Isolation of Three Possible Glycols of 2,5-Bis(hydroxybenzyl)-η^6-thiophenetricarbonylchromium

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Quenching of (η^6-2,5-dilithiothiophene)tricarbonylchromium with an excess of benzaldehyde resulted in the formation of three possible glycols *IIa*—*IIc* in the mass ratio 9:10:1, which were separated by flash chromatography. Complexes *IIa* and *IIc* proved to be two possible pseudoasymmetric *meso* forms, and *IIb* represented the *threo*-D,L pair. Decomplexation (O_2, $h\nu$) of *IIa* and *IIb* yielded pure, crystalline diastereomers of the free ligand. Similar behaviour was observed using n-butyraldehyde, i-butyraldehyde, and cinnamaldehyde as the quenching electrophile.

The concept of pseudoasymmetry in organic molecules having two identical chiral carbon atoms is well documented [1]. It is predicted that in such a case three possible stereoisomers could be isolated. The real isolation of these stereoisomers is usually complicated, and pseudoasymmetric α-glycols derived from benzene or pyridine were described as unseparable mixtures very recently [2]. On the other hand, two papers describing the successful isolation of the three stereoisomers of organometallic compounds were published [3, 4]. *Moise* [3] described the synthesis of pseudoasymmetric glycols of 1,2-disubstituted ferrocene derivatives, and *Besançon et al.* [4] have published the similar results with 1,2-disubstituted benzenetricarbonylchromium complexes. The ratio of the stereoisomers depends upon the way of preparation of glycol.

In our previous paper [5] we investigated the diastereoselectivity of the addition of (η^6-2-lithiothiophene)tricarbonylchromium, prepared by n-BuLi metallation of the parent (η^6-thiophene)tricarbonylchromium, to the different aromatic aldehydes. Only moderate diastereoselectivity (mass ratio of diastereoisomers 2.1—4.5:1) was observed. The 2,5-dimetallation of thiophene was described [6] and therefore it was of interest to study the dimetallation of (η^6-thiophene)tricarbonylchromium as well as the reactivity of intermediate.

The best results of the dimetallation of (η^6-thiophene)tricarbonylchromium were achieved when 2.5 mol of n-butyllithium was used, and the metallation was carried out in THF at −78 °C. The course of the metallation was followed by quenching the metallation product with an excess (3 mol) of benzaldehyde at the same temperature. The overall yield was 65 %. TLC of the reaction mixture revealed the presence of two main orange materials as well as the presence of a very tiny quantity of the third complex and a spot of the mixture of the decomplexed material (the R_f values were as follows: 0.32, 0.27, 0.21, and 0.14, respectively). The very low stability of the thiophene complexes caused problems at the separation of diastereomers. Nevertheless, the flash chromatography on silica column under the positive nitrogen pressure, using benzene—ethyl acetate mixture ($\varphi_r = 10:1$) as the eluent afforded the pure complexes, as shown in Scheme 1.

All materials had the satisfactory elemental analysis (C, H) and the structure assignation was based on their ^{1}H NMR spectra. In the *meso* forms of the complexes (*IIa* and *IIc*), both thiophene H_3 and H_4 protons should be in an equal diamagnetic field, and their chemical shift should be a singlet. In the *threo*-D,L pair (*IIb*) the protons mentioned above should be in a different diamagnetic field and therefore two doublets should be observed. In the ^{1}H NMR spectra of the complexes, measured in C_6D_6, multiplets of the phenyl ring protons centred at δ = 7.03 (10H) were observed but all other signals were different in accordance with the anticipation stated above.

The diastereomer *IIa*, ^{1}H NMR spectrum, δ: 4.91 (2H, d, J = 3.9 Hz, 2 × CH), 4.39 (2H, s, ThH), 1.80 (2H, d, J = 3.9 Hz, 2 × OH); the diastereomer *IIb*, δ: 4.97 (1H, d, J = 3.9 Hz, CH), 4.87 (1H, d, J = 3.9 Hz, CH), 4.70 (1H, d, J = 3.3 Hz, ThH), 4.40 (1H, d, J = 3.3 Hz, ThH), 1.96 (1H, d, J = 3.1 Hz, OH), 1.72 (1H, d, J = 3.1 Hz, OH); the diastereomer *IIc*, δ: 4.91 (2H, d, J = 3.9 Hz, 2 × CH), 4.70 (2H, s, ThH), 1.78 (2H, d, J = 3.9 Hz, 2 × OH).

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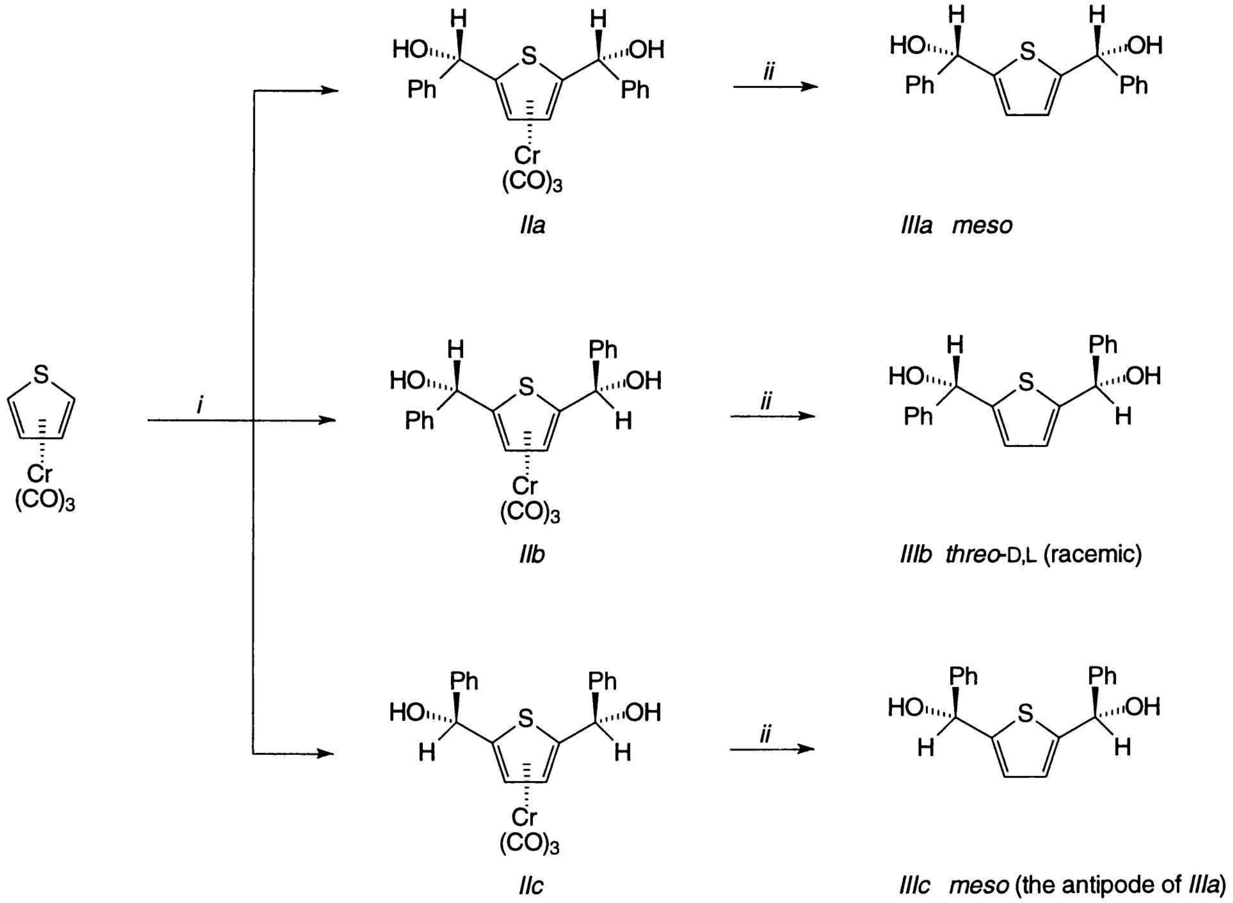

Scheme 1
Reagents and conditions: *i*) BuLi (2.5 M excess), THF at − 78 °C, then benzaldehyde: *ii*) *hν*, O_2, EtOH.

From the results mentioned above it follows that complexes *IIa* and *IIc* are two possible forms of the *meso* form (R,R and S,S or *vice versa*, respectively). The observed mass ratio of the isomers (8:10:1) (see Experimental) could be caused by the fact that the configuration of the diol complex can be fixed by the interaction of the OH groups with the Cr atom, then in the first *meso* form the large substituent (Ph group) is far away from the S atom (*IIa*) and in the second *meso* form it is close to the S atom (*IIc*). The interaction of OH-α group with the chromium atom in tricarbonylchromium complexes was proved several years ago [7, 8].

Exposure of the ethanolic solution of *IIa* to the sunlight afforded, after work-up, the microcrystalline powder of the *meso* form of the free ligand *IIIa* (m.p. = 55—56 °C), and the same procedure starting from *IIb* afforded the *threo*-D,L pair of the free ligand *IIIb* (m.p. = 128—138 °C) as white needles. Analogously, the complex *IIc* yielded *IIIc* (the antipode of *IIIa*) with the melting point' identical with *IIIa*. The ^{1}H NMR spectra of both isomers *IIIa* and *IIIb* were identical. The attempts at the chromatographic separation of *IIIa* and *IIIb* from their mixture were unsuccessful (in spite of the fact that their R_f values differ approximately by 0.03 using petroleum ether—diethyl ether (φ_r = 1 : 1) as the eluent at their TLC on SiO_2).

Preliminary experiments, we made, proved that quenching of (η^6-2,5-dilithiothiophene)tricarbonylchromium with n-butyraldehyde, i-butyraldehyde, and cinnamaldehyde gave similar results (the complexes in the mass ratio 1:1:0.1 were formed). Isolation of the isomers was not possible due to their easy decomplexation. Our attempts at isolation of the three possible glycols of 1,4- and 1,3-bis(α-hydroxyethyl)-η^6-2,5-benzenetricarbonylchromium failed, too. The results mentioned above allow us to suggest that at least in some cases diastereomers of some aromatic derivatives can be separated *via* their tricarbonylchromium complexes.

EXPERIMENTAL

The reactions were performed in flame-dried glassware under an atmosphere of argon and all solvents were deoxygenated. THF was distilled from

$LiAlH_4$ under an argon atmosphere just before use. Benzene and thiophene were distilled from sodium. n-Butyllithium (Aldrich Chemical Company) was used as a solution in hexane (c = 2.5 mol dm^{-3}). Benzaldehyde was purified by distillation under reduced pressure. The preparation of tricarbonyl(η^6-thiophene)chromium(0) was described in our previous paper [5]. Flash chromatography was performed on a silica gel (d = 40—100 μm) under a positive nitrogen pressure.

Melting points were determined on a Kofler hot-stage apparatus. ^{1}H NMR spectra were recorded in deuterochloroform at 80 MHz, with tetramethylsilane as internal standard.

Tricarbonyl[η^6-2,5-bis(hydroxyphenylmethyl)-thiophene]chromium(0) (*IIa—IIc*)

To a stirred solution of tricarbonyl (η^6-thiophene)chromium(0) (*I*) (110 mg; 0.5 mmol) in THF (20 cm^3) cooled to −78 °C n-butyllithium (0.5 cm^3, 1.25 mmol) was added dropwise. The solution was stirred at −78 °C for 1 h. Benzaldehyde (0.3 cm^3, 3 mmol) was added dropwise and stirring continued (−78 °C, 30 min). The reaction mixture was allowed to warm up to 0 °C, then it was poured into ice water (100 cm^3) containing 0.2 cm^3 of concentrated HCl and extracted with benzene (100 cm^3). The organic extract was dried (Na_2SO_4) and evaporated under reduced pressure to give a residue which was immediately fractionated by flash chromatography under nitrogen atmosphere with benzene—ethyl acetate (φ_r = 20:1) as the eluent. Hexamethylenetetramine (HMTA) (3.5 mg; 0.025 mmol) was added to each fraction as an internal standard (δ(H) = 4.69). After evaporation under reduced pressure the fractions were analyzed by ^{1}H NMR spectroscopy. The separated diastereomers were crystallized from benzene—light petroleum. In this way, the diastereomer *IIa* was obtained as orange needles (35 mg, 16 %), m.p. = 120 °C (decomp., transparent needles became dark maintaining the shape). w_i(Found): 58.2 % C, 3.8 % H. w_i($C_{21}H_{16}O_5CrS$): 58.3 % C, 3.70 % H; ^{1}H NMR spectrum, δ(H): 7.37 (10H, m, 2 × PhH), 5.58 (2H, d, J = 3.9 Hz, 2 × CH), 5.16 (2H, s, ThH), 2.66 (2H, d, J = 3.9 Hz, 2 × OH); R_f(benzene—ethyl acetate (φ_r = 10:1)) = 0.32; the diastereoisomer *IIb* as orange powder (43 mg, 20 %), m.p. = 49—51 °C, w_i(found): 58.7 % C, 3.9 % H. w_i($C_{21}H_{16}O_5CrS$): 58.3 % C, 3.70 % H; δ(H): 7.38 (10H, m, 2 × PhH), 5.63 (1H, d, J = 3.1 Hz, CH), 5.30 (1H, d, J = 3.3 Hz, ThH), 5.14 (1H, d, J = 3.3 Hz, ThH), 2.67 (1H, d, J = 3.1 Hz, OH), 2.46 (1H, d, J = 3.1 Hz, OH); R_f(benzene—ethyl acetate (φ_r = 10:1)) = 0.27; and the orange diastereoisomer *IIc* (4 mg, 2 %), m.p. = 63—65 °C, identified on the basis of ^{1}H NMR spectrum, δ(H): 7.37 (10H, m, 2 × PhH), 5.54 (2H, bs, 2 × CH), 5.31 (2H, s, ThH). R_f(benzene—ethyl acetate (φ_r = 10:1)) = 0.21. The fourth fraction was the colourless decomplexed ligand *IIIa* and *IIIb* (35 mg, 24 %).

2,5-Bis(hydroxyphenylmethyl)thiophene (*meso* Form) (*IIIa*)

The ethanolic solution of *IIa* had been exposed to sunlight for several hours until the bright orange colour of solution disappeared. After evaporation, the residue was dissolved in diethyl ether, filtered and recrystallized from diethyl ether—light petroleum yielding almost quantitatively the *meso* form *IIIa* as white microcrystalline powder, m.p. = 55—56 °C, w_i(found): 72.6 % C, 5.6 % H. w_i($C_{18}H_{16}O_2S$): 73.0 % C, 5.40 % H; δ(H): 7.37 (10H, m, 2 × PhH), 6.71 (2H, s, ThH), 5.97 (2H, d, J = 3.7 Hz, 2 × CH); R_f(benzene—ethyl acetate (φ_r = 10:1)) = 0.14.

2,5-Bis(hydroxyphenylmethyl)thiophene (racemic form) *IIIb* was prepared from the diastereoisomer *IIb* by the same procedure as *IIIa*. Recrystallization from diethyl ether—light petroleum afforded almost quantitative yield of the racemic form *IIIb* as white needles, m.p. = 128—130 °C, w_i(found): 72.5 % C, 5.5 % H. w_i($C_{18}H_{16}O_2S$): 73.0 % C, 5.40 % H; ^{1}H NMR spectrum and R_f(benzene—ethyl acetate (φ_r = 10:1)) value were identical with the *meso* form *IIIa*.

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