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Ferrocene Derivatives, Part 69 [1] Preparative Separation of Isomeric Trisubstituted Ferrocenes

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Summary. Mixtures of positional isomers of trisubstituted ferrocenes can conveniently be separated on a preparative scale by applying medium-pressure liquid chromatography to suitable intermediates. By this technique formyl, hydroxymethyl, and dimethylaminomethyl 1,2-dimethyl- and 1,2-tetramethylene ferrocene, resp., (**2, 3, 4** and **6, 7, 8**, resp.) were prepared as pure isomers (on a gram-scale) by appropriate interconversion and chromatographic separation steps.

Keywords. Isomeric formyl and dimethylaminomethyl ferrocenes; Mannich reaction; Medium pressure chromatography.

Präparative Isomerentrennung von trisubstituierten Ferrocenen. 69. Mitt. über Ferrocenderivate

Zusammenfassung. Mischungen von stellungsisomeren, trisubstituierten Ferrocenen können auch im präparativen Maßstab unter Anwendung der Mitteldruckchromatographie auf geeignete Zwischenprodukte glatt getrennt werden. Mit Hilfe dieser Technik wurden Formyl-, Hydroxymethyl- und Dimethylaminomethyl-1,2-dimethyl- bzw. 1,2-tetramethylen-ferrocen (**2, 3, 4** bzw. **6, 7, 8**) durch Anwendung geeigneter Umwandlungs- und Chromatographie-Schritte im Grammaßstab isomerenrein erhalten.

Introduction

Derivatives of ferrocene are of considerable interest not only from theoretical and stereochemical but also from an increasing practical point of view. Therefore from the beginning of ferrocene chemistry synthetic aspects have been in the center of attention [2]. Although several of the abundant aromatic substitution reactions can be applied to ferrocene (though with some restrictions), the general problem of regioselective polysubstitution seems to remain unsolved to a large extent [2, 3].

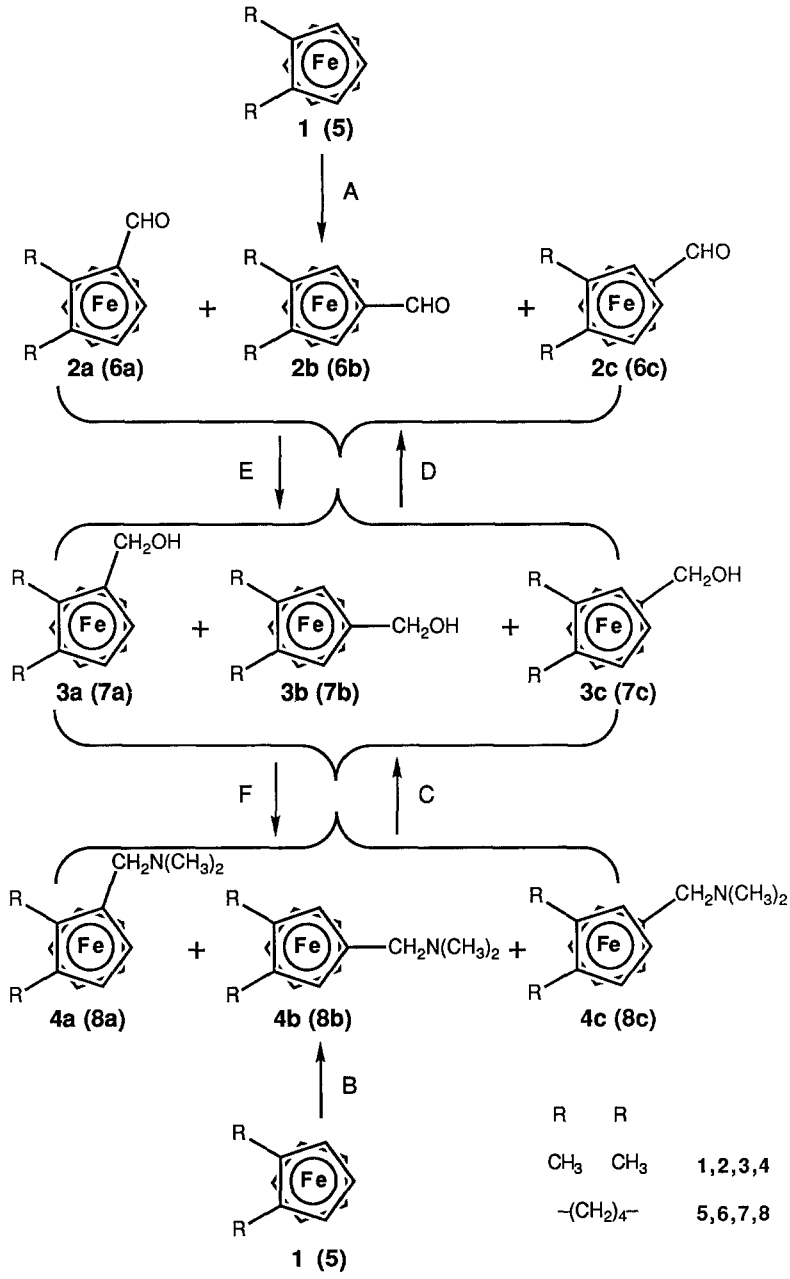
Whereas, e.g. for a trisubsituted ferrocene with three equal residues four positional isomers are possible, a substitution pattern A, A, B gives rise to 10 isomers (4 homo- and 6 heteroannular products, 4 of which are chiral and 6 are achiral) [4].

Apart from several 1,2-disubstituted ferrocenes which are selectively accessible by *ortho*-lithiation [2] the preparation of pure positional isomers requires (sometimes tedious) chromatographic separation methods.

We wish now to report that isomeric mixtures of trisubstituted ferrocenes can conveniently be separated into their components on a preparative scale by applying sequential chromatographic steps to appropriate interconvertible derivatives.

Results and Discussion

For the intended synthesis of torsional-isomeric biferrocenyls [5] we were interested in the preparation of pure C_s-symmetrical trisubstituted ferrocenes, such as (N,N-dimethylaminomethyl) dialkylferrocenes (**4b** and **8b**, resp.). The required starting



Scheme 1

compounds, 1,2-dimethyl and 1,2-tetramethylene ferrocene (**1** and **5**) are easily available, also in somewhat larger amounts [6]. The direct Mannich reaction of **1** and **5**, resp., as described in the literature [6a] affords mixtures of isomeric *mono*- and *bis*-Mannich bases. Under very mild conditions, however, (see exprimental part) the *mono*-substituted products **4a–c** and **8a–c** were obtained exclusively in ratios of 4:3:3 and 2:2:1, resp. (cf. Table 1). Their syntheses were also attempted via the corresponding aldehydes by the sequence A-E-F as outlined below (see Scheme 1).

Vilsmeyer formylation of **1** and **5**, resp., afforded the expected mixture of the three possible isomeric aldehydes: **2a**, **2b**, **2c** (1:2:1) and **6a**, **6b**, **6c** (2:3:1). Even under varied reaction conditions no preference for the symmetrical products **2b** and **6b** could be observed.

Preparative medium pressure chromatography (MPLC) of the mixtures on Al_2O_3 in petroleum ether/ethylacetate (9:1) yielded two fractions, *A* and *B*, containing **2a** and **2c** (**6a** and **6c**) [*A*] on the one hand and **2b** (**6b**) [*B*] on the other. Employing a preparative column (see experimental part) 1.5 g of the mixtures could be separated within 7 h into TLC-pure isomeres. A further separation of fraction *A* was possible after transformation of the aldehydes **2** (**6**) **a** and **c** into the Mannich bases **4** (**8**) **a** and **c**, which subsequently were separated by MPLC on Al_2O_3 or silicagel in petroleum ether/triethylamine (5:1).

Table 1. Trisubstituted ferrocenes

Compound[a]		Prepared by route (see Scheme)	Yield[b]	Route	Yield[b]	*Rf*-value[c]
2a	$C_{13}H_{14}FeO$	A-E-F-C-D	19	B-C-D	36	0.40
6a	$C_{15}H_{16}FeO$	A-E-F-C-D	19	B-C-D	33	0.42
2b	$C_{13}H_{14}FeO$	A	50	B-C-D	27	0.34
6b	$C_{15}H_{16}FeO$	A	48	B-C-D	32	0.34
2c	$C_{13}H_{14}FeO$	A-E-F-C-D	19	B-C-D	26	0.40
6c	$C_{15}H_{16}FeO$	A-E-F-C-D	10	B-C-D	16	0.42
3a	$C_{13}H_{16}FeO$	A-E-F-C	19	B-C	34	0.37
7a	$C_{15}H_{18}FeO$	A-E-F-C	20	B-C	33	0.36
3b	$C_{13}H_{16}FeO$	A-E	46	B-C-D-E	25	0.37
7b	$C_{15}H_{18}FeO$	A-E	45	B-C-D-E	30	0.36
3c	$C_{13}H_{16}FeO$	A-E-F-C	18	B-C-D-E	25	0.37
7c	$C_{15}H_{18}FeO$	A-E-F-C	11	B-C-D-E	15	0.36
4a	$C_{15}H_{21}FeO$	A-E-F	21	B	39	0.72
8a	$C_{17}H_{23}FeO$	A-E-F	22	B	37	0.64
4b	$C_{15}H_{21}FeO$	A-E-F	36	B-C-D-E-F	14	0.65
8b	$C_{17}H_{23}FeO$	A-E-F	33	B-C-D-E-F	22	0.48
4c	$C_{15}H_{21}FeO$	A-E-F	20	B-C-D-E-F	13	0.65
8c	$C_{17}H_{23}FeO$	A-E-F	12	B-C-D-E-F	11	0.46

[a] All compounds were characterized by their MS-spectra which are in agreement with the proposed structures. For ^{1}H-NMR see Table 2

[b] Isolated yields (based on recovered starting material)

[c] Al_2O_3 in petroleum ether/ethylacetate (9:1) for **2** and **6**; in petroleum ether/ethylacetate (7:4) for **3** and **7**; in petroleum ether/triethylamine (5:1) for **4** and **8**

Subsequently the amines can then be transformed into the corresponding aldehydes (i.e. **4** → **2**, **8** → **6**) by established synthetic methods [7]. The overall yields of isomerically pure amines amount to 72% (**4a–c**) and 67% (**8a–c**), resp. The yields recovered after the chromatographic purification are approx. 95%.

In addition to the aldehydes and amines mentioned, the ferrocenylmethanols **3** (**7**) are easily accessible either by reduction (from **2** or **6**) or by nucleophilic substitution of the trimethylammonium iodides derived from **4** (**8**) with OH^- (routes E and C, resp.)

Thus all isomeric trisubstituted ferrocenes shown in the scheme are accessible from two sides; depending on the desired isomer in every case the more convenient synthetic route may be applied (see Table 1).

Experimental Part

The syntheses of **2a** and **4b** are described in the following as typical examples for the reactions as outlined in Scheme 1. Conversions of corresponding derivatives were performed by analogous reactions.

Measurements: MS: Varian MAT-CH7; ^{1}H-NMR: Bruker WM 250 in $CDCl_3$ with tetramethylsilane as internal standard; m.ps.: Kofler-melting point apparatus, uncorrected.

A: *Vilsmeyer-Formylation of* **1**: *Dimethyl-formylferrocenes* (**2a–c**)

1.53 g (0.01 mol) of $POCl_3$ were added dropwise to a cooled solution of 2.14 g (0.01 mol) of 1,2-dimethylferrocene **1** in 1.35 g (0.01 mol) of N-methylformanilide and stirred at 0°C under Ar for 15 h. The resulting dark-red oil was quenched with 10 ml of 2 *M* NaOH and extracted with three 30 ml portions of ether. The combined organic extracts were washed thoroughly with water and dried over $MgSO_4$. After removal of the solvent, the residue was taken up in hexane/ethylacetate (9 : 1) and chromatographed on alumina (Woelm; 40–63 µm; column 47 × 3.5 cm). Elution with petroleum ether [hexane fraction, b.p.: 65–67°C/ethylacetate (9 : 1)] yielded three fractions: From the first band 0.38 g (18%) of unreacted starting material was recovered. The second band gave 0.86 g (42%) of a mixture of **2a** and **2c**, as shown by NMR. From the third band 1.02 g (50%) of (TLC-pure) **2b** was obtained which crystallized upon slow evaporation of the solvent; m.p.: 54–56°C. The maximum capacity of the column was appr. 300 mg per run. (For data of **2a–c** see Tables 1 and 2.)

E: *3,4-Dimethyl-hydroxymethylferrocene* (**3b**)

An excess of sodiumborohydride (0.16 g) was added to a solution of 1 g (4.13 mmol) of **2b** in 50 ml of ethanol-dioxane (4 : 1). After stirring for 1 h at r.t. the reaction mixture was poured into 150 ml of water and extracted with four 25 ml portions of ether. The organic layer was washed with water (3 × 25 ml) and dried over $MgSO_4$. After removal of the solvent under vacuum, the remaining oil crystallized after a few days to give 0.98 g (97%) of **3b** as yellow needles, m.p.: 30–32°C (see Table 1 and 2).

F: *3,4-Dimethyl-N,N-dimethylaminomethylferrocene* (**4b**)

A solution of 4.0 g (16.4 mmol) of **3b** in 25 ml of toluene was added dropwise at −20°C to a stirred solution of 2.05 g (20.7 mmol) of phosgene in toluene (15 ml) during 90 min. Subsequently the reaction mixture was allowed to warm to r.t. and (without isolation of the chloride) added at −20°C to a solution of 3.70 g (82 mmol) dimethylamine in 30 ml of isopropyl alcohol. After warming to 20°C the mixture was filtered and the solution evaporated to dryness. The residue was then taken up in benzene,

Table 2. ^{1}H-n.m.r.-data of ferrocenes **1–8** (250 MHz; δ-values in $CDCl_3$ relative to *TMS*)

Comp.	*Fc*-CH_3	*Fc*-H (ring 1)	*Fc*-H (ring 2)	*Fc*-CH_2–	–$N(CH_3)_2$/–CHO
1	1.91 (s, 6H)	3.96 (s, 8H)[a]			
2a	2.02 (s, 3H), 2.19 (s, 3H)	4.45 (d, 1H), 4.59(d,1H) J = 3 Hz	4.08 (s, 5H)		10.05 (s, 1H)
2b	2.03 (s, 6H)	4.64 (s, 2H)	4.09 (s, 5H)		9.82 (s, 1H)
2c	1.86 (s, 6H)	4.10 (m, 7H)			9.86 (s, 1H)
3a	1.88 (s, 3H), 1.92 (s, 3H)	4.23 (m, 2H)[b]	3.98 (s, 5H)	4.23 (m, 2H)[b]	
3b	1.93 (s, 6H)	4.09 (s, 2H)	4.00 (s, 5H)	4.21 (s, 2H)	
3c	1.90 (s, 6H)	3.98 (m, 7H)		4.26 (s, 2H)	
4a	1.92 (s, 3H), 1.94 (s, 3H)	3.94 (d, 1H), 3.97(d,1H) J = 2.5 Hz	3.91 (s, 5H)	3.18 (d, 1H), 3.35 (d, 1H) J = 12.4 Hz	2.15 (s, 6H)
4b	1.89 (s, 6H)	4.00 (s, 2H)	3.89 (s, 5H)	3.22 (s, 2H)	2.14 (s, 6H)
4c	1.90 (s, 6H)	3.94 (s, 3H)[a]	3.88 (m, 4H)	3.15 (s, 2H)	2.13 (s, 6H)

Comp.	–$(CH_2)_4$–	*Fc*-H (ring 1)	*Fc*-H (ring 2)	*Fc*-CH_2–	–$N(CH_3)_2$/–CHO
5	1.63 (m, 2H), 1.87 (m, 2H), 2.34 (m, 2H), 2.58 (m, 2H)	4.01 (s, 8H)[a]			
6a	1.74 (m, 2H), 1.97 (m, 2H), 2.63 (m, 2H), 2.86 (m, 2H)	4.42 (d,1H), 4.56(d,1H) J = 3 Hz	4.06 (s, 5H)		10.08 (s, 1H)
6b	1.71 (m, 2H), 1.86 (m, 2H), 2.45 (m, 2H), 2.60 (m, 2H)	4.65 (s, 2H)	4.15 (s, 5H)		9.90 (s, 1H)
6c	1.65 (m, 2H), 1.87 (m, 2H), 2.26 (m, 2H), 2.48 (m, 2H)	4.12 (m, 7H)			9.93 (s, 1H)
7a	1.66 (m, 2H), 1.86 (m, 2H), 2.34 (m, 2H), 2.54 (m, 2H)	4.27 (m, 2H)[b]	4.03 (s, 5H)	4.27 (m, 2H)	
7b	1.64 (m, 2H), 1.88 (m, 2H), 2.33 (m, 2H), 2.57 (m, 2H)	4.12 (s, 2H)	4.04 (s, 5H)	4.25 (s, 2H)	
7c	1.65 (m, 2H), 1.82 (m, 2H), 2.35 (m, 2H), 2.50 (m, 2H)	4.02 (m, 7H)		4.30 (s, 2H)	
8a	1.63 (m, 2H), 1.92 (m, 2H), 2.33 (m, 2H), 2.62 (m, 2H)	3.99 (d, 1H), 4.04(d,1H) J = 3 Hz	3.94 (s, 5H)	3.25 (d, 1H), 3.34 (d, 1H) J = 12.8 Hz	2.18 (s, 6H)
8b	1.62 (m, 2H), 1.87 (m, 2H), 2.31 (m, 2H), 2.55 (m, 2H)	4.03 (s, 2H)	3.95 (s, 5H)	3.19 (s, 2H)	2.18 (s, 6H)
8c	1.63 (m, 2H), 1.89 (m, 2H), 2.32 (m, 2H), 2.58 (m, 2H)	4.00 (s, 3H)[a]	3.93 (m, 4H)	3.27 (s, 2H)	2.18 (s, 6H)

[a] broad singulet
[b] overlapping

extracted with diluted H_3PO_4 (8.5%), washed with benzene, neutralized with Na_2CO_3 and finally extracted with benzene. After drying and evaporation of the solvent the residue (3.44 g) was purified by Kugelrohr-distillation (0.01 Torr, 120–130°C bath temp.) to give 2.92 g (66%) of pure **4b** (see Tables 1 and 2).

B: *Mannich Reaction of* **1**: *Dimethyl-N,N-dimethylaminomethylferrocenes* (**4a–c**)

2.14 g (0.01 mol) of dimethylferrocene (**1**) was added to a well stirred solution of 1.02 g (0.01 mol) of bis(dimethylamino)methane and 1.0 g of phosphoric acid in 20 ml of acetic acid. The resulting suspension was stirred under a slow stream of Ar for 12 h. Then the mixture was diluted with 25 ml of water. Unreacted **1** (0.6 g, 28%) was recovered by extraction with 3 × 25 ml of ether. The aqueous solution was then cooled to 0°C and made alkaline by adding 10 g of NaOH, whereupon the amine separated as an oil. The mixture was then extracted with three 25 ml portions of ether. The combined extracts were washed with water and dried over $MgSO_4$. After evaporation the crude mixture was purified by chromatography on alumina or silicagel (Al_2O_3: Woelm 40–63 μm, 47 × 3.5 cm; SiO_2: Merck Kieselgel 60, 30 × 3.5 cm). Elution with ether/triethylamine (5 : 1) yielded two fractions: The first one contained pure **4a**, while the second one consisted of a mixture of **4b** and **4c** (NMR see Table 2). Several runs gave a total of 0.83 g (39%) of **4a** and 1.25 g (60%) of **4b** and **4c** (see Tables 1 and 2).

C: *2,3-Dimethyl-hydroxymethylferrocene* (**3a**)

To a solution of **4a** (830 mg, 3.1 mmol) in 10 ml of methanol an excess of methyliodide was added, and the solution was left at r.t. for 30 min. After evaporation to dryness the residue was taken up in 20 ml of 2*N* NaOH and heated to reflux until the evolution of trimethylamine had ceased (about 2 h). Extraction of the cooled mixture with ether gave, after drying ($MgSO_4$) and evaporation, the alcohol **3a** as a yellow oil; yield 720 mg (96%) (see Tables 1 and 2).

D: *2,3-Dimethyl-formylferrocene* (**2a**)

0.2 g MnO_2 was added to a solution of **3a** (500 mg, 2.1 mmol) in chloroform (10 ml) and stirred for 10 min. MnO_2 was removed by filtration and the solution was dried over $MgSO_4$. Evaporation of the solvent gave 490 mg (99%) of **2a** as a red oil (see Tables 1 and 2).

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