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THIOMETHYLATION OF FERROCENE

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Summary

A one-step synthesis has been devised for making sulphides containing the ferrocenylmethyl group, of the type Fc—CH_2—S—R. These sulphides are formed by the reaction of ferrocene, formalin and a thiol, e.g. thioglycolic acid, in the presence of perchloric acid.

Introduction

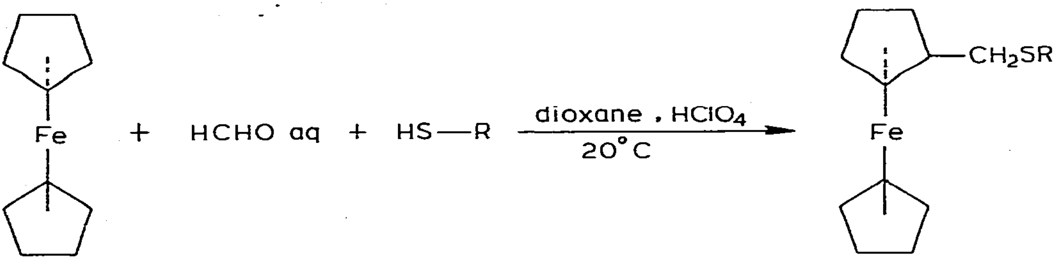
S-(1-Ferrocenylalkyl)thioglycolic acids are starting materials for the preparation of many other ferrocene derivatives. They react under mild conditions with mercuric chloride in water to form 1-ferrocenylalkyl alcohols, generally at high yields [1,2] while giving the corresponding methyl ethers in the presence of methanol [2], and amines containing the ferrocenylalkyl group in the presence of ammonia and primary or secondary amines [3,4]. A method for the formation of optically active 1-ferrocenylethanol [1] and 1-ferrocenylethylamine [3] involving a stereospecific cleavage of the C—S bond in (+)- and (—)-*S*-(1-ferrocenylethyl)thioglycolic acids has also been described.

Use of *S*-(1-ferrocenylethyl)thioglycolic acid gave optically active 1-ferrocenylethylamine, which is especially useful for the stereoselective synthesis of peptides [3]. Oxidation of the *S*-(ferrocenylmethyl)thioglycolic acid with manganese dioxide yields formylferrocene, and desulphurization by Raney nickel gives methylferrocene [5].

S-(Ferrocenylmethyl)thioglycolic acid has been previously prepared by the action of chloroacetic acid on sodium ferrocenylmethylthiolate [6], heating of ferrocenylmethanol with an excess of thioglycolic acid above 100°C [7], or reaction of stoichiomeric amounts of ferrocenylmethanol and thioglycolic acid in the presence of catalytic amounts of trifluoroacetic acid at room temperature [2].

Results and discussion

The method described below for preparing *S*-(ferrocenylmethyl)thioglycolic acid and its analogous, of general formula Fc—CH_2—S—R, consists of treatment of ferrocene with formalin (38% aqueous formaldehyde solution) and thioglycolic acid in dioxane in the presence of 60% perchloric acid as catalyst.

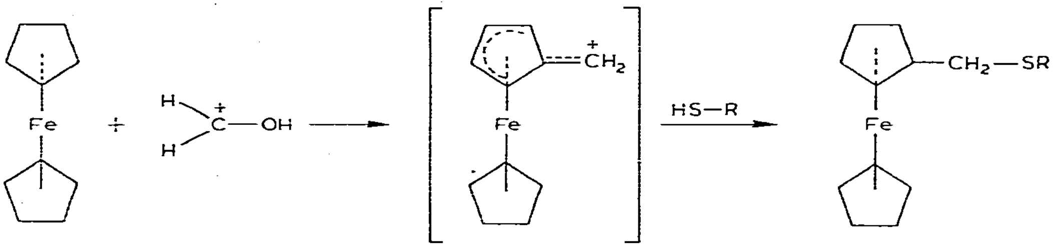


Thiosalicylic acid or 2-mercaptoethanol can be used instead of thioglycolic acid, to yield *S*-(ferrocenylmethyl)thiosalicylic acid and ferrocenylmethyl 2-hydroxyethyl sulphide respectively. We also examined the reaction of ferrocenylmethanol with thiosalicyclic acid in the presence of trifluoroacetic acid and found that the product obtained (yield 95%) was identical with the product II from thiomethylation of ferrocene.

The yields which are listed in Table 1 were in the range 60—67% which can be recorded as good taking into account the practicability of recovering the unreacted ferrocene from the reaction mixture.

For the reaction described, which gives compounds of the general formula Fc—CH_2—S—R we use the name "thiomethylation" of ferrocene. It resembles aminomethylation of ferrocene [8].

The thiomethylation probably involves electrophilic substitution of ferrocene by a protonated formaldehyde molecule (hydroxymethylation) followed by nucleophilic substitution (S_N1 mechanism) by the thiol (eq. 1).



(1)

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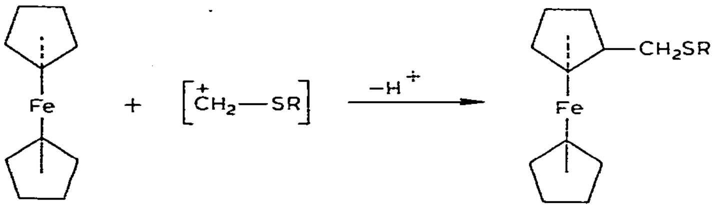

TABLE 1

THE PRODUCTS OF THIOMETHYLATION OF FERROCENE

Compound	R	% of ferrocene conversion	Yield (%) relative to ferrocene reacted
I	CH_2CO_2H	31	66
II	C_6H_4-*o*-CO_2H	30	67
III	CH_2CH_2OH	28	60

It is known that the reaction of ferrocene with formaldehyde under acidic conditions yields 1,2-diferrocenylethane, formed by dimerization of the cation radical [9]

$$C_5H_5FeC_5H_4CH_2^+ \rightleftharpoons C_5H_5FeC_5H_4CH_2^{\cdot}$$

In the case of the thiomethylation, if the ferrocenylmethyl cation is an intermediate then the presence of a thiol prevents this dimerization. The high reactivity of thiols towards 1-ferrocenylalkyl carbocations is well established [1,2].

An alternative mechanism (eq. 2) of formation of the Fc—CH_2—S—R compounds consists in formation of hemithioacetal $HOCH_2$—S—R from formaldehyde and thiol. In the presence of a strong acid the hemithioacetal would act as an electrophilic reagent towards ferrocene.

After several trials we have found that the system comprising ferrocene, formalin, thiol and perchloric acid in dioxane was the optimal one, and with it the reaction proceeds at room temperature. Attempts to shorten the reaction time by raising the temperature led to decomposition. With 85% phosphoric acid yields were comparable to those with perchloric acid, but the mixture had to be heated for 10 h under reflux. Use of 96% sulphuric acid in DMF yielded by-products which were difficult to separate.

Column chromatography enabled isolation of the main product of the thiomethylation with thioglycolic or thiosalicylic acids, and 5—10% of acidic material, probably a mixture of disubstituted thioalkyl derivatives 1,1′- and 1,2-isomers, was subsequently eluted.

Reactions of the *S*-(ferrocenylmethyl)thiosalicylic acid with water, methanol and amines in the presence of $HgCl_2$ are similar to those of the *S*-(ferrocenylmethyl)thioglycolic acid. Resolution of racemic *S*-(1-ferrocenylalkyl)thiosalicylic acids into their enantiomers may be advantageous because these would crystallize more readily [5].

Synthesis of the *S*-(ferrocenylmethyl)thioglycolic acid and its analogous by thiomethylation described here has the advantage of avoiding the necessity for preparing intermediate ferrocenylmethanol, which is a multi-step operation.

Taking into account the importance of chiral *S*-(1-ferrocenylalkyl)thioglycolic acids, it would be desirable to extend the reactions to use of aldehydes other than formaldehyde. Our preliminary trials with mixtures of ferrocene, acetaldehyde, thioglycolic acid and perchloric acid failed because of decomposition, but a successful preparation involving ferrocene, isobutyraldehyde and trifluoroacetic acid has been reported [10].

Experimental

For details of instrumentation and general remarks see [1].

S-(Ferrocenylmethyl)thioglycolic acid (I)

Ferrocene (1.86 g, 0.01 mol), thioglycolic acid (4.60 g, 0.05 mol), and formaldehyde (38%) (7.5 cm^3, 0.1 mol) were dissolved in 70 cm^3 of dioxane. The solution was cooled in a water-ice mixture and 10 cm^3 of 60% perchloric acid was added dropwise. The light red solution protected from air and was set aside for three days at room temperature. In order to remove some of the ferricenium ion formed 100 cm^3 of water and 10 mg of sodium dithionite were added. The solution was extracted with ether (3 X 50 cm^3), the extract was washed with water (5 X 20 cm^3) and extracted with 5% hydroxide solution. The ethereal layer was dried and evaporated leaving 0.980 g (53%) of ferrocene. The aqueous layer was acidified with 10% phosphoric acid (pH 5) and extracted with ether (3 X 20 cm^3).

The crude product was chromatographed on a silica gel column using a 10/1 benzene/acetone mixture as eluent. The product was the acid I (0.896 g, 66%); m.p. and spectroscopic data were identical with those reported previously [2]. A second fraction (ca. 10% yield) was eluted with acetone and probably consisted of a mixture of 1,1'- and 1,2-disubstituted acids.

S-(Ferrocenylmethyl)thiosalicylic acid (II)

The acid II (0.104 g, 67%), m.p. 177—178° C, was obtained from ferrocene (0.186 g, 0.001 mol) formaldehyde (0.75 cm^3, 0.01 mol) and thiosalicyclic acid (0.770 g, 0.005 mol), by the method described above. PMR (60 MHz), (δ, CD_3COCD_3); 4.03 (2H, s, CH_2), 4.24 (9H, s, $C_5H_5FeC_5H_4$), 7.05—8.10 (4H, m, C_6H_4). Mass spectrum (*m/e* (relative intensity)); M^+; 352(33), 274(25), 230(13), 200(18), 199(100), 181(12), 136(11), 121(53), 56(28). IR (cm^{-1}), (Nujol); 1680s (C=O). 0.102 g (55%) of unreacted ferrocene was recovered from the ethereal layer.

Ferrocenylmethyl-2-hydroxyethyl sulphide (III)

Applying the procedure used for the preparation of *S*-(ferrocenylmethyl)-thioglycolic acid, 0.077 g (60%) of the sulphide III was obtained from ferrocene (0.186 g, 0.001 mol), 2-mercaptoethanol (0.436 g, 0.005 mol) and formaldehyde (0.75 cm^3, 0.01 mol). The spectroscopic characteristics of the product were identical with those obtained from ferrocenylmethanol and 2-mercaptoethanol [2]. Some 0.098 g (53%), of the unreacted ferrocene was recovered.

Reaction of ferrocenylmethanol with thiosalicylic acid

Ferrocenylmethanol (1.08 g, 0.005 mol) and thiosalicylic acid (0.770 g, 0.005 mol) were dissolved in 20 cm^3 of 96% ethanol and 20 drops of trifluoroacetic acid were added. The solution was set aside for 24 h at room temperature. A crystalline yellow solid was filtered off and washed with ethanol at 0° C to give the acid II as orange crystals (1.672 g, 95%)

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