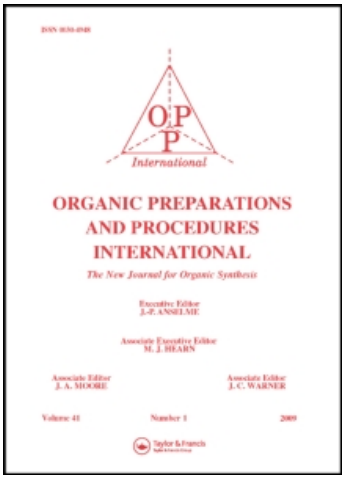

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SIMPLE PROCEDURES FOR THE PREPARATION OF α,ω-HYDROXYALKANETHIOLS

Luis E. Iglesias[a]; Alicia Baldessari[a]; Eduardo G. Gros[a]
[a] Departamento de Qumica Orgnica, Facultad de Ciencias Exactas y Naturales Universidad de Buenos Aires, Buenos Aires, ARGENTINA

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SIMPLE PROCEDURES FOR THE PREPARATION OF α,ω-HYDROXYALKANETHIOLS

Luis E. Iglesias, Alicia Baldessari* and Eduardo G. Gros

Departamento de Qumica Orgnica, Facultad de Ciencias Exactas y Naturales
Universidad de Buenos Aires, Pab.2, Ciudad Universitaria, 1428, Buenos Aires, ARGENTINA

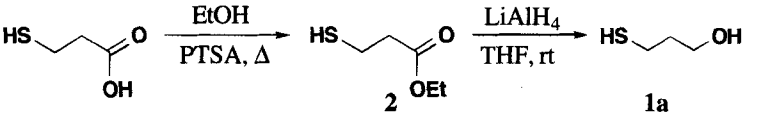
α,ω-Hydroxyalkanethiols (**1**) have an extensive scope of applications. They are used in organic synthesis, as intermediates in preparation of 1,3-oxathiane compounds used in *umpolung* reactions[1,2] and in electrochemistry as monolayers on gold electrodes.[3-5] Moreover the thiol group develops multiple biological actions and compounds with free-SH are considered important protectors against radiation-induced damage to DNA.[6] Due to this property, hydroxyalkanethiols can be used in cancer radiotherapy[7] and are employed in cosmetic preparations reducing actinic damage to human skin due to over-exposure to sunlight.[8] Finally, their O-acyl derivatives are significant molecular weight controlling agents in chain polymerization.[9] During the development of our research on enzymatic acylation of bifunctional and polyfunctional hydroxyalkanethiols[10-13] we were in need of α,ω-hydroxyalkanethiols (**1**):

$HS-(CH_2)_n-OH$ **a)** n = 3 **b)** n = 4 **c)** n = 8 **d)** n = 12

1

These compounds have been prepared by several methods,[14-17] but the different procedures were not effective, because of low yields due to the concomitant production of sulfides or/and disulfides. We now describe improved preparation of compounds **1** through simple transformations carried out under reductive conditions in order to avoid the formation of undesirable side-products.

3-Mercapto-1-propanol (**1a**) was obtained in two steps from 3-mercaptopropionic acid as shown in Eq. 1.

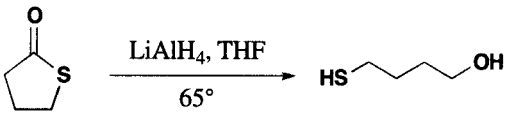


2 **1a** (1)

We had initially tested the direct reduction of 3-mercaptopropionic acid to the hydroxyalkanethiol (**1a**) with sodium *bis*(2-methoxyethoxy)aluminum hydride (SMEAH) and sodium borohydride in sulfuric acid, a procedure specifically indicated for reduction of carboxylic acids.[18] Unfortunately,

we obtained poor results because of products resulting from incomplete reductions and leading to β-thiopropiolactone as the main by-product. Lithium aluminum hydride has also been used in the reduction of 2-mercaptopropionic acid but the alcohol was obtained in 39% yield.[15] We performed the reduction on the ethyl ester of 3-mercaptopropionic acid (**2**), obtained by refluxing the acid in ethanol with *p*-toluenesulfonic acid as catalyst. The subsequent treatment with lithium aluminum hydride gave the expected product with an overall yield of 64%.

To our knowledge, no hydroxyalkanethiol had been obtained by reduction of a thiolactone. We obtained 4-mercapto-1-butanol (**1b**) by reduction of γ-thiobutyrolactone (γ-TBL) with lithium aluminum hydride in tetrahydrofuran (Eq. 2). The temperature and $LiAlH_4$/γ-TBL ratio had a significant influence on the relation of the different products produced.

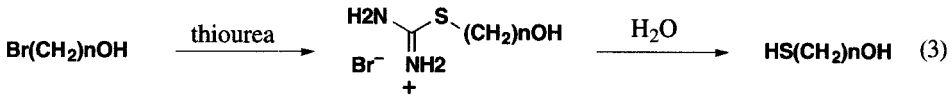


(2)

1b

The best results were achieved at 65° and with a hydride to lactone ratio between 5 and 8, pure (**1b**) being obtained in 76% yield.

Both 8-mercapto-1-octanol (**1c**) and 12-mercapto-1-dodecanol (**1d**) were prepared through reaction of the corresponding ω-bromo-1-alkanol with thiourea[19] followed by hydrolysis. The two isothiouronium salts **3** and **4** were obtained in approximately 80% yield. According to the literature,[19]



(3)

3, n = 8 **4**, n = 12

isothiouronium salts can be hydrolyzed by reflux in sodium hydroxide solution. While this procedure was successful for the preparation of 8-mercapto-1-octanol (**1c**), treatment of the isothiouronium salt from 12-bromo-1-dodecanol (**4**) under similar conditions afforded a 1:1 mixture of 12-mercapto-1-dodecanol (**1d**) and 12-hydroxy-1-dodecyldisulfide. The difference in behavior might be explained by the consideration that high-molecular weight thiols are susceptible to oxidation to disulfides in alkaline media.[20] To avoid disulfide formation, the cleavage of the intermediate S-(12-hydroxy-1-dodecyl)-isothiouronium bromide (**4**) was examined with different reagents. While treatment of **4** with aqueous $NaHCO_3$ failed to accomplish the cleavage, $NaBH_4$ not only cleaved the salt but also led to disulfide production. Zinc in acetic acid was the only reagent which yielded pure 12-mercapto-1-dodecanol (**1d**) without disulfide formation.

The synthetic schemes outlined above for the preparation of hydroxyalkanethiols offer alternative and improved routes to these compounds.[3,15,21,22]

EXPERIMENTAL SECTION

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Silica gel for column chromatography was Merck Kieselgel 60 (70-230 mesh). Analytical GC was performed on a Hewlett Packard 5840 gas chromatograph with glass packed columns with 12% DGS or OV 225 on Chromosorb W-AW-DMCS. Infrared spectra were recorded on a Nicolet Magna-550 FT/IR spectrophotometer . ^1H and ^{13}C NMR spectra were recorded with a Varian XL-100-15FT spectrometer at 100.1 and 25.2 MHz respectively and with a Bruker AC-200 spectrometer at 200 and 50.2 MHz respectively using tetramethylsilane as internal standard; solvents are indicated in each case. GC-MS was performed using a gas chromatograph coupled to a Varian Mat CH7-A mass spectrometer interfaced to a Varian-Mat Data System 166 computer and on a VG-TRIO-2 GC-MS instrument. FAB-MS on a VG-ZAB BEQ instrument. Elemental analyses were performed by UMYMFOR (CONICET-FCEN).

Ethyl 3-Mercaptopropionate (2).- A solution of 3-mercaptopropionic acid (40 g , 377 mmol) and *p*-toluensulfonic acid (400 mg , 2 mmol) in ethanol (350 mL) was refluxed for 15 hrs and then 70 mL of ethanol were added. A fractional distillation apparatus was adapted to the system and distillation was performed for 2 hrs, until no more distillate was observed. Excess ethanol was evaporated *in vacuo*; the residue was washed with saturated sodium bicarbonate solution, extracted with methylene chloride, dried over sodium sulfate and evaporated to dryness, affording 39.2 g (77%) of **2** as an oil. IR (film): 1719 (C=O) cm^{-1} . ^1H NMR ($CDCl_3$) : δ 1.26 (t, 3H, J = 7 Hz, $-CH_3$), 1.56-1.74 (m, 1 H, -SH), 2.50-2.92 (m, 4 H, $-C\underline{H}_2-C\underline{H}_2SH$), 4.20 (q, 2H, J = 7 Hz, $-OCH_3-$). ^{13}C NMR ($CDCl_3$): δ 14.3 (C-5), 19.8 (C-3), 38.5 (C-2), 60.6 (C-4), 171.4 (C-1). MS (EI) (m/z,%): 134 (M^+, 67), 101 (5), 89 (43), 88 (100), 87 (19), 61 (29), 60 (22).[23]

3-Mercapto-1-propanol (1a).- A solution of ethyl 3-mercaptopropionate (1.13 g , 8.4 mmol) in 10 mL of dry tetrahydrofuran was added slowly to a stirred suspension of lithium aluminum hydride (38 mmol) in 25 mL of dry tetrahydrofuran. All procedures were carried out under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 18 hrs and then poured into cold 10% sulfuric acid. The obtained slurry was filtered and the solid was washed with ethanol. The filtrate was extracted with ethyl acetate and both the extract and the washings were combined, dried over sodium sulfate and evaporated *in vacuo*. The residue was purified by flash column chromatography (eluted with 7:3 methylene chloride-ethyl acetate) to afford 610 mg (84%) of an unpleasant smelling liquid, pure by gas chromatography. ^1H NMR ($CD_3OD + D_2O$): δ 1.79-1.97 (m, 2H, $-CH_2C\underline{H}_2CH_2-$), 2.60 (t, J = 8 Hz, 2H, $-C\underline{H}_2SH$), 3.68 (t, J = 6 Hz, $-C\underline{H}_2OH$).[24] ^{13}C NMR ($CDCl_3$): δ 21.2 (C-2), 36.2 (C-3), 60.8 (C-1). MS (EI) (m/z,%): 92 (M^+,60), 74 (56), 61 (39), 58 (87), 47 (46), 45 (26), 43 (50), 41 (100).

4-Mercapto-1-butanol (1b).- A solution of γ-thiobutyrolactone (996 mg, 9.8 mmol) in dry tetrahydrofuran (10 mL) was added slowly, under nitrogen atmosphere, to a stirred suspension of lithium aluminum hydride (2.92 g , 77 mmol) in tetrahydrofuran (70 mL), in a bath at 0°. After addition of the thiolactone the resulting suspension was refluxed for 90 min. The mixture was allowed to cool to room temperature and 2N sulfuric acid was added until precipitation. The precipitate was filtered and washed with ethanol. Both precipitate and washings were extracted with methylene chloride. The extract was washed with water, dried over sodium sulfate, and evaporated to dryness, giving 727 mg

(76% yield) of a disagreeable smelling liquid. ^{1}H NMR ($CDCl_3$): δ 1.29 (t, 1H, J = 8Hz, SH), 1.59-1.83 (m, 4 H, $HOCH_2C\underline{H}_2C\underline{H}_2CH_2$-), 2.13 (s, 1H, OH), 2.47-2.58 (m, 2 H, $HSC\underline{H}_2$-), 3.61 (t, J = 7Hz, 2 H, -$C\underline{H}_2OH$). ^{13}C NMR ($CDCl_3$): δ 24.4 (C-3), 30.2 (C-4*), 31.3 (C-2*), 62.1 (C-1).MS (EI) (m/z,%): 106 (M^+, 3), 88 (100), 73 (10), 60 (72), 47 (52), 45 (25), 43 (25).

S-(8-Hydroxy-1-octyl)isothiouronium Bromide (3).- To a solution of 8-bromo-1-octanol (456 mg , 2.4 mmol) in ethanol (5 mL) thiourea (198 mg , 2.6 mmol) was added, and the mixture was refluxed for 3 hrs. The solvent was removed to dryness, and the resulting crude residue was recrystallized from diethyl ether-ethanol, affording 461 mg (74%) of S-(8-hydroxy-1-octyl) isothiouronium bromide (**3**) as a white solid of mp. 64-66°. IR (KBr): 3354 (OH), 3160 (NH_2), 2851 (N^+H_3), 1655 (C=N) cm^{-1}. ^{1}H NMR (CD_3OD): δ 1.37-1.77 (m, 16H), 3.15 (t, 2H, J = 8Hz, -CH_2S-), 3.55 (t, 2H, J = 8Hz, -$C\underline{H}_2OH$). ^{13}C NMR (CD_3OD): δ 26.7 (C-3), 29.3 (C-5*), 29.6 (C-6*), 30.0 (C-4), 30.2 (C-7), 32.0 (C-8), 33.5 (C-2), 62.9 (C-1), 173.1 (C-9). MS (EI) (m/z,%): 205 (M^+,21), 87 (17), 82 (20), 77 (45), 76 (49), 69 (70), 67 (28), 55 (62), 43 (100), 41 (73).

Anal. Calcd. for $C_9H_{21}BrN_2OS$: C, 37.89: H, 7.37; N, 9.82; S, 11.23; Br, 28.07

Found: C, 38.12; H, 7.61; N, 10.14; S, 11.61; Br, 28.67

8-Mercapto-1-octanol (1c).- Thiourea (765 mg, 10 mmol) was added to a solution of 8-bromo-1-octanol (1.94 g , 9.3 mmol) in ethanol (20 mL) and the mixture was refluxed for 3 hrs. After cooling, 10% sodium hydroxide (4 mL) was added and the mixture was refluxed for 2 hrs. Then, the system was cooled to 0°, 2N hydrochloric acid was added to decrease the pH to 2-3 and the mercaptoalcohol was extracted with methylene chloride. The organic extracts were washed with water, dried over sodium sulfate and the solvent removed at reduced pressure, affording 915 mg (67% yield) of a liquid pure by gas chromatography. IR (film): 3358 (OH), 2855 (SCH_2.), 2556 (SH). ^{1}H NMR ($CDCl_3$): δ 1.28-1.36 (m, 12H), 1.53-1.61 (m, 1H, -SH), 2.16 (s,1H, -OH), 2.52 (q, 2H, J = 8Hz, -$C\underline{H}_2SH$), 3.63 (t, 2H, J = 7Hz, -$C\underline{H}_2OH$).^{13}C NMR ($CDCl_3$) δ 24.4 (C-8), 25.5 (C-3), 28.3 (C-6), 29.1 (C-4*), 29.5 (C-5*), 32.5 (C-2), 33.8 (C-7), 62.6 (C-1). MS (EI) (m/z,%): 144 (2), 129 (1), 115 (13), 101 (44), 87 (58), 61 (15), 47 (38), 41 (100).

S-(12-Hydroxy-1-dodecyl)isothiouronium Bromide (4).- This compound was prepared as described above for S-(8-hydroxy-1-octyl) isothiouronium bromide **(3)** using 1.02 g (3.9 mmol) of 12-bromo-1-dodecanol. Pure **4** (1.06 g, 80% yield) had mp. 95-97°. IR (KBr): 3330 (OH), 3160 and 3100 (NH_2), 2810 ($^+NH_3$), 1630 (C=N).^{1}H NMR (CD_3OD): δ 1.32-1.79 (m, 20H), 2.16 (s, -OH), 2.18 (s, -SH), 3.16 (t, 2H, J = 8Hz, HS-$C\underline{H}_2$), 3.54 (t, 2H, J = 8 Hz, HO-$C\underline{H}_2$). ^{13}C NMR (CD_3OD): δ 26.9 (C-3), 29.4 (C-10), 29.6 (C-9), 30.4 (C-6 and C-7), 30.5 (C-5 and C-8), 30.6 (C-4 and C-11), 32.0 (C-12), 33.6 (C-2), 63.0 (C-1), 173.2 (C-13). MS (EI) (m/z, %): 261 (M^+, 2), 115 (27), 101 (71), 87 (81), 76 (52), 55 (100), 43 (68); 41 (88). FAB-MS (m/z, %) : 261 (M^+, 100).

Anal. Calcd. for $C_{13}H_{29}BrN_2OS$: C, 45.75; H, 8.50; N, 8.21; S, 9.38; Br, 23.46

Found: C, 45.47; H, 8.84; N, 8.09; S, 9.00; Br, 23.85

12-Mercapto-1-dodecanol (1d) from (4).- The bromide **4** (748 mg , 2.2 mmol) was dissolved in acetic acid (20 mL) by heating in a water bath at 40-50°. The solution was allowed to cool to room

temperature and then zinc powder (1.11 g ; 17 mmol), previously treated with 10% aqueous hydrochloric acid, was added. The suspension was stirred at room temperature for 20 hrs. Excess zinc and a light gray solid were filtered and washed with methanol and acetone. Both filtrate and washings were carefully neutralized with sodium bicarbonate solution. At pH 5-6 precipitation of a solid occurred; at pH 7, the mixture was filtered, the solid washed with acetone and the filtrate and the washings extracted with methylene chloride and ethyl acetate. The extract was washed with water, dried over sodium sulfate and evaporated to dryness, affording a crude solid. After recrystallization from hexane, it afforded 235 mg (50 %) of a white solid, mp. 39-40°. IR (KBr): 3370 (OH), 2850 (SCH_2), 2520 (SH) cm^{-1}. ^1H NMR ($CDCl_3$ + CD_3OD): δ 1.29-1.34 (m, 20H), 1.51-1.58 (m, 1H, -SH), 2.20 (s, 1H, -OH), 2.51 (t, 2H, J = 8Hz, -C<u>H</u>$_2$SH), 3.57 (t, 2H, J = 8Hz, -C<u>H</u>$_2$OH). ^{13}C NMR ($CDCl_3$ + CD_3CN) : δ 24.2 (C-12), 25.4 (C-3), 28.5 (C-10), 28.8 (C-4), 29.1 (C-5 and C-8), 29.2 (C-6 and C-7), 29.4 (C-9), 31.8 (C-2), 32.4 (C-11), 62.3 (C-1). MS (EI) (m/z,%) : 218 (M^+, 1), 200 (9), 185 (1), 115 (28), 101 (76), 87 (100), 61 (25), 47 (15), 43 (94), 41 (50).

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