Synthesis, proton magnetic resonance spectra, and biological activity of haloacylferrocenes

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Received 18 January 1973

Friedel—Crafts acylation of ferrocene and cinnamoylferrocene with halogenated acyl chlorides has been carried out and the p.m.r. spectra of the products are discussed. Some of the described derivatives show interesting antibacterial activity.

The preparation of some haloacylferrocenes has been described [1—6]. However, attention has been paid neither to their biological activity nor to their p.m.r. spectra. The aim of the present work is to supplement the existing knowledge in this area and to show the possibility to prepare haloacyl derivatives of ferrocene by Friedel—Crafts acylation.

Experimental

Melting points were determined on a Kofler hot stage. Isolation of the compounds was done by chromatography of the reaction mixtures on silica gel (Kavalier, Votice) using benzene as the mobile phase. Analytical data of the prepared compounds and yields (based on starting ferrocene or cinnamoylferrocene) are given in Table 1.

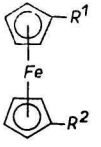
Infrared spectra (Nujol, 700—2000 cm^{-1}) were obtained on a Zeiss UR-20 instrument calibrated with a standard polyethylene foil. High-resolution p.m.r. spectra were measured at 80 MHz using a Tesla BS 487 A spectrometer. Tetramethylsilane was the internal standard (3% v/v); the concentration of the substrate in deuteriochloroform (99.5% D isotope) being 6.6%. Chemical shifts were measured with the accuracy of 0.8 Hz (23°C) and the interaction constants with the accuracy of ± 1.6 Hz.

Acylation of ferrocene. Preparation of I—IX

A solution of acyl chloride (0.02 mole) and anhydrous aluminium chloride (0.022 mole) in dichloromethane (40 ml) was added dropwise and with stirring to a cooled (water bath) solution of ferrocene (0.02 mole) in dichloromethane (40 ml). When the addition was complete the reaction mixture was stirred at room temperature for four hours and then poured into ice water (500 ml) followed by the addition of sodium hydrosulfite

Table 1

Analytical data of haloacylferrocenes



No.	R^1	R^2	Formula	*M*	Calculated/found % Fe	Calculated/found % X	Yield [%]	M.p. [°C] Solvent
I	Chloroacetyl	H	$C_{12}H_{11}ClFeO$	262.5	—	—	14.5	92—93[a] Benzene—petroleum ether
II	2-Chloropropionyl	H	$C_{13}H_{13}ClFeO$	276.5	20.00 18.96	12.87 12.51	5.5	39—41 From a melt
III	3-Chloropropionyl	H	$C_{13}H_{13}ClFeO$	276.5	20.00 19.87	12.87 13.04	36.3	60—62[b] *n*-Hexane
IV	3-Bromopropionyl	H	$C_{13}H_{13}BrFeO$	320.9	17.40 17.43	24.89 25.30	30.3	79—81 Petroleum ether
V	4-Chlorobutyryl	H	$C_{14}H_{15}ClFeO$	290.6	19.02 19.24	12.20 12.25	40.3	57—60[c] Benzene—petroleum ether
VI	Chloroacetyl	Cinnamoyl	$C_{21}H_{17}ClFeO_2$	392.7	14.21 14.25	9.03 8.97	31	134—135 Benzene—acetone
VII	2-Chloropropionyl	Cinnamoyl	$C_{22}H_{19}ClFeO_2$	406.7	13.73 13.99	8.71 8.38	29.3	118—120 Benzene—petroleum ether
VIII	3-Chloropropionyl	Cinnamoyl	$C_{22}H_{19}ClFeO_2$	406.7	13.73 14.04	8.71 8.75	63.4	117—119 Benzene—petroleum ether
IX	4-Chlorobutyryl	Cinnamoyl	$C_{23}H_{21}ClFeO_2$	420.7	13.27 13.27	8.42 8.67	43.1	108—111 Benzene—petroleum ether

a) In agreement with [1]; *b*) 61—63°C [4]; *c*) 85—86°C [4].

(to reduce ferrocenium to ferrocene). Organic material was extracted with dichloromethane and the resulting dichloromethane solution was washed with water, dried (sodium sulfate), concentrated and the crude product was purified by chromatography. Ferrocene was eluted first (16—59%), then the desired product followed by some halogen-free material. (*Note*: In the case of acylation of ferrocene with bromoacyl chlorides it is of advantage to add powdered aluminium chloride to the solution of the substrate and bromoacyl chloride in dichloromethane.)

Acylation of cinnamoylferrocene was done with the following molar ratio of the reagents cinnamoylferrocene—acyl chloride—aluminium chloride = 0.005 : 0.0075 : 0.015. Elution from a silica gel column gave the unchanged cinnamoylferrocene (3—30%) and the desired product followed by some halogen-free material which was not further examined.

3-Chloropropylferrocene (X)

Anhydrous aluminium chloride (0.47 g; 0.0035 mole) in dry ether (15 ml) was added to the suspension of lithium aluminium hydride (0.14 g; 0.0035 mole) in dry ether (15 ml) and the mixture was stirred at room temperature for 10 minutes. Dropwise and with continued stirring a solution of 3-chloropropionylferrocene (0.85 g; 0.003 mole) in dry ether (15 ml) was added and stirring was continued for 15 minutes. The excess reducing agent was decomposed by the addition of water and the organic layer was separated, washed with water, and dried (anhydrous sodium sulfate). Concentration was followed by chromatography on alumina (Brockmann II, Reanal, Budapest) which gave, by elution with petroleum ether, 0.66 g (80.5%) of oily 3-chloropropylferrocene.

For $C_{13}H_{15}ClFe$ (262.57) calculated: 21.26% Fe, 13.73% Cl; found: 20.87% Fe, 13.28% Cl. PMR data [δ]: 4.06 (s), 4.1 (s), 3.5 (t), 1.95 (q), 2.6 (t).

Results and discussion

Friedel—Crafts acylation of ferrocene and cinnamoylferrocene is a smooth reaction and gives generally satisfactory yields of the desired products. The only exception is the acylation with α-haloacyl chlorides (chloroacetyl and 2-chloropropionyl chloride) which is probably caused by the α-haloacyl cation which is a strong electrophile and oxidizes preferentially ferrocene to ferrocenium. This explanation is supported by the high percentage of recovered ferrocene (up to 59% in the case of acylation with 2-chloropropionyl chloride). Low yields of the desired product by the acylation of ferrocene with chloroacetyl and dichloroacetyl chlorides has been reported by *Schlögl* [1]. The acylation of cinnamoylferrocene with α-haloacyl chlorides proceeds more satisfactorily because of the lowered oxidability of iron in ferrocene caused by the presence of electron-withdrawing carbonyl group of the cinnamoyl group.

In all acylations a small amount of halogen-free material was isolated. In two cases, where the amount of this material was relatively large, these substances were identified. The by-product isolated from the reaction mixture of chloroacylation of ferrocene with chloroacetyl chloride was acetylferrocene (2.5%), which is in agreement with [2], and the one isolated from the reaction of 2-chloropropionyl chloride with ferrocene was propionylferrocene (6%). As acylation with β-haloacyl chlorides yielded but negligible amount of side-products the loss of the halogen can be attributed to the lability of α-chloroacyl chlorides towards the action of aluminium chloride [2]. Elimination of hydrogen halide was observed in the case of 3-chloropropionyl- and 3-bromopropionylferrocenes, when the compound stood on a silica gel column for a long period of time

Table 2

Infrared and proton magnetic resonance spectral data of haloacylferrocenes

No.	δ^a	δ^b	CH=CH	δ	Others	δ	$\tilde{\nu}$(C=O) [cm^{-1}]
I	4.84 (t) 4.59 (t)	4.24 (s)			$-COCH_2Cl$	4.42 (s)	1690
II	4.86 (m)	4.23 (s)			$-COCH(Cl)-$	4.86 (m)	1685
	4.56 (t)				$-CH_3$	1.70 (d)	
III	4.79 (t) 4.53 (t)	4.23 (s)			$-COCH_2$ $-CH_2Cl$	3.90 (t) 3.16 (t)	1668
IV	4.81 (t) 4.53 (t)	4.25 (s)			$-COCH_2$ $-CH_2Br$	3.72 (t) 3.29 (t)	1665
V	4.78 (t) 4.49 (t)	4.20 (s)			$-COCH_2$ $-CH_2Cl$ $-CH_2-$	3.68 (t) 2.92 (t) 2.18 (q)	1680
VI	4.92 (t) 4.80 (t)	4.59 (m)	(J = 16.2 Hz)	7.82 7.04	$-CH_2Cl$	4.35 (s)	1656, 1692
VII	4.88 (m)	4.60 (m)	(J = 16 Hz)	7.81	$-COCH(Cl)-$	4.88 (m)	1660, 1680
				7.05	$-CH_3$	1.70 (d)	
VIII	4.94 (t) 4.77 (t)	4.61 (t) 4.53 (t)	(J = 15.6 Hz)	7.83 7.09	$-COCH_2$ $-CH_2Cl$	3.28 (t) 3.11 (t)	1668, 1684
IX	4.95 (t) 4.68 (t)	4.59 (t) 4.51 (t)	(J = 15.3 Hz)	7.82 7.07	$-COCH_2$ $-CH_2Cl$ $-CH_2-$	3.64 (t) 8.86 (t) 2.14 (q)	1655, 1678

s — singlet; d — doublet; t — triplet; q — quintet; m — multiplet.

a) The α and β protons of the substituted cyclopentadienyl ring; *b*) protons of the unsubstituted cyclopentadienyl ring.

or during concentration of large amounts of their benzene solutions under atmospheric pressure.

3-Chloropropionyl- and 3-bromopropionylferrocenes were previously prepared [4] by the reaction of acryloylferrocene with hydrogen halides in 79—81% yield. It is unquestionably more advantageous to prepare these substances by direct acylation of ferrocene.

The proof of the structure of the described compounds was established by the analysis of their i.r. and p.m.r. spectra (Table 2). The i.r. spectra of all monosubstituted derivatives display bands in the region of 1005—1110 cm^{-1} showing thus the presence of an unsubstituted cyclopentadienyl ring [7]. An absorption band in the region of 1665—1690 cm^{-1} corresponding to the C=O stretching vibrations with the frequencies decreasing with increasing distance of the halide from the carbonyl group increases was also observed. It is interesting that this band is in the case of monosubstituted derivatives rather wide, which may be caused by different conformations of the compounds under investigation. This is supported by the finding that the spectra of *III* and *IV*, taken in carbon tetrachloride, contain a sharp absorption band while the spectrum of *I* shows two bands at 1684 and 1703 cm^{-1}.

On the i.r. spectra of the disubstituted derivatives two pronounced simple bands in the region of the C=O stretching vibrations can be seen. The bands at 1655—1670 cm^{-1} and at 1680—1692 cm^{-1} correspond to $\tilde{\nu}$(C=O) of the cinnamoyl and haloacyl groups, respectively.

A strong singlet at δ 4.23 (corresponding to the five protons of the unsubstituted cyclopentadienyl ring) can be seen in the p.m.r. spectra of monosubstituted derivatives. At δ 4.8 and 4.55 ($\Delta\delta$ = 0.25—0.30) two apparent triplets corresponding to the α and β protons of the substituted cyclopentadienyl ring are visible. Referring to previous works [8—10] the triplet in the lower field of the spectra belongs to α protons and that in the upper field to β protons. The position of the apparent triplets corresponding to α and β protons depends upon the position of the halogen in the chain; the farther the halogen the higher the field at which the signals of these protons appear. The coupling constants of the triplets are 1—2 Hz. In addition, the proton-resonance signals of the groups of the chain with clear-cut coupling constants can be seen in the spectra of this group of compounds.

The spectra of the disubstituted derivatives contain complex multiplets at δ 7—8 corresponding to the aromatic protons. In the same region a well resolved quartet of the *trans* protons of the ethylenic linkage with the chemical shift of about 7.5 δ and coupling constant of 16 Hz can be seen. Owing to the cinnamoyl substitution the protons of the second cyclopentadienyl ring cease to be equivalent and thus both the rings can be in all cases distinguished. α and β protons of the two cyclopentadienyl rings in *VII* are not resolved and the situation becomes even more complicated owing to the fact that the resonance signals of the methine proton are located in the same region. In the spectrum of *VI* there is also observed a not well resolved four-proton multiplet of the cyclopentadienyl ring containing cinnamoyl.

The substitution with cinnamoyl is responsible for the decreased value of $\Delta\delta = \delta_\alpha - \delta_\beta$ in all derivatives of this class ($\Delta\delta$ = 0.08).

The fact that the protons of the cyclopentadienyl ring in *VI* and *VII* are not resolved can be attributed to the presence of a substituent on the neighbouring ring (chlorine in the α position to the carbonyl group) owing to which the carbonyl group is bent out of the plane of the cyclopentadienyl ring weakening thus the effect of this group upon the position of the resonance signals of α and β protons. The possibility of such a steric

interaction of the halogen atom with the cinnamoyl carbonyl group can be seen on Dreiding models of the respective compounds.

Some of the compounds under investigation, mainly *II*—*IV*, show pronounced inhibiting effects upon the growth of *Bacillus subtilis* and *Escherichia coli* (10 μg/ml), yeast-like microorganisms, such as *Candida pseudotropicalis* (50 μg/ml), *Mycobacteria* BCG, and *M. fortuitum* (100/10 and 300/100, respectively). Experiments on protozoa *Trypanosoma cruzi* and *Euglena gracilis* show that the derivatives are not or only slightly toxic (lethal concentration 100 or 250). Substitution of hydrogen in *II* and *III* with cinnamoyl (compounds *VII* and *VIII*) caused about fivefold decrease in the efficiency. It follows from the foregoing that the substances from which hydrogen halide can be easily liberated are the most effective ones (a double bond in conjugation with the carbonyl group is formed). This hypothesis is supported by the fact that 3-chloropropylferrocene (*X*) and 4-chlorobutylferrocene are not effective at all. An exception from this rule was found to be compound *VI* which shows exceptional inhibiting effects (upon the bacteria 5—10 μg/ml) but also this compound loses halogen easily [11].

Acknowledgements. The authors wish to thank Dr E. Greipelová (Institute of Chemistry, Komenský University) for microanalyses and Dr A. Perjéssy (Department of Organic Chemistry and Biochemistry, Faculty of Natural Sciences, Komenský University) for i.r. measurements.

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Translated by P. Kováč