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Two New Chiral Equivalents of H_2S: a Thio- and a Dithiocarboxylic Acid

Pedro de March,* Marta Figueredo,* Josep Font, Lluïsa González, and Antonio Salgado

Departament de Química. Universitat Autònoma de Barcelona. 08193 Bellaterra (Barcelona). Spain.

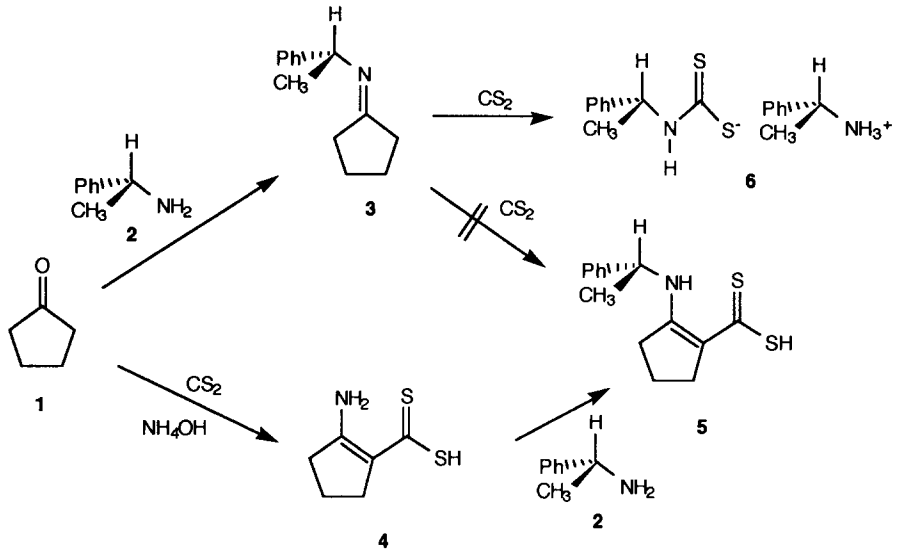
Abstract.- The syntheses of the two new chiral mercapto derivatives (*R*)-2-[*N*-(1-phenylethyl)-amino]-1-cyclopentenedithiocarboxylic acid, **5**, and (1*S*,4*R*)-1-(4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane)thiocarboxylic acid, **9**, are described through easy transformations in good yields.

The preparation of non-racemic chiral molecules becomes every day a more important and necessary goal in organic chemistry. During some of our synthetic studies we were faced with the problem of generating a β-mercaptocarboxylic acid derivative with a stereogenic center at the β-position. The conjugate addition of heteronucleophiles to α,β-unsaturated carbonyl groups is one of the most general methods for the β-functionalization of carbonyl derivatives, but the number of described examples of asymmetric Michael-type reactions using sulfur nucleophiles is relatively small.[1] To the best of our knowledge, there is only one described case in which an enantiopure thiol[1g] is used as nucleophile in a conjugate addition and the thus formed adducts are subjected to diastereoisomeric separation followed by an elimination of the sulfur derivative, but they are not used as synthetic intermediates incorporating the sulfur atom. Probably, the comparatively small number of examples of asymmetric conjugated addition using sulfur nucleophiles is due to the fact that the synthesis of non-racemic chiral thiols has not received much attention.[2,3]

To solve our synthetic problem we visualized the use of chiral mono- or dithiocarboxylic acids as the most appropriate derivatives, since hydrolysis of the corresponding adducts would generate the free thiol function. The number of known enantiopure thiocarboxylic acids is very small.[4] Herein we report the easy preparation of two new sulfur derivatives, which are chiral synthetic equivalents of hydrogen sulfide.[2]

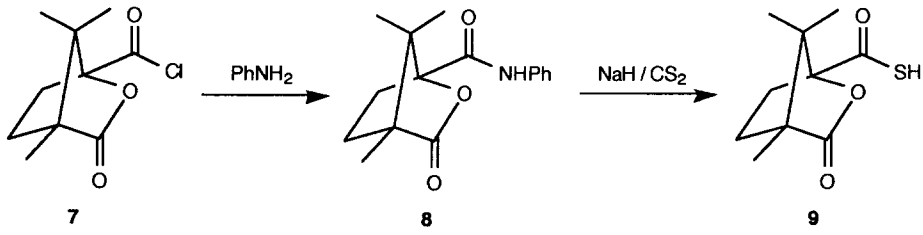
Our first target was the β-aminodithioic acid **5**, whose synthesis may be undertaken by two approaches according to general methods for the preparation of dithioacids previously described (Scheme 1): condensation of cyclopentanone, **1**, with a chiral amine, for instance **2**, and subsequent reaction of the formed ketimine **3** with carbon disulfide[5] or by an amine exchange reaction from the enaminodithioacid **4**.[6] We tried the first route and the imine **3** was obtained as a colorless liquid after distillation in 95% yield. We have fully characterized the known compound **3**[7] by its spectroscopic data, specific rotation at the sodium D line, and elemental analysis. Unfortunately, none of our attempted reactions between **3** and carbon disulfide led to the isolation of the desired thioacid **5**, but instead the salt **6**[8] was obtained. The second route proved more successful and the reaction of the dithiocarboxylic acid **4**[9] with the amine **2** gave the desired new compound **5** as a yellow oil in 53% yield. The ^{13}C nmr spectrum of compound **5** shows absorptions at δ 190.1, 170.5, and 118.8 corresponding to the thiocarboxylic group and the β and α olefinic carbon atoms respectively. The uv spectrum of **5** presents a maximum at $\lambda = 416$ nm with $\varepsilon = 30500$ and the specific rotation $[\alpha]_D^{20}$ of **5** has a value of

+2102. The crystallization of **5** was difficult and only an analytical crystallized sample could be obtained.



Scheme 1

The synthesis of the thiocarboxylic acid **9** was also undertaken (Scheme 2). The reaction of amides with base and carbon disulfide is a well known method for the synthesis of thioacids.[10] We chose as starting material a cheap carboxylic acid derivative with a stereogenic center at the α position with bulky substituents and containing other polar groups that seemed to us a good candidate to deliver high asymmetric induction in addition reactions. Treatment of commercial (1*S*)-(-)-camphanic acid chloride, **7**, with aniline afforded the known anilide **8**[11] in 92% yield. A solution of **8** in *N,N*-dimethylacetamide and benzene[10] was consecutively treated with sodium hydride and carbon disulfide giving the thioacid **9** as a white solid in 81% yield. Its structural elucidation is based on the weak absorption at 2565 cm^{-1} in the ir spectrum, assigned to the thiol group, and the signals at δ 195.9 and 177.2 in the ^{13}C nmr spectrum attributed to the thioacid and lactone functions respectively.



Scheme 2

The use of **5** and **9** as chiral auxiliaries for the incorporation of a thiol group through conjugated additions is the object of ongoing investigations in our laboratories.

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EXPERIMENTAL SECTION

The organic extracts were dried over anhydrous sodium sulfate. Reaction solutions were concentrated using a rotary evaporator at 15-20 Torr. Flash chromatographies were performed on silica gel (230-400 mesh). Infrared spectra were recorded on a Nicolet 5 ZDX spectrophotometer. ^1H nmr and ^{13}C nmr spectra were recorded on a Bruker AC-250-WB instrument and chemical shifts are given in δ values. Mass spectra were performed on a Hewlett-Packard 5985B instrument at 70 eV.

(R)-2-[N-(1-Phenylethyl)amino]-1-cyclopentenedithiocarboxylic acid, **5**

To a magnetically stirred solution of dithiocarboxylic acid **4**[9] (400 mg, 2.5 mmol) in methanol (4 mL) at the reflux temperature, (*R*)-(+)-*N*-(1-phenylethyl)amine (1.2 mL, 9.4 mmol) was added. The mixture was maintained at the same temperature for 4.5 h obtaining a red solution. The addition of water (11.2 mL) and acetic acid (1.2 mL) to the mixture promoted the formation of a precipitate (659 mg) which was filtered. Flash chromatography of this crude material using ethyl acetate-hexane (1:3) as eluent afforded the following fractions: i) (*R*)-2-[*N*-(1-phenylethyl)amino]-1-cyclopentenedithiocarboxylic acid, **5**, (348 mg, 1.3 mmol, 53% yield) as a yellow oil, that was very difficult to crystallize; ii) (*R*)-*N*-cyclopentylidene-*N*-(1-phenylethyl)amine, **3**,[7] (134 mg, 0.7 mmol); iii) (*R,R*)-*N,N*-bis-(1-phenylethyl)thiourea[12] (130 mg, 0.5 mmol); and iv) starting amine **2** (17 mg, 0.1 mmol). **3**: ir (film) 3124, 3045, 2966, 2876, 1672 cm^{-1}; ^1H nmr ($CDCl_3$, 250 MHz) 7.38-7.15 (m, 5 H), 4.40 (q, *J* = 7.3 Hz, 1 H), 2.40-2.20 (m, 3 H), 2.05 (m, 1 H), 1.85-1.60 (m, 4 H), 1.45 (d, *J* = 7.3 Hz, 3 H); ^{13}C nmr ($CDCl_3$, 62.5 MHz) 178.7 (C=N), 145.3/128.0/126.3/126.2 (Ph), 61.6 (CHN), 36.3, 28.5, 24.6, 24.3, 23.8; ms *m/z* 187 (M^+, 21), 172 (9), 105 (100); $[\alpha]_D^{20}$ = +87 (*c* = 3.0, $CHCl_3$). Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.88; H, 9.02; N, 7.42. **5**: mp 165-167 °C (ethyl acetate/hexane); uv λ_{max} = 241 nm ε = 5240, λ_{max} = 416 nm ε = 30500; ir (film) 2966, 2931, 1588, 1489, 1271 cm^{-1}; ^1H nmr ($CDCl_3$, 250 MHz) 7.26-7.18 (m, 5 H), 4.70 (q, *J* = 7.3 Hz, 1 H), 3.15-2.95 (m, 2 H), 2.75-2.60 (m, 1 H), 2.40-2.30 (m, 1 H), 1.90-1.70 (m, 2 H), 1.54 (d, *J* = 7.3 Hz, 3 H); ^{13}C nmr ($CDCl_3$, 62.5 MHz) 190.1 (CS), 170.5 (C-2), 142.2/128.8/127.5/125.7 (Ph), 118.8 (C-1), 56.2 (CHN), 33.8/33.5 (C-3/C-5), 24.3 (Me), 20.0 (C-4); $[\alpha]_D^{20}$ = +2102 (*c* = 0.37, $CHCl_3$). Anal. Calcd for $C_{14}H_{17}NS_2$: C, 63.83; H, 6.51; N, 5.32; S, 24.34. Found: C, 63.71; H, 6.49; N, 5.27; S, 24.30.

(1S,4R)-1-(4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane)thiocarboxylic acid, **9**.

Sodium hydride (520 mg, 13.0 mmol from a 60% dispersion in mineral oil) was suspended in anhydrous *N,N*-dimethylacetamide (10 mL) and anhydrous benzene (10 mL) at room temperature under argon atmosphere. Amide **8**[11] (3.01 g, 11.0 mmol) was added and a rapid gas evolution took place. The reaction mixture was cooled to 0 °C and carbon disulfide (966 μl, 16.0 mmol) was added dropwise affording a red solution. After 30 min, ice-water (*ca.* 10 mL) and concentrated HCl (10 mL) were added. The organic phase was separated and the aqueous layer was washed with benzene (10 mL). The combined organic phase was extracted with 5% NaOH solution (20 mL) and this aqueous solution was acidified again with HCl solution and extracted with methylene chloride (3 x 20 mL). The solvent was removed under vacuum yielding (1*S*,4*R*)-1-(4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane)thiocarboxylic acid, **9** (1.91 g 8.9 mmol, 81% yield) as a white solid. Purification was done by sublimation (60 °C/0.2 Torr). **9**: mp 43-46 °C; ir (KBr) 2980, 2565, 1792, 1686, 1454, 1335, 1222, 1166, 1089, 1018, 927, 807 cm^{-1}; ^1H nmr ($CDCl_3$, 250 MHz) 4.92 (br s, 1 H, SH), 2.41-2.29 (m, 1 H, H-6*exo*), 2.00-1.82 (m, 2 H, H-5*endo*, H-6*endo*), 1.72-1.55 (m, 1 H, H-5*exo*), 1.05 (s, 3 H, Me at C-4), 0.97 (s, 3 H, Me at C-7), 0.95 (s, 3 H, Me at C-7); ^{13}C nmr ($CDCl_3$, 62.5 MHz) 195.9 (COS), 177.2 (COO), 95.6 (C-1), 55.6 (C-7), 54.7 (C-4), 30.7 (C-5), 28.6 (C-6), 16.5 (Me at

C-7), 16.2 (Me at C-7), 9.5 (Me at C-4); ms *m/z* 214 (M^+, 1), 186 (17), 125 (31), 97 (42), 83 (100), 67 (27), 55 (50), 43 (21), 41 (59); $[\alpha]_D^{20} = -71$ ($c = 3$, $CHCl_3$). Anal. Calcd for $C_{10}H_{14}O_3S$: C, 56.05; H, 6.58; S, 14.96. Found: C, 55.87; H, 6.58; S, 14.69.

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