79 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 147.27, 128.11, 126.66, 126.06, 82.53, 77.83, 39.84, 37.01, 35.42, 23.65. Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 80.88; H, 7.91.

1,1′-(1,2-Ethanediyl)bis(cyclopentanol) (7a).[19b] The procedure was identical with that described above for the synthesis of **6a**. **7a**: yield 45%; mp 128−130 °C (MCH) (lit.[19b] mp 134 °C); IR ($CHCl_3$, cm^{-1}) 3610 and 3410 (OH, free and H-bonded); ^{1}H NMR ($CDCl_3$) δ 1.60−1.89 (m, 22H); ^{13}C NMR ($CDCl_3$) δ 82.25, 39.83, 36.39, 23.79. Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.48; H, 10.98.

Acknowledgment. The investigation was supported by the National Hellenic Research Foundation.

Supporting Information Available: General experimental comments, including information for the preparation of alcohols **2**, tables with the yields, mps or bps of the products, and full details of their spectral data (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9703010