
**SYNTHESIS AND REACTIVITY OF METHYL ESTER
OF 1'-(CHLOROMETHYL)FERROCENECARBOXYLIC ACID**

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The reaction of methyl ester of 1'-(hydroxymethyl)ferrocenecarboxylic acid with PCl_3 afforded methyl ester of 1'-(chloromethyl)ferrocenecarboxylic acid. The reactivity of the ester with selected O, S, N and C-nucleophiles has been investigated. In all cases the high yields of the products of substitution of the chlorine of chloromethyl group were obtained.

Till now, chloromethylferrocene was not isolated in the pure state and thus it has not found wider application in the organic synthesis^{1,2}. In place of this compound, hydroxymethylferrocene^{3,4} and particularly ferrocenylmethyltrimethylammonium iodide^{5,6} and also (N-ferrocenylmethyl)pyridinium salts such as *p*-toluenesulphonate, picrate, and iodide⁷ have been used as ferrocenylmethylating agents. The synthesis of 1,1'-disubstituted ferrocene derivatives was accomplished with the use of 1,1'-bis(chloromethyl)ferrocene^{8,9} or N,N'-(1,1'-ferrocenylenedimethylene)dipyridinium chloride resp. chloride-tosylate¹⁰ as ferrocenylenedimethylation agents.

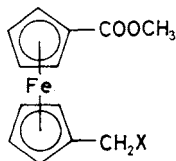
The aim of the present work was to develop the method of the synthesis of methyl ester of 1'-(chloromethyl)ferrocenecarboxylic acid and to examine its reactivity toward different nucleophiles. Another aim of the study was to verify whether the reactions of this compound proceed preferentially on the ester or the chloromethyl group.

To synthesize methyl ester of 1'-(chloromethyl)ferrocenecarboxylic acid it was necessary to prepare the intermediate product, *i.e.* methyl ester of 1'-(hydroxymethyl)ferrocenecarboxylic acid. For the synthesis of this compound we have chosen the partial reduction of dimethylester of 1,1'-ferrocenedicarboxylic acid with LiAlH_4 in diethyl ether. The expected product was obtained by this way in 7 to 27% yields and the reaction mixture contained both the starting compound and the product of the total reduction, *i.e.* 1,1'-bis(hydroxymethyl)ferrocene. We have not succeeded in increasing the yields of the required methyl ester by adding portionwise LiAlH_4 to the reaction mixture. Attempts at partial reduction of dimethyl ester of 1,1'-ferrocenedicarboxylic acid with $\text{LiAlH}_4/\text{SiO}_2$ according to Kamitori *et al.*¹¹ or partial esterification of 1,1'-ferrocenedicarboxylic acid adsorbed on Al_2O_3 by diazomethane

reported by Chihara¹² have not been successful even though these methods were found to be very effective in the synthesis of terephthalic acid derivatives. This is presumably due to the fact that in the case of terephthalic acid the functional groups are sufficiently spacially remote, which is not the case with 1,1'-ferrocenedicarboxylic acid.

The chloromethyl derivative was prepared by using PCl_3 in dry tetrahydrofuran in the presence of pyridine. The reaction is extremely sensitive to moisture traces. For that reason, we have not purified the methyl ester of 1-(chloromethyl)ferrocenecarboxylic acid formed but used the raw material directly in further reaction. As nucleophiles, we have used sodium salts of phenol, thiophenol, N-methylaniline, acetylacetone, and of ethyl formamidomalonate. Except for the

TABLE I
Elemental analyses of the compounds



| No. | X | Formula (m. wt.) | Calculated/found | | | | Reaction time, h temp., °C | Yield, % (m.p., °C ^a) |
|-----|--|---|------------------|--------------|----------------|--------------|----------------------------------|--------------------------------------|
| | | | % C | % H | % Fe | % S, N | | |
| 1 | —O—C ₆ H ₅ | C ₁₉ H ₁₈ FeO ₃ (350.2) | 65.16 65.00 | 5.19 5.20 | 15.95 16.05 | — | 4 <i>b</i> | 68.6 (78—79.5) |
| 2 | —S—C ₆ H ₅ | C ₁₉ H ₁₈ FeO ₂ S (366.2) | 62.30 62.19 | 4.96 4.84 | 15.25 15.40 | 8.75 8.92 | 2 <i>b</i> | 98.1 (46—47.5) |
| 3 | CH ₃ —N—C ₆ H ₅ | C ₂₀ H ₂₁ FeO ₂ N (363.3) | 66.13 66.30 | 5.84 5.88 | 15.37 15.78 | 3.86 3.78 | 9 <i>b</i> | 96 (69—71.5) |
| 4 | COCH ₃ —CH—COCH ₃ | C ₁₈ H ₂₀ FeO ₄ (356.2) | 60.69 60.62 | 5.67 5.77 | 15.68 15.85 | — | 10 <i>b</i> | 97.5 (71—73.5) |
| 5 | COOC ₂ H ₅ —C—COOC ₂ H ₅ NHCHO | C ₂₁ H ₂₅ FeO ₇ N (459.3) | 54.92 55.11 | 5.50 5.58 | 12.16 12.00 | 3.05 3.10 | 19 80 | 95.0 (124—126) |

^a Crystallized from benzene-petroleum ether. ^b Room temperature.

alkylation of phenol, the reactions proceeded essentially quantitatively (Table I). In the former reaction, the yield was lower (68.6%), due to the shorter reaction time used. The ^1H NMR spectra of all the products show singlet of the methyl group (Table II), which proves that the reactions took place on the chloromethyl group of the starting ester. This demonstrates that even electron-accepting methoxycarbonyl group bonded to ferrocene did not decrease the reactivity of the chloromethyl group or the stability of the ferrocenylmethyl cation.

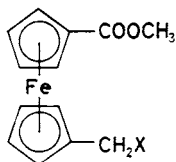
EXPERIMENTAL

^1H NMR spectra were measured on Tesla BS-487 A spectrometer working at 80 MHz, using tetramethylsilane as internal reference. The compounds were dissolved in C^2HCl_3 (98% ^2H -isotope). Melting points were determined on Kofler hot plate and are not corrected.

Dimethyl ester of 1,1'-ferrocenedicarboxylic acid was prepared by esterification of the acid⁸ or by the reaction of sodium methoxycarbonylcyclopentadienide with anhydrous FeCl_2 in tetrahydrofuran¹³. Both reactions were carried out under nitrogen.

TABLE II

^1H NMR spectra of the compounds



| No. ^a | C_5H_4 | C_5H_4 | CH_3/CH_2 | Other signals |
|------------------|------------------------|--------------------------------|--------------------------------|--|
| 1 | 4.27 (4 H, m) | 4.80 (2 H, t) 4.40 (2 H, t) | 3.77 (3 H, s) 4.71 (2 H, s) | 6.98 (3 H, m, C_6H_5) 7.25 (2 H, m, C_6H_5) |
| 2 | 4.12 (4 H, m) | 4.76 (2 H, t) 4.37 (2 H, t) | 3.78 (3 H, s) 3.81 (2 H, s) | 7.25 (5 H, m, C_6H_5) |
| 3 | 4.12 (4 H, m) | 4.78 (2 H, t) 4.37 (2 H, t) | 3.82 (3 H, s) 4.20 (2 H, s) | 2.82 (3 H, s, $\text{CH}_3\text{—N}$), 6.75 (3 H, m, C_6H_5) 7.21 (2 H, m, C_6H_5) |
| 4 | 4.07 (4 H, m) | 4.74 (2 H, t) 4.35 (2 H, t) | 3.80 (3 H, s) 2.80 (2 H, d) | 2.1 (6 H, s, $\text{CH}_3\text{—CO}$) 3.75 (1 H, t, CH) |
| 5 | 4.20 (4 H, m) | 4.78 (2 H, t) 4.20 (2 H, m) | 3.84 (3 H, s) 3.37 (2 H, s) | 1.26 (6 H, t, $\text{CH}_3\text{—CH}_2$), 4.20 (4 H, m, $\text{CH}_2\text{—CH}_3$) 6.67 (1 H, s, NH), 8.10 (1 H, s, CHO) |

^a Chemical shifts given in δ scale.

Synthesis of Methyl Ester of 1'-(Hydroxymethyl)ferrocenecarboxylic Acid

To a stirred suspension of LiAlH_4 (0.38 g; 0.01 mol) in dry diethyl ether, a solution of dimethyl ester of 1,1'-ferrocenedicarboxylic acid (3.02 g; 0.01 mol) in dry benzene (70 ml) was dropwise added. The reaction mixture was heated to reflux for 3 h with stirring. Then the reaction mixture was allowed to cool to ambient temperature and moist ether and water were added successively to the reaction mixture. The organic layer was separated and dried over Na_2SO_4 . After solvent removal by distillation, the residue was chromatographed on Al_2O_3 , using benzene-ether as eluent. The first band afforded the starting compound (0.60 g, 22%), the second band yielded the product, *i.e.* methyl ester of 1'-(hydroxymethyl)ferrocenecarboxylic acid (0.68 g, 25%). After crystallization from benzene-petroleum ether, the product melted at 62 to 63°C. For $\text{C}_{13}\text{H}_{14}\text{FeO}_3$ (274.15) calculated: 56.96% C, 5.16% H, 20.37% Fe; found: 56.73% C, 5.21% H, 20.61% Fe. ^1H NMR spectrum (in δ scale): 2.32 (OH, 1 H, s), 3.82 (CH_3 , 3 H, s), 4.22 (C_5H_4 , 4 H, s), 4.31 (CH_2 , 2 H, s), 4.41 (H_β , 2 H, t), 4.80 (H, 2 H, t). The last band gave 1,1'-bis-(hydroxymethyl)ferrocene (1.33 g, 54%), m.p. 105–107°C, in accordance with reported data⁸.

Synthesis of Methyl Ester of 1'-(Chloromethyl)ferrocenecarboxylic Acid

To a stirred solution of methyl ester of 1'-(hydroxymethyl)ferrocenecarboxylic acid (2.74 g; 0.01 mol) in dry tetrahydrofuran (75 ml), 0.6 ml of dry pyridine were added, followed by dropwise addition of a solution of 0.69 g (0.005 mol) of freshly distilled PCl_3 in 15 ml of dry tetrahydrofuran. After stirring for 3 h at room temperature, the solution was decanted from the precipitated H_3PO_3 and the acid was washed with another 30 ml of dry tetrahydrofuran. The combined solutions of the product in tetrahydrofuran were taken to the reaction.

Reaction of Methyl Ester of 1'-(Chloromethyl)ferrocenecarboxylic Acid with Nucleophiles

To a stirred solution of 15 mmol of the corresponding nucleophile in 15 ml of dry dimethylformamide, 0.64 g (15 mmol) of NaH were added. The so prepared reaction mixture was allowed to react with the calculated amount of tetrahydrofuran solution of methyl ester of 1'-(chloromethyl)ferrocenecarboxylic acid (see above). The reaction mixture was stirred at a given temperature. The reaction course was checked by TLC (Table I). After completion of the reaction, the solvent was evaporated, the residue was dissolved in a small amount of CH_2Cl_2 and then it was chromatographed on Al_2O_3 , using benzene-ethyl acetate as an eluent. The yields and melting points of the products are presented in Table I, along with elemental analyses; ^1H NMR spectra of the products are given in Table II.

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