Organometallic Chemistry

Model solid-state reactions for the formation of a peripheral layer of organometallic dendrimers. Solid-state α-ferrocenylethylation of phenols

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With the aim of modifying solid dendrite structures, the solid-state reactions of (*S*)-(−)-(1-trimethylammonio)ethylferrocene iodide with substituted phenols were studied.

Key words: solid-state reaction, (*S*)-(−)-(1-trimethylammonio)ethylferrocene iodide, substituted phenols.

In the last decade, the design and studies of macromolecular structures with a nontraditional architecture, such as dendrimers, calyxarenes, *etc.*, were among the major lines of investigations in organic chemistry. A large number of dendrite structures have already been constructed, and studies are currently directed toward the search for procedures for the modification of the known molecules by introducing particular functions or fragments, which can impart required properties to these compounds.[1–3] These investigations are substantially complicated by the fact that high-molecular-weight compounds are often poorly soluble. Hence, a search for and studies of reactions proceeding with the participation of high-molecular-weight compounds in the absence of solvents and, in particular, in the solid state are topical problems. This work marks the beginning of studies of solid-state reactions, which can be used for the synthesis and modification of dendrimers containing organometallic fragments.

Many dendrite molecules contain free or substituted hydroxyl groups of phenol rings in the peripheral layer.[3] With the aim of examining the possibilities of solid-state modification of these groups and introduction of optically active organometallic fragments into the peripheral layers of dendrimers, in this work we studied the solid-state reactions of optically active (*S*)-(−)-(1-trimethylammonio)ethylferrocene iodide (**1**) with several substituted phenols **2a—e** (Scheme 1).

Generally, reactions of ferrocenylalkylamine methiodide with nucleophilic compounds in solutions are performed in the presence of alkali or sodium carbonate to bind hydroiodic acid that is eliminated.[4] In the solid-state reactions, we used anhydrous K_2CO_3 for this purpose.

To search for the optimum conditions of the solid-state reactions of methiodide **1**, we used its reaction with *p*-hydroxybenzaldehyde (**2a**) as the model process. The course of the reaction was monitored by TLC of samples of the reaction mixtures dissolved in acetone with a 5 : 1 benzene—ether eluent. In this system, the initial methiodide remained at the start and only the reaction product was eluted. After completion of the reaction, the mixture was extracted with hexane, the solvent was evaporated *in vacuo*, and spectrally pure product **3a**, which did not require further treatment, was obtained.

Taking into account the low thermal stability of methiodide **1**, which is prone to elimination yielding vinylferrocene upon heating,[5] particular attention was given to the search for the optimum temperature conditions of the reaction. It appeared that the reaction

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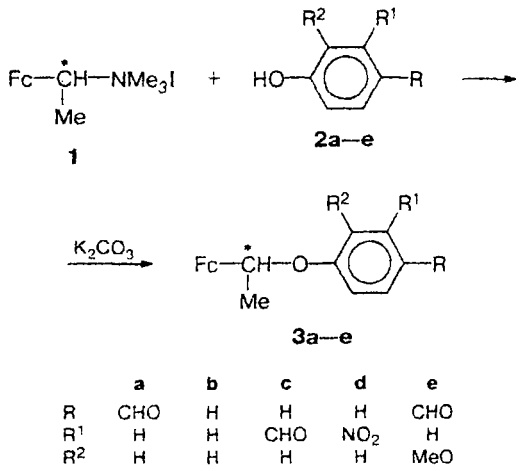
Scheme 1



	a	b	c	d	e
R	CHO	H	H	H	CHO
R^1	H	H	CHO	NO_2	H
R^2	H	H	H	H	MeO

virtually did not proceed at 50 °C (after 5 h, only traces of the reaction product were detected by TLC). An increase in the temperature to 70 °C led to a substantial increase in the yield of compound **3a** as the only reaction product (70—80%). A further increase in the temperature to 90 °C resulted in the formation of vinylferrocene as an admixture.

It was found that a decrease in the reaction time from 5 to 3 h at 70 °C led to only an insignificant decrease in the yield of the product (by 5—10%). To the contrary, the amount of K_2CO_3 used in the solid-state reactions affected substantially the yield of ether **3a**. Previously, it has been demonstrated[6—8] that oily reaction mixtures can form in the course of the solid-state reactions even when both the starting compounds and the reaction products are solids. In some cases, the formation of a viscous oil hinders stirring and restricts the diffusion of the reagents resulting in a decrease both in the reaction rate and the yield of the products. Because of this, we intended to use K_2CO_3 in the solid-state ferrocenylethylation not only as a reagent for binding the acid that formed but also as a carrier which allows one to keep the reaction mixture as a solid bulk material when the reaction mixture or the products occur as oils.

It was found that the yield of product **3a** in the reaction of 1 equiv. of **1** with 2 equiv. of **2a** (5 h, 70 °C) depends on the amount of K_2CO_3:

K_2CO_3 (equiv.)	2	10	15	30
Yield of **3a** (%)	<10	83	71	49

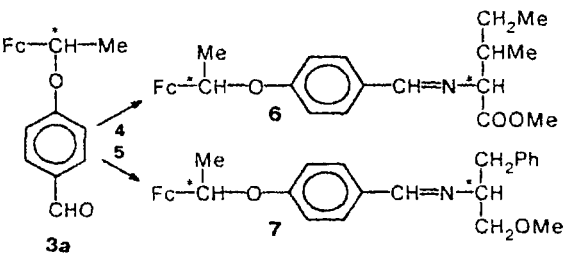
When the reaction mixture was triturated and heated in the presence of only 2 equiv. of K_2CO_3, a solid sintered mixture, which was difficult to stir, was obtained and the yield of the product was <10%. The maximum yield of **3a** was attained with the use of 10 equiv. of K_2CO_3. In this case, the reaction mixture remained solid and bulk throughout the process and the reaction rate was rather high. A further increase in the amount of K_2CO_3 led to a gradual decrease in the yield due, apparently, to the fact that the reaction was slowed down because of dilution of the solid mixture with potassium carbonate.

Therefore, heating (5 h, 70 °C) of a mixture of 1 mol-equiv. of methiodide **1**, 2 mol-equiv. of phenol, and 10 mol-equiv. of K_2CO_3 is the optimum procedure for the solid-state (1-ferrocenyl)ethylation of phenols.

The solid-state ferrocenylethylation of phenols **2a—e** with methiodide **1** under the optimum conditions afforded the corresponding ethers **3a—e** in high yields. The resulting products are rather air-stable crystalline or oily orange substances, which are readily hydrolyzed. Thus purification of compound **3a** by chromatography on a column with SiO_2 afforded 1-ferrocenylethanol in quantitative yield along with the initial compound **2a**. Heating of ether **3e** in aqueous acetone was accompanied by complete hydrolysis of **3e** to form 1-ferrocenylethanol and vanillin **2e**.

Chiral ethers **3a—e** are optically active compounds, *i.e.*, the solid-state reactions of methiodide **1** with phenols proceed stereoselectively. However, the values of optical rotation do not allow one to conclude that racemization is completely absent in the course of the reaction. With the aim of determining the degree of stereoselectivity of the reactions, we prepared derivatives, which are diastereomers with respect to the carbonyl group of ether **3a**, using two enantiomerically pure amines, *viz.*, methyl L-(+)-isoleucine hydrochloride **4** and *S*-(−)-2-amino-1-methoxy-3-phenylpropane hydrochloride **5** (Scheme 2).

Scheme 2



The solid-state synthesis of these derivatives was also performed according to procedures reported previously.[9,10] Each compound that formed in the reactions of compounds **6** and **7** contains two chiral centers one of which (adjacent to the N atom) is enantiomerically pure. In both reactions, either one diastereomer or a mixture of two diastereomeric compounds can be formed depending on the enantiomeric purity of chiral ether **3a**. However, the ^1H NMR spectra of samples of both reaction mixtures recorded at different stages of the reactions have only one set of signals of the products (Table 1) corresponding to one diastereomer. This fact indicates that the enantiomeric purity of the chiral center is retained in the course of the solid-state ferrocenylethylation of the phenols.

It can be suggested that, as in the case of nucleophilic substitution in the series of α-ferrocenylalkylamines in solutions,[5] the solid-state reactions under study

Table 1. Spectral characteristics and the yields of compounds **6** and **7**

Compound	^{1}H NMR,[a] δ, (*J*/Hz)	Mass spectrum[b]	Yield (%)[c]
6	0.84 (m, 6 H, 2 Me); 1.07 (m, 1 H, CH_2); 1.47 (m, 1 H, CH_2); 1.64 (d, 3 H, Me, *J* = 7.1); 2.07 (m, 1 H, CH); 3.62 (d, 1 H, CH—N); 3.66 (s, 3 H, OMe); 4.07 (m, 7 H, C_5H_5+C_5H_4); 4.13 (m, 2 H, C_5H_4); 5.22 (q, 1 H, CH—Fc, *J* = 7.1); 6.93 (m, 2 H, Ar); 7.65 (m, 2 H, Ar); 8.09 (s, 1 H, CH=N)	357 $[M]^+$ (53)	67
7	1.40 (d, 3 H, Me, *J* = 7.2); 2.97 (m, 2 H, CH_2); 3.09 (s, 3 H, OMe); 3.50 (m, 2 H, CH_2); 3.64 (m, 1 H, CH—N); 3.88 (m, 2 H, C_5H_4); 3.97 (s, 5 H, C_5H_5); 4.04 (m, 2 H, C_5H_4); 4.94 (q, 1 H, CH—Fc, *J* = 7.2); 6.80 (m, 2 H, Ar); 6.96—7.20 (m, 5 H, Ar); 7.66 (m, 2 H, Ar); 7.88 (s, 1 H, CH=N)	377 $[M]^+$ (20)	86

[a] The spectra were recorded on a Bruker-200-WP instrument in $CDCl_3$ (**6**) and C_6D_6 (**7**). [b] *m/z* (I_{rel} (%)). [c] The yields were determined from the ratio of the integrated intensities of the signals for the aldimine and residual aldehyde protons in the ^{1}H NMR spectra.

proceed with retention of the configuration of the chiral center bound to the ferrocenyl group.

Experimental

The ^{1}H NMR spectra were recorded on a Bruker-200-WP instrument in $(CD_3)_2CO$. The mass spectra were obtained on a Kratos MS-890 spectrometer (EI, 70 eV). The $[\alpha]_D$ values were measured on an EPO-1 polarimeter in acetone. The TLC control was performed on Silufol plates.

Solid-state reaction of methiodide 1 with substituted phenols 2a—e (general procedure). A mixture of methiodide **1** (0.1 mmol), phenol **2** (0.2 mmol), and K_2CO_3 (1 mmol) was stirred with a glass rod in a round-bottom flask until the reaction mixture became homogeneous. Then the mixture was heated on an oil bath at 70 °C for 5 h and extracted with several portions of hexane (10 mL) until the hexane extract remained colorless (4—5 times). The combined hexane extracts were filtered and concentrated *in vacuo*. Spectrally pure products **3a—e**, which were not subjected to further purification, were obtained.

4-(1-Ferrocenylethoxy)benzaldehyde (3a). A yellow oil, which slowly crystallized out upon storage; the yield was 83%, $[\alpha]_D^{21}$ 93° (*c* 0.59). ^{1}H NMR, δ: 1.96 (d, 1 H, Me, *J* = 7.6 Hz); 4.49 (m, 7 H, C_5H_5 and C_5H_4); 4.57 (m, 2 H, C_5H_4); 5.90 (q, 1 H, CH, *J* = 7.6 Hz); 7.43 (m, 2 H, Ar); 8.12 (m, 2 H, Ar); 10.15 (s, 1 H, CHO). Found (%): C, 68.30; H, 5.76; Fe, 16.94. $C_{19}H_{18}FeO_2$. Calculated (%): C, 68.29; H, 5.43; Fe, 16.71.

(1-Ferrocenylethoxy)benzene (3b). Orange crystals; the yield was 73%, m.p. 60—61 °C, $[\alpha]_D^{21}$ 115° (*c* 0.26). ^{1}H NMR, δ: 1.88 (d, 3 H, Me, *J* = 6.3 Hz); 4.42 (m, 7 H, C_5H_5 and C_5H_4); 4.52 (m, 2 H, C_5H_4); 5.62 (q, 1 H, CH, *J* = 6.3 Hz); 7.05—7.59 (m, 5 H, Ar). Found (%): C, 70.48; H, 6.23; Fe, 18.18. $C_{18}H_{18}FeO$. Calculated (%): C, 70.61; H, 5.93; Fe, 18.24.

3-(1-Ferrocenylethoxy)benzaldehyde (3c). A yellow oil; the yield was 75%, $[\alpha]_D^{21}$ 54° (*c* 0.63). ^{1}H NMR, δ: 1.94 (d, 3 H, Me, *J* = 7.5 Hz); 4.40 (m, 7 H, C_5H_5 and C_5H_4); 4.54 (m, 2 H, C_5H_4); 5.77 (q, 1 H, CH, *J* = 7.5 Hz); 7.44—7.81 (m, 4 H, Ar); 10.27 (s, 1 H, CHO). Found (%): C, 68.69; H, 5.85. $C_{19}H_{18}FeO_2$. Calculated (%): C, 68.29; H, 5.43.

3-(1-Ferrocenylethoxy)nitrobenzene (3d). An orange oil; the yield was 88%, $[\alpha]_D^{21}$ 65.1° (*c* 0.38). ^{1}H NMR, δ: 1.96 (d, 3 H, Me, *J* = 7.3 Hz); 4.43 (m, 7 H, C_5H_5 and C_5H_4); 4.58 (m, 2 H, C_5H_4); 5.84 (q, 1 H, CH, *J* = 7.3 Hz); 7.73—8.16 (m, 4 H, Ar). Found (%): C, 62.11; H, 5.10. $C_{18}H_{17}FeNO_3 \cdot 0.1C_6H_{14}$. Calculated (%): C, 62.09; H, 5.16.

4-(1-Ferrocenylethoxy)-3-methoxybenzaldehyde (3e). A yellow oil; the yield was 57%, $[\alpha]_D^{21}$ 87° (*c* 0.52). ^{1}H NMR, δ: 1.94 (d, 3 H, Me, *J* = 7.7 Hz); 4.10 (s, 3 H, OMe); 4.43 (m, 7 H, C_5H_5 and C_5H_4); 4.53 (m, 2 H, C_5H_4); 5.77 (q, 1 H, CH, *J* = 7.7 Hz); 7.38—7.76 (m, 4 H, Ar); 10.04 (s, 1 H, CHO). MS, *m/z* (I_{rel} (%)): 364 $[M]^+$ (94).

Solid-state reactions of aldehyde 3a with compounds 4 and 5 (general procedure). A mixture of aldehyde **3a** (0.1 mmol), amine **4** or **5** (0.1 mmol), and K_2CO_3 (1 mmol) was stirred with a glass rod in a round-bottom flask until the reaction mixture became homogeneous. Then the mixture was kept at 20 °C for 7 days (for **4**) or at 70 °C for 5 h (for **5**), extracted with chloroform, filtered off from the precipitate, and concentrated. The ^{1}H NMR spectra of the resulting products were recorded without further purification. The yields of imines **6** and **7** were determined from the ratio of the integrated intensities of the signals for the aldimine and residual aldehyde protons in the ^{1}H NMR spectra. The spectral characteristics and the yields of compounds **6** and **7** are given in Table 1.

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