Solid-state interaction of trimethylammonioalkylferrocene iodides with primary amines

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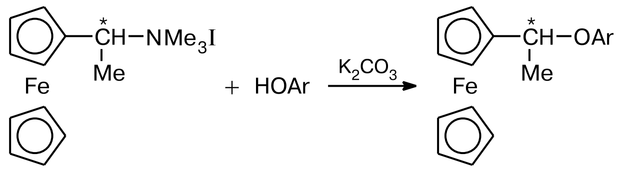
The syntheses of several aminoalkylferrocenes by the solid-state reactions of trimethylammoniomethylferrocene iodides and (*S*)-(—)-(1-trimethylammonio)ethylferrocene with primary amines are described. New ferrocenylalkylamines were synthesized: 1-(4-toluidino)ethylferrocene, 1-(2-pyridylamino)ethylferrocene, 2-pyridylaminomethylferrocene, and *N*,*N*-bis(ferrocenylmethyl)-2-pyridylamine.

Key words: solid-state interaction, trimethylammonioalkylferrocene iodides, primary amines, aminoalkylferrocenes.

One of the methods of introduction of the ferrocenylalkyl group into nucleophilic compounds is their interaction with quaternary salts of dimethylaminoalkylferrocenes. Among these salts, dimethylaminomethylferrocene methoiodide is most accessible and widely used. Its homologs, in particular, 1-trimethylammonioethylferrocene iodide, are used much more rarely because of their affinity to thermal elimination with the formation of vinylferrocene. However, these are precisely the compounds that are of interest from the point of view of stereochemistry, because they can be obtained in the enantiomeric form and used for introduction into compounds of optically active organometallic fragments. In addition, in recent years researchers are greatly interested in electron-active dendrimers containing ferrocenyl groups in the peripheral layer. Solid-state methods can be very helpful in the syntheses of these compounds.[1]

In this work, we studied the solid-state reactions of dimethylaminomethylferrocene methoiodide and enantiomerically pure (*S*)-(—)-(1-dimethylamino)ethylferrocene with several primary aromatic amines. We have previously shown[2] that optically active (*S*)-(—)-(1-trimethylammonio)ethylferrocene iodide (**1**) reacts easily with substituted phenols in the solid state, *i.e.*, in the absence of a solvent, to form the corresponding ethers (Scheme 1).

Scheme 1

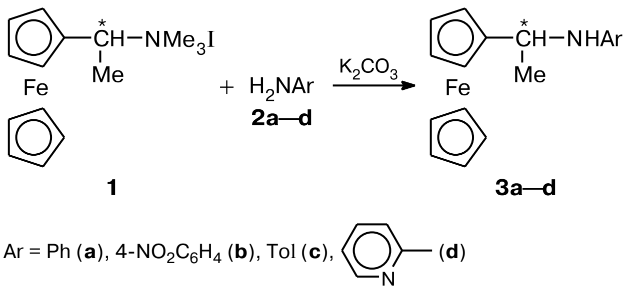


Ar = 4-$CHOC_6H_4$, Ph, 3-$CHOC_6H_4$, 3-$NO_2C_6H_4$, 2-CHO-4-$MeOC_6H_3$

The conditions of the solid-state reaction (duration, temperature regime, ratio of reactants, amount of used K_2CO_3) were studied in detail. The most substantial factors were the rather narrow temperature interval of the reaction (60—70 °C) and the use of tenfold K_2CO_3 excess to obtain the maximum yield of the product.

Based on these data, we carried out the solid-state reactions of methoiodide **1** with several aromatic amines (Scheme 2).

Scheme 2



The reaction occurred on heating of a mixture of the starting reactants in the absence of a solvent for 2 h. In all cases, the starting methoiodide was almost completely converted within this time. The products formed were extracted with chloroform and chromatographed.

The resulting amines **3** were orange oily or crystalline substances stable in air. As the corresponding products of the reaction of compound **1** with phenols, amines **3** are optically active, indicating that the solid-state reaction is stereoselective.

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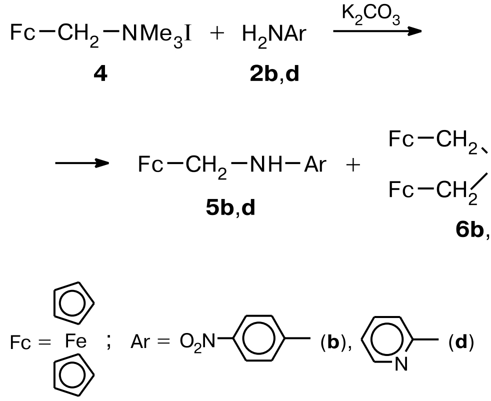
Our further studies were aimed at studying the possibility of the solid-state interaction of dimethylaminomethylferrocene methoiodide (**4**), which is less reactive in nucleophilic substitution (Scheme 3), with amines.

Scheme 3



In the first experiment, the reaction of **4** with **2b** was carried out under conditions developed for enantiomerically pure compound **1**. However, heating of the reaction mixture at 70 °C for several hours (2—4 h) did not give the desirable product. The high thermal stability of methoiodide **4** (unlike **1**) made it possible to increase the reaction temperature to 110 °C, after 2 h resulting in the complete conversion of the starting compounds. After the standard treatment of the reaction mixture followed by chromatography, a mixture of two products was obtained: secondary amine **5b** and tertiary amine **6b**. The attempt of their complete separation failed. When this reaction is carried out in a solution (H_2O, 100 °C, 7 h), no formation of tertiary amine was detected.[3]

Probably, compound **6b** is a product of the reaction of formed amine **5b** with methoiodide **4**, which suggests that secondary amines also can react with **4** in the solid state. We studied the influence of the ratio of the starting reactants under the standard solid-state conditions on the relative yield of secondary and tertiary amines **5b** and **6b**.

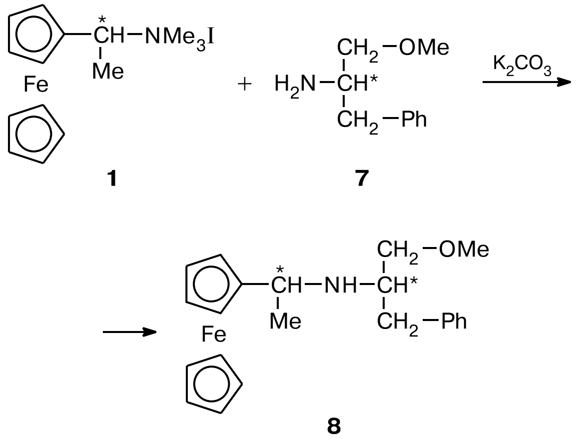
4/2b	**5b/6b**
3/1	2/1
1/1	4/1
1/3	7.5/1

The relative yields were determined from the ratio of integral intensities of the well discernible signals from aromatic protons (6.58 ppm for **5b** and 6.76 ppm for **6b**) in the proton spectra of samples of the reaction mixtures. In all cases, secondary amine **5b** is mainly formed. Even the use of threefold methoiodide excess does not sufficiently increase the yield of tertiary amine **6b**. Probably, more drastic reaction conditions should be selected for the ~100% interaction of methoiodide with secondary aromatic amines.

The reaction of compound **4** with 2-aminopyridine **2d** occurs analogously (see Scheme 3). In this case, a mixture of secondary and tertiary amines with a great predomination of the first one is formed and can difficultly be separated by chromatography.

The reaction of compound **1** with enantiomerically pure 3-methoxy-1-phenyl-2-propylamine (**7**) demonstrated the possibility of the solid-state interaction of methoiodides with aliphatic primary amines (Scheme 4).

Scheme 4



Under standard conditions, the solid-state reaction of methoiodide **1** with **7** occurs within 2 h with the complete conversion of the starting methoiodide. The single product was isolated by chromatography in 79% yield. Its ^{1}H NMR spectrum showed one set of signals corresponding to structure **8**. We failed to isolate compound **8** in the analytically pure state. Taking into account the presence of two chiral centers in molecule **8**, we can consider the formation of the single diastereomer as an evidence favoring that the enantiomeric purity is retained during the solid-state reaction at the chiral α-ferrocenyl carbon atom.

In all reactions studied in this work, the reaction mixture remains solid and friable during the whole interaction due to a great excess of K_2CO_3 used. As we have shown previously,[2] a decrease in the amount of K_2CO_3 results in oiling of the reaction mixture and a decrease in the yield of the products. Melting of crystalline organic compounds during the interaction in the absence of a solvent was observed so often by us in the previous works and by other authors[4] that this fact was specially studied and discussed.[5] Note that using the term "solid-state reaction" we imply organic reactions of solid starting compounds in the absence of a solvent.

Experimental

^{1}H NMR spectra were recorded on Bruker-200-WP and Bruker-AMX-400-ST instruments. The optical rotation values $[\alpha]_D$ were determined on an EPO-1 polarimeter in acetone.

Iodides **1** and **4** were synthesized by a previously described procedure[**6**] from (*S*)-(–)-*N*,*N*-dimethyl-1-ferrocenylethylamine (Fluka) and dimethylaminomethylferrocene (Aldrich). Reaction mixtures were homogenized in an ML-1 vibratory ball mill (Ekoniks State Scientific Production Enterprise) with a frequency of 50 Hz in a hermetically sealed titanium 62-cm^3 reactor using titanium balls as the activating packing (2 balls, diameter 1.3 cm, weight 10 g).

Solid-state reactions of methoiodides 1 and 4 with amines 2a—d and 7 (general procedure). A mixture of methoiodide (0.1 mmol), amine (0.1 mmol) or amine hydrochloride (for **2a**), and K_2CO_3 (1 mmol) was stirred for 1 min in a ball mill. A uniform powder formed was placed in a round-bottom flask and heated for 2 h in an oil bath at 70 °C (110 °C for **4**). Then the reaction mixture was extracted with chloroform and filtered, and a residue was chromatographed on a column with silica gel ($CHCl_3$—MeOH, 100 : 0—90 : 10). The products obtained were crystallized if necessary from an appropriate solvent.

1-Anilinoethylferrocene (3a). Yellow oil (Ref. 3: m.p. 50—52 °C), 86.8% yield (0.0265 g), $[\alpha]_D^{20}$ +18.9 (*c* 0.66, acetone). ^{1}H NMR (acetone-d_6), δ: 1.56 (d, 3 H, Me, *J* = 6.4 Hz); 4.05 (m, 2 H, C_5H_4); 4.16 (m, 7 H, C_5H_5 and C_5H_4); 4.42 (m, 1 H, CH); 4.69 (m, 1 H, NH); 6.47—7.39 (m, 5 H, C_6H_5).

1-(4-Nitroanilino)ethylferrocene (3b).[7] Orange crystals, 93.1% yield (0.0326 g), m.p. 115—116 °C (hexane—benzene), $[\alpha]_D^{20}$ –23.3 (*c* 0.82, acetone). ^{1}H NMR (C_6D_6), δ: 1.53 (d, 3 H, Me, *J* = 7.1 Hz); 4.17 (m, 9 H, C_5H_5 and C_5H_4); 4.41 (m, 1 H, CH); 4.76 (m, 1 H, NH); 6.53, 8.07 (both m, 2 H each, C_6H_4). Found (%): C, 62.37; H, 5.52; N, 8.25. $C_{18}H_{18}FeN_2O_2 \cdot 0.1C_6H_6$. Calculated (%): C, 62.40; H, 5.24; N, 7.82.

1-(4-Toluidino)ethylferrocene (3c). Orange crystals, 67% yield (0.0214 g), m.p. 85—87 °C, $[\alpha]_D^{20}$ +9.4 (*c* 0.54, acetone). ^{1}H NMR (acetone-d_6), δ: 1.37 (d, 3 H, Me, *J* = 7.2 Hz); 2.11 (s, 3 H, Me); 4.07 (m, 2 H, C_5H_4); 4.17 (m, 7 H, C_5H_5 and C_5H_4); 4.37 (m, 2 H, CH and NH); 6.62, 6.89 (both m, 2 H each, C_6H_4). Found (%): C, 71.16; H, 6.66; N, 4.31; Fe, 17.37. $C_{19}H_{21}FeN$. Calculated (%): C, 71.49; H, 6.63; N, 4.39; Fe, 17.49.

1-(2-Pyridylamino)ethylferrocene (3d). Orange crystals, 85% yield (0.0259 g), m.p. 82—83 °C. ^{1}H NMR ($CDCl_3$), δ: 1.54 (d, 3 H, Me, *J* = 6.0 Hz); 4.15 (m, 2 H, C_5H_4); 4.21 (m, 7 H, C_5H_5 and C_5H_4); 4.71 (m, 2 H, CH and NH); 6.40, 6.57, 7.42, 8.12 (all m, 1 H each, C_5H_4N). Found (%): C, 66.56; H, 5.91; N, 9.21. $C_{17}H_{18}FeN_2$. Calculated (%): C, 66.69; H, 5.93; N, 9.15.

4-(Nitroanilino)methylferrocene (5b). Orange crystals, 7.4% yield (0.0025 g), m.p. 142—144 °C (Ref. 3: m.p. 143.5—145.5 °C). ^{1}H NMR ($CDCl_3$), δ: 4.07 (m, 2 H, C_5H_4); 4.21 (m, 7 H, C_5H_5 and C_5H_4); 4.25 (m, 2 H, CH_2); 4.70 (br.s, 1 H, NH); 6.58 (m, 2 H, C_6H_4, *J* = 9.0 Hz); 8.12 (d, 2 H, C_6H_4, *J* = 9.0 Hz).

2-Pyridylaminomethylferrocene (5d). Orange crystals, 30% yield (0.0089 g), m.p. 138—140 °C. ^{1}H NMR (acetone-d_6), δ: 4.07 (m, 2 H, C_5H_4); 4.16 (s, 5 H, C_5H_5); 4.25 (m, 4 H, C_5H_4 and CH_2); 5.71 (m, 1 H, NH); 6.50 (m, 2 H, C_5H_4N); 7.35, 8.01 (both m, 1 H each, C_5H_4N). Found (%): C, 65.18; H, 5.42; N, 9.36. $C_{16}H_{16}FeN_2 \cdot 0.1H_2O$. Calculated (%): C, 65.37; H, 5.55; N, 9.53.

***N*,*N*-Bis(ferrocenylmethyl)-2-nitroaniline (6b).** Orange crystals, 7.5% yield (0.0020 g), m.p. 213—215 °C (Ref. 3: m.p. 217—219 °C). ^{1}H NMR ($CDCl_3$), δ: 4.17 (m, 4 H, 2 C_5H_4); 4.20 (m, 14 H, 2 C_5H_5 and 2 C_5H_4); 4.40 (s, 4 H, 2 CH_2); 6.76 (d, 2 H, C_6H_4, *J* = 9.4 Hz); 8.10 (d, 2 H, C_6H_4, *J* = 9.4 Hz).

***N*,*N*-Bis(ferrocenylmethyl)-2-pyridylamine (6d).** Orange crystals, 7.5% yield (0.0019 g), m.p. 165—167 °C. ^{1}H NMR (acetone-d_6), δ: 4.08 (m, 4 H, 2 C_5H_4); 4.17 (s, 10 H, 2 C_5H_5); 4.29 (m, 4 H, 2 C_5H_4); 4.50 (s, 4 H, 2 CH_2); 6.48, 6.68, 7.40 (all m, 1 H each, C_5H_4N); 8.10 (m, 1 H, C_5H_4N). Found (%): C, 66.13; H, 5.57; N, 5.67. $C_{27}H_{26}Fe_2N_2$. Calculated (%): C, 66.02; H, 5.54; N, 5.70.

***N*-(1-Ferrocenylethyl)-3-methoxy-1-phenyl-2-propylamine (8).** Orange oil, 79% yield (0.0298 g). ^{1}H NMR (C_6D_6), δ: 1.36 (d, 3 H, Me, *J* = 7.0 Hz); 1.71 (m, 1 H, NH); 2.28 (m, 2 H, CH_2Ph); 3.12 (s, 3 H, OMe); 3.28 (m, 3 H, CH and CH_2); 3.65 (q, 1 H, CHFe, *J* = 7.0 Hz); 3.97 (m, 2 H, C_5H_4); 4.08 (s, 5 H, C_5H_5); 4.10, 4.14 (both m, 1 H each, C_5H_4).

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