SYNTHESIS OF TETRAHYDROFURAN-STABLE ω-LITHIOXY-AZAALKYLLITHIUMS

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Abstract

ω-Hydroxy-azaalkyl phenyl sulfides **2** have been synthesized from the corresponding chloroalkyl phenyl sulfides **1** by reaction with 2-methylamino-ethanol. Regiospecific cleavage of the C-SPh bond of the sulfides **2** by lithium dispersion in tetrahydrofuran (THF), in the presence of magnesium 2-ethoxyethoxide, led to the synthesis of ω-lithioxy-azaalkyllithiums **3**, which are stable in THF solutions. Reaction of organolithiums **3** with benzaldehyde yielded the aza-diols **4** with yields in the range of 57 - 85 %.

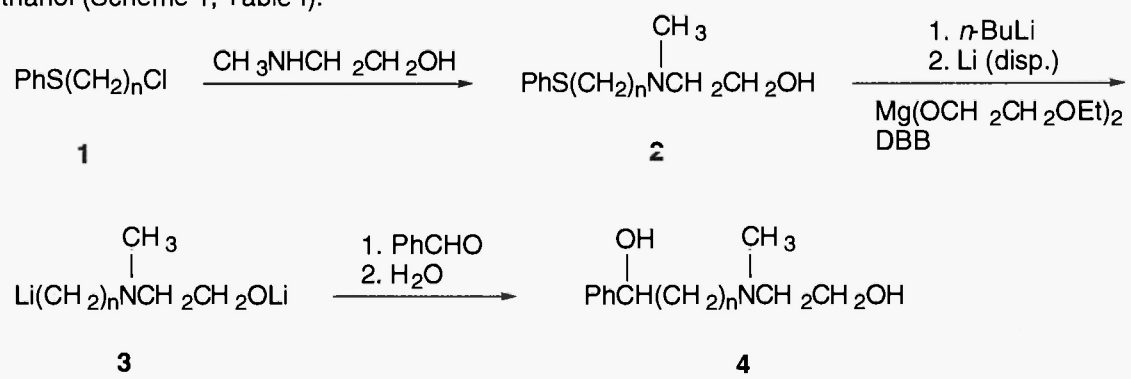
Introduction

Oxygen- and nitrogen-containing organolithiums are certainly of synthetic utility [1]. Such reagents can introduce into a chemical structure a carbon skeleton in which an oxygen or nitrogen occupy predetermined positions. A number of such organolithium reagents bearing additional functionality has been reported [1]. Specifically, the utility of nitrogen-substituted organolithium reagents has been amply demonstrated in the synthesis of amines and their derivatives [2]. Some aza-organolithiums which in addition bear the lithioxy functional group, have also appeared in the literature [3].

Recently, we have reported a method for the synthesis of substituted 3-(lithioxyalkyl)- and 4-(lithioxyalkyl)lithiums, modified with magnesium 2-ethoxyethoxide, as room temperature-stable THF solutions [4]. The method involves the regiospecific cleavage of C-SPh bond of the corresponding sulfides with lithium dispersion in the presence of the magnesium alkoxide [5]. Organolithium reagents form complexes with magnesium 2-ethoxyethoxide and these complexes exhibit markedly diminished metalating ability, hence their stability in THF solutions at room temperature. Otherwise they exhibit normal behavior toward ordinary electrophiles e.g. carbon dioxide and carbonyl compounds. The present report provides information on the extension of the methodology to the synthesis of tetahydrofuran-stable ω-lithioxy-azaalkyllithiums **3**.

Results and Discussion

The starting ω-hydroxy-azaalkyl phenyl sulfides **2** were synthesized in yields ranging from 62-79 %, by reacting the corresponding ω-chloroalkyl phenyl sulfides **1** with 2-methylamino-ethanol (Scheme 1, Table I).



1 **2** **3** **4**

n = 3, 4, 5, 6
DBB = di -*tert* -butylbiphenyl

(Scheme 1)

The procedure involved the conversion of the ω-hydroxy-azaalkyl phenyl sulfides to the corresponding lithium alkoxides by reaction with one equivalent of *n*-BuLi, in THF/methylcyclohexane and subsequent cleavage of the C-SPh bond by lithium dispersion, assisted by a catalytic amount of di-*tert*-butylbiphenyl (DBB). The cleavage reaction was carried out at 0-20 °C while the molar ratio sulfide/magnesium alkoxide was approximately 1:1. The presence of methylcyclohexane in the solvent system results from the butyllithium used for the deprotonation of **2**. The resulting organolithium reagents **3**, complexed with magnesium 2-ethoxyethoxide, were derivatized by reaction with benzaldehyde. Thus, the corresponding aza-diols **4** were prepared in yields ranging from 57 to 85 %, (Scheme 1, Table I). The yields of the aza-diols, which are taken to represent the yield of the organometallic reagents, are quite good and indicate that the cleavage reaction takes place with the usual regiospecificity, i.e., to the alkyllithium and lithium thiophenoxide [6] [7]. Exceptions to the latter mode of cleavage have been observed [8].

Table I. Preparation and cleavage of aza-sulfides **2**. Reaction of the organolithiums **3** with benzaldehyde.

Entry	Chloroalkyl phenyl sulfide	Aza-sulfide	Yield (%)	b.p. °C (mmHg)	Organo-lithium	Diol[a]	Yield (%)
1	**1a:** n = 3	**2a**	70	143 (0.05)	**3a**	**4a**	57
2	**1b:** n = 4	**2b**	71	154-157 (0.05)	**3b**	**4b**	60
3	**1c:** n = 5	**2c**	79	170-185 (0.2)[b]	**3c**	**4c**	77
4	**1d:** n = 6	**2d**	62	165 (0.08)	**3d**	**4d**	85

[a] Pure products were isolated as oils by column chromatography over aluminium oxide by using mixtures of hexane/AcOEt as eluents. [b] Crystallized upon standing and recrystallized from hexane yielding a white solid, m.p. 34.0-35.5 °C.

In conclusion, a general method has been illustrated for the synthesis of ω-lithioxy-azaalkyllithiums **3**, as room temperature-stable THF solutions, by the regiospecific cleavage of the C-SPh bond of the corresponding aza-sulfides **2** with lithium dispersion.

Experimental Section

General Comments

The chloroalkyl phenyl sulfides **1** [9] and magnesium 2-ethoxyethoxide [10] were made by known procedures. Lithium dispersion was prepared from lithium metal, mineral oil and palmitic acid stabilizer, as a mixture of about 30% in Li; before its use, it was freed from the oil by washing with dry hexane. NMR spectra were recorded at 300 MHz (^{1}H NMR). GCMS analyses were performed on a Varian Saturn 2000 with a 30 m DB5-MS column. MS data were obtained by EI.

Preparation of Sulfides 2. Typical Procedure.

A solution of 3-chloropropyl-phenyl sulfide **(1a)** (46.7 g, 250 mmol) and 2-methylamino-ethanol (40 mL, 500 mmol) in ethanol (200 mL) was refluxed for 50 h. The solvent was removed by evaporation, the residue was dissolved in toluene and washed with a 15% aqueous solution of NaOH (70 mL) and then with water (50 mL). The organic phase was dried over K_2CO_3, filtered and evaporated to dryness, yielding 52 g of the crude product as an oil. Isolation of pure product was carried out by distillation, yielding the sulfide **2a** (39.5 g, 70%), bp 143 °C (0.05 mmHg).

Spectroscopic data

3-Methyl-6-phenylthio-3-aza-hexan-1-ol ***(2a)***: ^{1}H NMR ($CDCl_3$, δ ppm): 7.33-7.13 (m, 5H, H_{arom}), 3.57 (t, ^3J = 5.3 Hz, 2H, CH_2O), 2.94 (t, ^3J = 7.1 Hz, 2H, CH_2S), 2.77 (brs, 1H, OH), 2.53-2.47 (m, 4H, CH_2NCH_2), 2.20 (s, 3H, NCH_3), 1.84-1.75 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, δ ppm): 136.38, 129.09, 128.88 and 125.85 (Ph), 58.89, 58.37, 56.17, 41.45, 31.41 and 26.52 (5 × CH_2 and CH_3). MS (EI) *m / z* (rel intensity) 225 (M^+, 8), 194 ([M^+-CH_2OH], 100).

3-Methyl-7-phenylthio-3-aza-heptan-1-ol ***(2b)***: ^{1}H NMR ($CDCl_3$, δ ppm): 7.32-7.13 (m, 5H, H_{arom}), 3.55 (t, ^3J = 5.3 Hz, 2H, CH_2O), 2.92 (t, ^3J = 6.9 Hz, 2H, CH_2S), 2.66 (brs, 1H, OH), 2.49 (t, ^3J = 5.4 Hz, 2H, NCH_2), 2.39 (t, ^3J = 6.9 Hz, 2H, NCH_2), 2.21 (s, 3H, NCH_3), 1.68-1.58 (m, 4H, 2 × CH_2). ^{13}C NMR ($CDCl_3$, δ ppm): 136.58, 129.00, 128.79 and 125.76 (Ph), 58.73, 58.29, 57.13,

41.42, 33.48, 26.77 and 26.31 (6 × CH_2 and CH_3). MS (EI) *m / z* (rel intensity) 239 (M^+, 4), 165 ([M^+-$N(CH_3)CH_2CH_2OH$], 100).

3-Methyl-8-phenylthio-3-aza-octan-1-ol ***(2c)***: ^{1}H NMR ($CDCl_3$, δ ppm): 7.33-7.13 (m, 5H, H_{arom}), 3.56 (t, ^3J = 5.3 Hz, 2H, CH_2O), 2.91 (t, ^3J = 7.3 Hz, 2H, CH_2S), 2.49 (t, ^3J = 5.3 Hz, 2H, NCH_2), 2.38 (t, ^3J = 6.8 Hz, 2H, NCH_2), 2.21 (s, 3H, NCH_3), 2.51-2.21 (brs, 1H, OH), 1.70-1.61 (m, 2H, CH_2), 1.46-1.42 (m, 4H, 2 × CH_2). ^{13}C NMR ($CDCl_3$, δ ppm): 136.75, 128.89, 128.78 and 125.68 (Ph), 58.70, 58.26, 57.48, 41.50, 33.47, 28.98, 26.81 and 26.42 (7 × CH_2 and CH_3). MS (EI) *m / z* (rel intensity) 253 (M^+, 5), 179 ([M^+-$N(CH_3)CH_2CH_2OH$], 100).

3-Methyl-9-phenylthio-3-aza-nonan-1-ol ***(2d)***: ^{1}H NMR ($CDCl_3$, δ ppm): 7.29-7.12 (m, 5H, H_{arom}), 3.54 (t, ^3J = 5.3 Hz, 2H, CH_2O), 3.17 (brs, 1H, OH), 2.87 (t, ^3J = 7.2 Hz, 2H, CH_2S), 2.46 (t, ^3J = 5.3 Hz, 2H, NCH_2), 2.33 (t, ^3J = 7.3 Hz, 2H, NCH_2), 2.18 (s, 3H, NCH_3), 1.66-1.56 (m, 2H, CH_2), 1.47-1.26 (m, 6H, 3 × CH_2). ^{13}C NMR ($CDCl_3$, δ ppm): 136.72, 128.94, 128.67 and 125.49 (Ph), 58.77, 58.29, 57.54, 41.50, 33.30, 28.87, 28.49, 26.86 and 26.70 (8 × CH_2 and CH_3). MS (EI) *m / z* (rel intensity) 267 (M^+, 5), 236 ([M^+-CH_2OH], 100).

Synthesis of ω-lithioxy-azaalkyllithiums ***3*** *and their Reaction with Benzaldehyde. Typical Procedure.*

A solution of *n*-BuLi (27.2 mL of 1.84 M solution in methylcyclohexane, 50 mmol) was added to a solution of the sulfide **2a** (11.25 g, 50 mmol) in THF (20 mL) at -78 °C, under argon. A suspension of an excess of lithium dispersion (2.5 g, 357 mmol, free from mineral oil) in THF (50 mL) was then added together with magnesium 2-ethoxyethoxide (11.3 g) and di-*tert*-butylbiphenyl (0.25 g), with ice-water bath cooling, after which the mixture was warmed slowly to room temperature and stirred overnight. Benzaldehyde (5.30 g, 50 mmol) was then added with ice-water bath cooling and stirred for 0.5 h. Water was then added, and after filtration, the product was extracted with toluene. The organic phase was washed with a 35% aqueous solution of NaOH (20 mL), dried over K_2CO_3, filtered and evaporated to dryness, yielding 8.35 g of the crude product as a yellow oil. Isolation of the pure product was carried out by column chromatography, yielding **4a** (6.4 g, 57%) as an oil.

Spectroscopic data

3-Methyl-7-phenyl-3-aza-heptan-1,7-diol ***(4a)***: ^{1}H NMR ($CDCl_3$, δ ppm): 7.33-7.19 (m, 5H, H_{arom}), 5.48 (s, 2H, 2 × OH), 4.57 (m, 1H, CH), 3.63 (t, ^3J = 5.1 Hz, 2H, CH_2O), 2.64-2.41 (m, 4H, CH_2NCH_2), 2.27 (s, 3H, NCH_3), 1.87-1.43 (m, 4H, 2 × CH_2). ^{13}C NMR ($CDCl_3$, δ ppm): 145.23, 128.23, 126.97 and 125.65 (Ph), 73.71 (CH), 59.81, 58.90, 57.95, 42.06, 39.16 and 24.32 (5 × CH_2 and CH_3). MS (EI) *m / z* (rel intensity) 224 ([M^++H], 15), 192 ([M^+-CH_2OH], 100).

3-Methyl-8-phenyl-3-aza-octan-1,8-diol ***(4b)***: ^{1}H NMR ($CDCl_3$, δ ppm): 7.33-7.25 (m, 5H, H_{arom}), 4.65 (t, ^3J = 6.5 Hz, 1H, CH), 3.58 (t, ^3J = 5.1 Hz, 2H, CH_2O), 2.93 (brs, 2H, 2 × OH), 2.52 (t, ^3J = 5.0 Hz, 2H, NCH_2), 2.41 (t, ^3J = 7.0 Hz, 2H, NCH_2), 2.23 (s, 3H, NCH_3), 1.81-1.71 (m, 2H, CH_2), 1.50-1.27 (m, 4H, 2 × CH_2). ^{13}C NMR ($CDCl_3$, δ ppm): 144.90, 128.40, 127.42 and 125.80 (Ph), 74.28 (CH), 58.90, 58.21, 57.33, 41.51, 38.69, 26.64 and 23.31 (6 × CH_2 and CH_3). MS (EI) *m / z* (rel intensity) 238 ([M^++H], 8), 206 ([M^+-CH_2OH], 100).

3-Methyl-9-phenyl-3-aza-nonan-1,9-diol ***(4c)***: ^{1}H NMR ($CDCl_3$, δ ppm): 7.33-7.23 (m, 5H, H_{arom}), 4.65 (t, ^3J = 6.6 Hz, 1H, CH), 3.56 (t, ^3J = 5.2 Hz, 2H, CH_2O), 2.85 (brs, 2H, 2 × OH), 2.50 (t, ^3J = 5.2 Hz, 2H, NCH_2), 2.37 (t, ^3J = 7.2 Hz, 2H, NCH_2), 2.21 (s, 3H, NCH_3), 1.77-1.72 (m, 2H, CH_2), 1.47-1.30 (m, 6H, 3 × CH_2). ^{13}C NMR ($CDCl_3$, δ ppm): 144.92, 128.39, 127.42 and 125.84 (Ph), 74.38 (CH), 58.77, 58.21, 57.47, 41.50, 38.98, 27.01, 26.87 and 25.55 (7 × CH_2 and CH_3). MS (EI) *m / z* (rel intensity) 250 ([M^+-H], 5), 219 ([M^+-CH_2OH_2], 100).

3-Methyl-10-phenyl-3-aza-decan-1,10-diol ***(4d)***: ^{1}H NMR ($CDCl_3$, δ ppm): 7.36-7.25 (m, 5H, H_{arom}), 4.65 (t, ^3J = 6.6 Hz, 1H, CH), 3.57 (t, ^3J = 5.0 Hz, 2H, CH_2O), 2.56 (brs, 2H, 2 × OH), 2.51 (t, ^3J = 5.1 Hz, 2H, NCH_2), 2.38 (t, ^3J = 7.3 Hz, 2H, NCH_2), 2.23 (s, 3H, NCH_3), 1.77-1.70 (m, 2H, CH_2), 1.44-1.29 (m, 8H, 4 × CH_2). ^{13}C NMR ($CDCl_3$, δ ppm): 144.92, 128.40, 127.44 and 125.86 (Ph), 74.51 (CH), 58.73, 58.17, 57.61, 41.50, 39.01, 29.29, 27.10, 26.91 and 25.70 (8 × CH_2 and CH_3). MS (EI) *m / z* (rel intensity) 264 ([M^+-H], 4), 234 ([M^+-CH_2OH], 100).

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