

Reactions of Ferrocenecarboxylic Acid and ω -Ferrocenyl- ω -oxoalkanoic Acids with 2-Aminothiophenol

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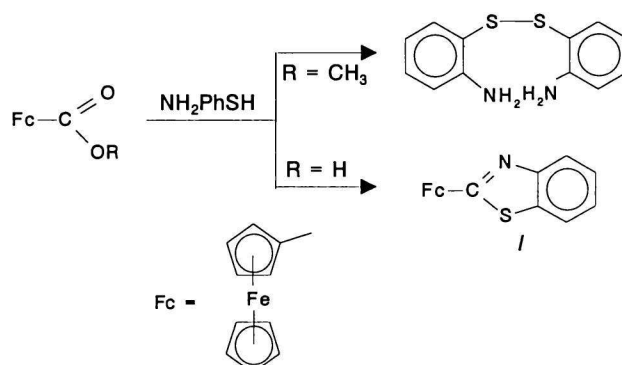
Received 30 June 1992

Reactions of the title compounds with 2-aminothiophenol have been studied. Ferrocenecarboxylic acid afforded 2-ferrocenylbenzothiazole, ω -ferrocenyl- ω -oxoalkanoic acids, depending on the number n of $-\text{CH}_2-$ groups, gave either 2-(ω -ferrocenyl- ω -oxoalkanoyl)benzothiazoles ($n = 3, 4$), or derivatives of ferrocenylbenzothiazocine ($n = 2$), resp. ferrocenylbenzothiazonine ($n = 3$). Some reactions of 2-ferrocenylbenzothiazole were studied, too.

2-Aminothiophenol is widely used as starting material at the synthesis of different type of heterocycles, especially benzothiazole derivatives [1, 2]. 2-Substituted benzothiazole derivatives can be prepared from 2-aminothiophenol and acyl chlorides [3], esters [4], or nitriles [5], etc. Recently 2-substituted derivatives of benzothiazole were prepared from esters and 2-aminothiophenol by heating both reagents to 180 °C with polyphosphoric acid as a catalyst [6]. Good yields of 2-substituted benzothiazoles were obtained in rather mild conditions when carboxylic acid and 2-aminothiophenol were heated to reflux of dichloroethane, with hexamethyldisiloxane and P_2O_5 as condensation agents [7].

The aim of this work was to find out whether those methods could be applied for the synthesis of 2-ferrocenylbenzothiazole as well as 2-(ω -ferrocenyl- ω -oxoalkanoyl)benzothiazoles. In the latter case the presence of carbonyl and carboxyl groups in one moiety could change the course of the reaction [8].

Results of our attempts at the synthesis of 2-ferrocenylbenzothiazole (I) from methyl ferrocenecarboxylate are presented in Scheme 1. Reaction of ferrocenecarbonyl chloride afforded desired 2-ferrocenylbenzothiazole in 30–50 % yields. The best method for the synthesis of the desired product proved to be reaction of ferrocenecarboxylic acid and 2-aminothiophenol with hexamethyldisiloxane and P_2O_5 . The reproducible yields (60–65 %) of 2-ferrocenylbenzothiazole (I) have been obtained (Scheme 1).



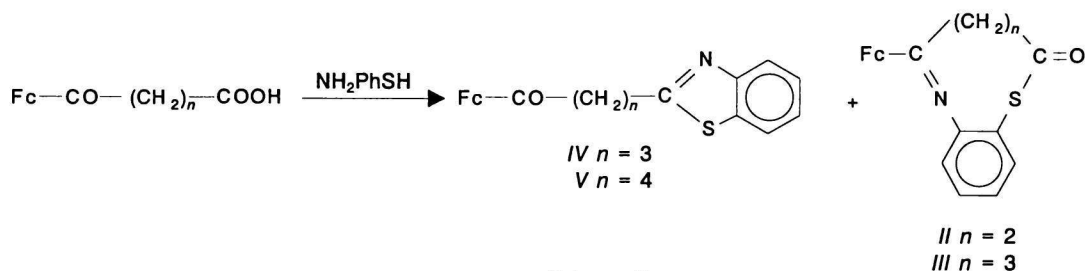
Scheme 1

The same conditions were applied in the reactions of 2-aminothiophenol with $\text{Fc}-\text{CO}-\text{(CH}_2\text{)}_n-\text{COOH}$, $n = 2, 3, 4$ (Scheme 2).

4-Ferrocenyl-4-oxobutanoic acid ($n = 2$) afforded 5-ferrocenylbenzo[*g*]-1,6-thiazocin-2-one (II) in 75 % yield. No other new product was isolated. It means that after acylation of $-\text{SH}$ group of 2-aminothiophenol condensation of $-\text{NH}_2$ group with the present $-\text{CO}-$ group took place.

5-Ferrocenyl-5-oxopentanoic acid ($n = 3$) gave two products, the ratio of which varied from 2 : 1 to 5 : 1. The first product was analogous with II, i.e. 6-ferrocenylbenzo[*h*]-1,7-thiazonin-2-one (III), the other one was 2-(4-ferrocenyl-4-oxobutyl)benzothiazole (IV).

6-Ferrocenyl-6-oxohexanoic acid ($n = 4$) afforded only benzothiazole derivative, i.e. 2-(5-ferrocenyl-5-

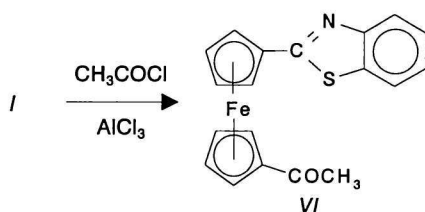


Scheme 2

oxopentyl)benzothiazole (V). From these results one can conclude that formation of the higher cycles by intramolecular reaction is a rather difficult task.

Having 2-ferrocenylbenzothiazole, we made some attempts to study its reactivity. First of all we made the attempts at its alkylation with methyl iodide and benzyl bromide. No reasonable results have been obtained, as complicated mixture of products was formed and we did not succeed in their isolation and purification.

Formation of ammonium salts does not seem to be favourable, as acetyl chloride with 2-ferrocenylbenzothiazole did not give corresponding ammonium salt, but product of Friedel–Crafts reaction was isolated as the sole new compound (Scheme 3). This can be explained by very high reactivity of ferrocene moiety (higher than the benzothiazole moiety) towards electrophilic reagents [9, 10]. The structure of 2-(1'-acetylferrocenyl)benzothiazole (VI) has been proved by elemental analysis and ^1H NMR spectrum.



Scheme 3

On the other hand, reactivity of benzothiazole moiety towards electrophilic reagents has to be higher than the reactivity of benzene, as nitration of 2-phenylbenzothiazole afforded 2-phenyl-5-nitrobenzothiazole as the main product [11, 12]. Nitration of 2-ferrocenylbenzothiazole could not be studied because ferrocene decomposes at those conditions.

EXPERIMENTAL

Melting points were determined on a Kofler block. Flash column chromatography was performed on a silica gel (Lachema, Brno; the size of particles ranging from 0.1555 to 0.42 nm), mixtures of hexane and ethyl acetate being eluent. ^1H NMR spectra of the prepared compounds were measured in CDCl₃ solutions on a B 8587 FT spectrometer (Tesla) with working frequency of 80 MHz and with tetramethylsilane as internal standard at 23 °C.

Reactions of 2-Aminothiophenol with Ferrocene Containing Carboxylic Acids

To a stirred mixture of P₂O₅ (0.005 mol) and hexamethyldisiloxane (0.015 mol) in dichloroethane (10

cm³) heated to reflux for 30 min under nitrogen, corresponding carboxylic acid (0.005 mol) and 2-aminothiophenol (0.01 mol) were added. Reaction mixture was heated to reflux and stirred for 2 h, then poured into 50 cm³ of 5 % solution of NaOH. Organic material was extracted into dichloromethane, washed with water and dichloromethane solution was dried over anhydrous Na₂SO₄ which was then filtered off and the solvent was evaporated. The residue was chromatographed and separated products were further purified by crystallization.

Ferrocenecarboxylic acid afforded 60–65 % of 2-ferrocenylbenzothiazole (I), deep red crystals, m.p. = 121–122 °C (hexane–benzene). For C₁₇H₁₃FeNS (*M_r* = 319.1) *w_i*(calc.): 63.96 % C, 4.10 % H, 4.38 % N, 17.49 % Fe; *w_i*(found): 64.44 % C, 4.14 % H, 4.39 % N, 17.00 % Fe. ^1H NMR spectrum, δ : 4.15 (s, 5H, C₅H₅), 4.48 (t, 2H, C₅H₄), 4.99 (t, 2H, C₅H₄), 7.25–8.15 (m, 4H, C₆H₄).

Preparation of 2-ferrocenylbenzothiazole (I) from ferrocenecarbonyl chloride and 2-aminothiophenol in benzene at room temperature afforded 30–50 % of the desired product, depending on the quality of the starting chloride.

Reaction of methyl ferrocenecarboxylate and 2-aminothiophenol by heating of both components with polyphosphoric acid to 180 °C gave the reaction mixture from which the starting ester and bis(2-aminophenyl) disulfide were isolated.

4-Ferrocenyl-4-oxobutanoic acid afforded 76 % of 5-ferrocenylbenzo[*g*]-1,6-thiazocin-2-one (II), orange crystals, m.p. = 149–151 °C (hexane–benzene). For C₂₀H₁₇FeNOS (*M_r* = 375.3) *w_i*(calc.): 64.01 % C, 4.56 % H, 3.73 % N, 14.88 % Fe; *w_i*(found): 64.37 % C, 4.44 % H, 3.70 % N, 14.74 % Fe. ^1H NMR spectrum, δ : 2.60–3.22 (m, 4H, CH₂), 4.02 (s, 5H, C₅H₅), 4.18 (br s, 4H, C₅H₄), 7.01–7.36 (m, 3H, C₆H₄), 7.60–7.77 (m, 1H, C₆H₄).

5-Ferrocenyl-5-oxopentanoic acid afforded 20–50 % of 6-ferrocenylbenzo[*h*]-1,7-thiazonin-2-one (III), orange-red crystals (from the first chromatographic fraction), m.p. = 165–168 °C (hexane–benzene). For C₂₁H₁₉FeNOS (*M_r* = 389.2) *w_i*(calc.): 64.80 % C, 4.92 % H, 3.59 % N, 14.46 % Fe; *w_i*(found): 65.63 % C, 4.94 % H, 3.48 % N, 13.59 % Fe. ^1H NMR spectrum, δ : 1.37–1.75 (m, 2H, CH₂), 2.0–2.65 (m, 4H, CH₂), 3.75 (s, 5H, C₅H₅), 3.95–4.22 (m, 4H, C₅H₄), 6.97–7.37 (m, 3H, C₆H₄), 8.13–8.32 (m, 1H, C₆H₄).

From the second fraction 10–12 % of 2-(4-ferrocenyl-4-oxobutyl)benzothiazole (IV) was isolated in the form of orange-red crystals, m.p. = 92–96 °C. For C₂₁H₁₉FeNOS (*M_r* = 389.2) *w_i*(calc.): 64.80 % C, 4.92 % H, 3.59 % N, 14.46 % Fe; *w_i*(found): 65.23 % C, 4.94 % H, 3.57 % N, 14.20 % Fe. ^1H NMR spectrum, δ : 2.1–2.5 (m, 2H, CH₂), 2.88 (t, 2H, CH₂),

3.25 (t, 2H, CH₂), 4.17 (s, 5H, C₅H₅), 4.47 (t, 2H, C₅H₄), 4.77 (t, 2H, C₅H₄), 7.25–7.55 (m, 2H, C₆H₄), 7.75–8.12 (m, 2H, C₆H₄).

6-Ferrocenyl-6-oxohexanoic acid afforded 12 % of 2-(5-ferrocenyl-5-oxopentyl)benzothiazole (V), orange-red crystals, m.p. = 80–81.5 °C. For C₂₂H₂₁FeNOS (*M_r* = 403.3) *w_i*(calc.): 65.52 % C, 5.24 % H, 3.47 % N, 13.84 % Fe; *w_i*(found): 65.61 % C, 5.22 % H, 3.46 % N, 14.05 % Fe. ¹H NMR spectrum, δ: 1.94 (m, 4H, CH₂), 2.77 (t, 2H, CH₂), 3.17 (t, 2H, CH₂), 4.17 (s, 5H, C₅H₅), 4.49 (t, 2H, C₅H₄), 4.78 (t, 2H, C₅H₄), 7.25–8.10 (m, 4H, C₆H₄).

Acetylation of 2-Ferrocenylbenzothiazole

To a stirred mixture of 2-ferrocenylbenzothiazole (15 mmol) and acetyl chloride (30 mmol) in dichloromethane (30 cm³) anhydrous AlCl₃ (37 mmol) was added during 30 min under nitrogen atmosphere. Reaction mixture was stirred at room temperature for 2 h, then poured into 100 cm³ of water. Organic material was extracted into dichloromethane, dichloromethane solution was dried over anhydrous Na₂SO₄. After filtering Na₂SO₄ and evaporation of the solvent, the residue was chromatographed. From the first fraction 3 % of starting 2-ferrocenylbenzothiazole was isolated; from the next fraction 95 % of 2-(1'-acetylferrocenyl)benzothiazole (VI), red crystals, m.p. = 87 °C (hexane–benzene), was isolated.

For C₁₉H₁₅FeNOS (*M_r* = 361.2) *w_i*(calc.): 63.18 % C, 4.18 % H, 3.87 % N, 15.46 % Fe; *w_i*(found): 63.93 % C, 4.28 % H, 3.80 % N, 15.25 % Fe. ¹H NMR spectrum, δ: 2.34 (s, 3H, CH₃), 4.51 (t, 2H, C₅H₄), 4.57 (t, 2H, C₅H₄), 4.79 (br s, 2H, C₅H₄), 5.08 (br s, 2H, C₅H₄), 7.3–7.67 (m, 2H, C₆H₄), 7.8–8.2 (m, 2H, C₆H₄).

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Translated by M. Sališová