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RESOLUTION OF *S*-(1-FERROCENYLETHYL)THIOGLYCOLIC ACID. A NEW METHOD OF PREPARATION OF OPTICALLY ACTIVE 1-FERROCENYLETHANOL

ALEKSANDER RATAJCZAK and BOGUSŁAW MISTERKIEWICZ
Department of Organic Chemistry. The Silesian University, 40-006 Katowice (Poland)
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Summary

A simple method for the preparation of optically active (+)- and (—)-1-ferrocenylethanol has been developed, which consists of a stereospecific cleavage of the carbon—sulphur bond in resolved (+)- and (—)-*S*-(1-ferrocenylethyl)-thioglycolic acids brought about by mercuric chloride in the presence of water.

Introduction

In recent years significant attention has been paid to the preparation of optically active compounds, e.g. alcohols and amines, bearing a ferrocenyl group at the α-carbon atom [1-5]. These compounds are very useful in studies of the mechanism of nucleophilic substitution [3] and 1-ferrocenylethylamine can be used for the synthesis of peptides through a stereoselective, four-component condensation [1].

Until now, these compounds have been prepared by Ugi's method [3], which consists of the resolution of racemic *N,N*-dimethyl-1-ferrocenylethylamine through fractional crystallization of the hydrogen tartrates [2]. Other optically-active derivatives (including 1-ferrocenylethanol) can then be obtained from an optically-active ammonium salt by nucleophilic substitution [3-5]. This method has been recently extended to the preparation of cyclic ferrocene derivatives [4,5].

Results and discussion

We have developed in our laboratory an alternative simple method for the preparation of optically-active 1-ferrocenylethanol, in which all stages of the synthesis can be performed under mild conditions, at temperatures below 25°, with high yield. The crucial step in this method consists of the stereospe-

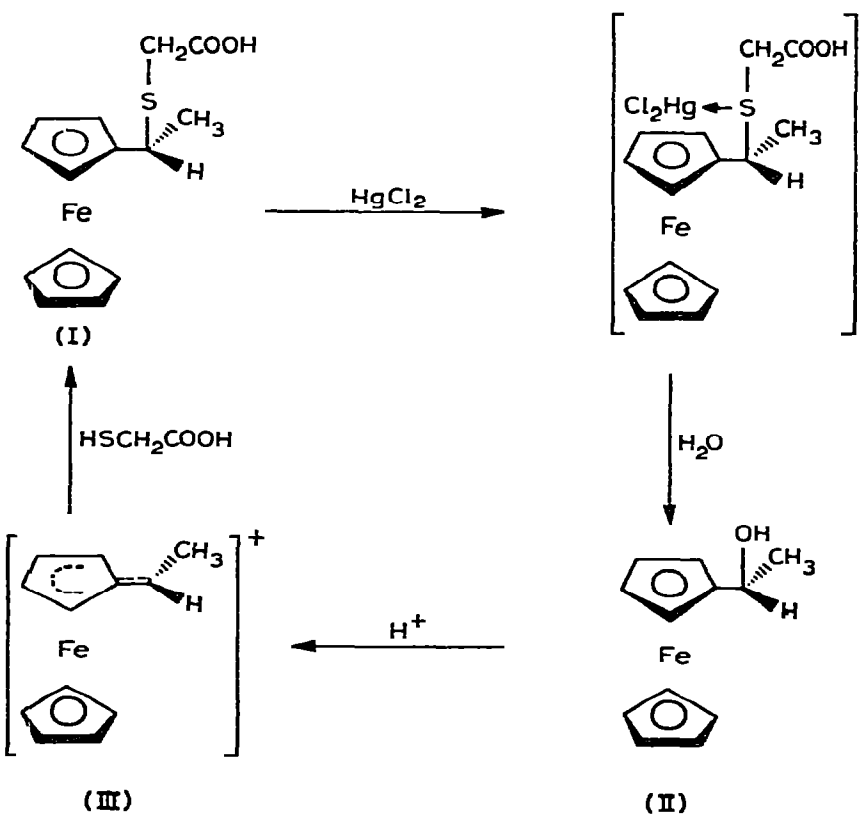
cific cleavage of the carbon—sulphur bond in the optically-active *S*-(1-ferrocenylethyl)thioglycolic acid by means of mercuric chloride in the presence of water.

(±)-*S*-(1-Ferrocenylethyl)thioglycolic acid (I) was obtained in 92% yield by the reaction of an acetone solution of (±)-1-ferrocenylethanol with thioglycolic acid in the presence of trifluoroacetic acid (TFA) as catalyst. The methyl ester of the acid I was obtained through reaction of the acid with an ethereal diazomethane solution.

During our experiments we have found that the reported formation of the ferrocenylmethyl ester of thioglycolic acid $FcCH_2OOCCH_2SH$ through reaction of ferrocenylmethanol with thioglycolic acid [10] is erroneous; we find [7] that the product of this reaction is identical with *S*-(1-ferrocenylmethyl)thioglycolic acid $FcCH_2SCH_2COOH$, described in refs. 8 and 9.

The acid I was resolved into enantiomers through fractional crystallization from methanol of the diastereomeric salts with ephedrine. Two-fold crystallization gave a salt, m.p. 171-173°. The (+)-I acid, $[\alpha]_{546}^{24}$ + 22.5° was liberated from this salt using 10% phosphoric acid. From an oily residue left after methanol evaporation the (—)-I acid, $[\alpha]_{546}^{20}$ — 20° was isolated as described above.

SCHEME I



Treatment of the (+)-I acid with a suspension of finely-powdered mercuric chloride in 1/1 acetone—water mixture gave (*R*)-(—)-1-ferrocenylethanol (II), $[\alpha]_{546}^{22}$ — 30°. By dissolution of II in 100% TFA, the (+)-1-ferrocenylethylcarbonium ion (III), $[\alpha]_{546}^{25}$ + 390° (lit. [6] $[\alpha]_{546}^{25}$ + 475°) was prepared; this permitted an estimate of the optical purity of (+)-I and (*R*)-(—)-II alcohol as at least 82 ± 2%.

The absolute configuration of the (+)-I acid obtained can be determined by the treatment of II with an acetone solution of thioglycolic acid in the presence of a catalytic amount of TFA. This reaction gave the acid (+)-I, $[\alpha]_{546}^{19}$ + 20.5°. It is known that all the nucleophilic substitution reactions for these systems studied so far proceed with a full retention of configuration [3], hence the absolute configuration *R* has been ascribed to the (+)-I acid. It can be also deduced that carbon—sulphur bond cleavage in the acid I proceeds with a retention of configuration (Scheme 1).

Studies of the determination of the degree of stereospecifity of carbon—sulphur bond cleavage in the $FcCHSCH_2COOH$ acids by means of mercuric chloride, and of the usefulness of the method described above for the preparation of cyclic homo- and hetero-annularly bridged and other acyclic α-ferrocenyl alcohols, are to be continued.

Experimental

Instrumentation

The NMR spectra were obtained on a Jeol 60 MHz instrument, using 5% $CDCl_3$ solutions, and TMS as internal standard. The IR spectra were obtained on a Carl Zeiss (Jena) UR-20 spectrometer. The optical rotation was measured on a Carl Zeiss (Jena) Polamat A photopolarimeter. The block melting temperatures are not corrected. TLC chromatographic analyses and preparative separation on plates were performed using Silicagel H supplied by Merck. The plates were activated at 150° for 2 h. Spots were developed in iodine vapours. Extracts were dried over anhydrous sodium sulphate.

Starting materials

(±)-1-Ferrocenylethanol was prepared by the method of Arimoto and Haven [11]. Benzene, methanol, and acetone were distilled before use. Thioglycolic acid and mercuric chloride were used as supplied by POCh Gliwice. 100% trifluoroacetic acid was supplied by Fluka A.G., Buchs S.G. Ephedrine was freshly prepared from its hydrochloride (L.A. Cefarm, Katowice) using 10% sodium hydroxide, and was extracted with ether; m.p. 40°.

Synthesis of (±)-S-(1-ferrocenylethyl)thioglycolic acid (I)

Method A. Thioglycolic acid 2.024 g (0.022 mol) in a 50 ml flask was treated with a solution of 4.6 g (0.02 mol) of (±)-1-ferrocenylethanol (II) in 20 ml of acetone; 5 drops of 100% TFA was added and the stoppered flask, protected from light with black paper, was allowed to stand overnight at room temperature. The dark-red solution was poured into a separatory funnel, 40 ml of ether added and the mixture washed with water (2 × 20 ml). The acid I was extracted from the ether layer with saturated aqueous sodium carbonate

solution (2 × 15 ml). The aqueous layer was acidified by stirring with small portions (35 ml) of 10% phosphoric acid. A dark-red oil educed and the aqueous layer changed colour from orange to yellow. The mixture was extracted with ether (3 × 20 ml) and washed with water until it was neutral to litmus. The ether extract was dried overnight, and then the ether was evaporated. 5.6 g (92%) of the acid I in the form of the dark-red oil was obtained. The oil crystallized after 10-15 days giving a dark-yellow precipitate.

Method B. (±)-1-Ferrocenylethanol (2.3 g, 0.01 mol) was finely powdered and dissolved in 7.4 ml (0.1 mol) of 100% TFA at −5°. The solution in a flask was placed in a salt—ice mixture and 8 ml (0.1 mol) of thioglycolic acid (previously cooled to −5°) was slowly added dropwise with vigorous stirring. After the addition of water (20 ml), the colour of the solution changed from green to yellow-green.

50 ml of ether was then added; the aqueous layer was separated and the ether layer washed with water (3 × 20 ml) and extracted with 10% sodium hydroxide. The aqueous layer was slowly acidified with 10% phosphoric acid until an oily precipitate educed. The mixture was then extracted with benzene (3 × 15 ml) and the extract dried overnight. After the benzene had been removed on a rotary evaporator, 2.2 g (72%) of I was obtained as a dark-red oil, which after standing for several days at room temperature crystallized in the form of a dark-yellow precipitate, m.p. 80-82°. Acid equivalent found: 307; calcd.: 303.

NMR δ(ppm), $CDCl_3$ soln.: 1.77, d, 3H (CH_3); 3.25, s, 2H (CH_2); 4.05, q (partly covered), 1H (CH); 4.25, s (broadened), 9H ($C_5H_5FeC_5H_4^-$). IR (cm^{-1}) CCl_4 soln.: 685 w(C—S); 1705 s(C=O); 2586 w(O—H); 2690 w(O—H).

Methyl ester of (±)-S-(1-ferrocenylethyl)thioglycolic acid

(±)-*S*-(1-Ferrocenylethyl)thioglycolic acid (0.120 g) was dissolved in 5 ml of absolute ether and the ether diazomethane solution was slowly added dropwise until nitrogen evolution ceased. Water (5 ml) was then added carefully, the aqueous layer was separated, the ether layer washed with water (2 × 5 ml), and the ether evaporated. The raw product was chromatographically purified in a column (i.d. 1 cm, height 7 cm, Silicagel 200/300 mesh) and developed with benzene. The eluate I containing the main fraction was collected, leaving impurities at the origin. After the benzene had been removed on a rotary evaporator, 0.110 g (89%) of ester in the form of yellow needles, m.p. 56°, was obtained. This layer chromatography with benzene confirmed the purity of the product.

Analysis found: C, 56.60; H, 5.74; S, 9.81. $C_{15}H_{18}FeO_2S$ calcd.: C, 56.64; H, 5.70; S, 10.08%.

NMR δ (ppm), $CDCl_3$ soln.: 1.74, d, 3H (CH_3); 3.20, s, 2H (CH_2); 3.78, s, 3H (OCH_3); 3.98, q (partly covered), 1H (CH); 4.22, s (broadened), 9H (C_5H_5-$FeC_5H_4^-$). IR (cm^{-1}) CCl_4 soln.: 680 w(C—S): 1140 s(C—O—C); 1735 s(C=).

Synthesis of (±)-1-ferrocenylethanol (II) from (±)-S-(1-ferrocenylethyl)thioglycolic acid (I)

Method A. 0.608 g (0.002 mol) of the acid I was dissolved in 6 ml of a 1/1 acetone—water mixture and cooled in a salt-ice mixture. The flask was vigorously shaken for 1 min; 1.088 g (0.004 mol) of finely powdered mercuric chloride

was added and the flask was again shaken for 3 min. The precipitate was filtered off, the solution was poured into a separatory funnel, 20 ml of ether added and the ether layer successively washed with 10% ammonium chloride (4 × 6 ml), 6 ml of water, 6 ml of saturated sodium carbonate and 6 ml of water. After the solution had been dried and the drying agent removed, ether was removed on a rotary evaporator. The raw product was crystallized from n-hexane. After 24 h standing at room temperature, a yellow precipitate educed. The precipitate was separated by decantation and washed with 2 ml n-hexane at 0°. The rest of the alcohol II was isolated preparatively from the solution on plates (20 × 10 cm), putting 30-50 mg of the substance on a plate and developing in 10/1 benzene—acetone. The yield was 0.345 g (75%) of (±)-1-ferrocenylethanol (II).

The homogeneity of the product obtained was established by TLC in 5/1 benzene—acetone.

The qualitative trials of the preparation of (±)-1-ferrocenylethanol (II) from the acid I by use of 96% sulphuric acid, 100% TFA, silver nitrate and silver acetate were also performed. The reaction products were controlled by TLC, as above.

Method B. 90 mg of the acid I was dissolved in 1 ml of 96% sulphuric acid and very carefully dropped in to a small flask (placed in a salt—ice mixture) containing 5 ml of saturated aqueous sodium carbonate solution. The flask content was extracted with ether, the ether layer was washed with water until the latter gave a neutral reaction with litmus. The yield of (±)-1-ferrocenylethanol was about 20%.

Method C. A procedure analogous to B was undertaken using 100% TFA. The yield of (±)-1-ferrocenylethanol was ca. 5%; the unreacted acid I was recovered.

Method D. The procedure was as in A, but silver nitrate was used instead of mercuric chloride. Large amounts of a dark-green precipitate formed, which subsequently decomposed.

Method E. The procedure was as in A, but silver acetate was used. No alcohol II was found in the reaction products. The unreacted acid I and traces of of acetylferrocene were identified.

Resolution of (±)-S-(1-ferrocenylethyl)thioglycolic acid into enantiomers

3.32 g (0.2 mol) of ephedrine was dissolved in 100 ml of methanol at room temperature and a solution of 5.6 g (0.0184 mol) of (±)-I acid in 50 ml of methanol was added.

The flask was allowed to stand in the dark for 2 days at room temperature, after which 3 g of yellow-orange salt, m.p. 174-176° (dec.) was found to have crystallized. The salt was finely-powdered, crystallized from 70 ml of methanol, and the sample was allowed to stand at room temperature for 1 day. A crystalline precipitate in the form of compact orange plates was filtered off, 2.1 g, m.p. 172-174°C (dec.). The filtrate was concentrated to 20 ml and after 2 h an orange precipitate (0.6 g, m.p. 173-175° (dec.)) had separated. Both portions of the precipitate (2.7 g) were recrystallized together from 55 ml of methanol and allowed to stand overnight at room temperature. A salt (1.88 g) of m.p. 170-172° (dec.) was obtained. The solution was concentrated to 20 ml and after 3 h 0.390 g of

the salt (m.p. 172-173° (dec.)) was filtered off. Both portions (2.27 g) were finely powdered together, 20 ml of ether and 20 ml of 10% phosphoric acid were added and the slurry was shaken in a separatory funnel till dissolution of the solid was complete. The aqueous layer was separated and the ether layer washed with 5% phosphoric acid (2 × 10 ml) and water (3 × 5 ml). The mixture was dried and the ether distilled off leaving 1.44 g (99%) of (+)-*S*-(1-ferrocenylethyl)-thioglycolic acid $[\alpha]_{546}^{24}$ + 22.5°, (*c*, 10; methanol; *l*, 0.1), in form of a dark-red oil.

The mother liquor was concentrated to 75 ml and allowed to stand in a refrigerator at 0° for 24 h. Fine crystals precipitated (0.130 g, m.p. 160-162° (dec.)) and were then filtered off. The solution was again concentrated to 36 ml and a further portion of fine crystals (0.250 g, m.p. 162-164° (dec.)) was obtained. After complete evaporation of the methanol, 20 ml of acetone was added and the solution allowed to stand for 6 days at 0° when a yellow precipitate (0.120 g, m.p. 170-172° (dec.)) separated. The acetone was then removed by evaporation leaving an oily salt from which the free acid I was isolated by the procedure described previously. Moreover, the acid was converted into its sodium salt by extraction with 10% sodium hydroxide solution the impurities being left in the ether layer. The free acid was obtained after acidifying the aqueous layer with 10% phosphoric acid and subsequently extracting with ether. After the extract had been dried and the ether had been evaporated, 2.24 g of the (—)-*S*-(1-ferrocenylethyl)thioglycolic acid in the form of a dark-red oil, was obtained ($[\alpha]_{546}^{22}$ —20° *c*, 10; methanol; *l*, 0.1).

Synthesis of (R)-(—)-1-ferrocenylethanol from (+)-S-(1-ferrocenylethyl)thioglycolic acid by reaction with mercuric chloride

The reaction was performed by the method described above. 0.730 g (75%) of (*R*)-(—)-1-ferrocenylethanol, $[\alpha]_{546}^{22}$ —30°, (*c*, 5; benzene; *l*, 0.2), was obtained from 1.3 g of the (+)-*S*-(1-ferrocenylethyl)thioglycolic acid, $[\alpha]_{546}^{22}$ + 22.5° (*c*, 10; methanol; *l*, 0.1).

The rotation of the carbocation prepared by the dissolution of the alcohol in 100% trifluoroacetic acid was $[\alpha]_{546}^{25}$ +390° (*c*, 1; TFA; *l*, 0.1).

Synthesis of the (R)-(+)-S-(1-ferrocenylethyl)thioglycolic acid from (R)-(—)-1-ferrocenylethanol

The reaction was carried out under the same conditions as in the case of synthesis of the racemic acid. 0.133 g of the (*R*)-(+)-*S*-(1-ferrocenylethyl)thioglycolic acid in form of a dark-red oil, $[\alpha]_{546}^{19}$ + 20.5° (*c*, 8.8; methanol; *l*, 0.1) was obtained from 0.115 g (0.0005 mol) of the (*R*)-(—)-1-ferrocenylethanol $[\alpha]_{546}^{22}$ —30° (*c*, 5; benzene; *l*, 0.2).

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