Formation and Cycloaddition Reactions of Ferrocenyl Nitrones

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This paper is dedicated to the memory of Professor Raymond N. Castle

Ferrocenyl nitrones derived from aldehydes or oximes react with electron deficient alkenes to give ferrocenylisoxazolidines. 5-Methoxycarbonylisoxazolidines are further transformed to ferrocenylpyrrolidinones by reductive cleavage. The regio- and stereoselectivity of the reactions are discussed.

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Since its discovery in 1951 [2], the fascinating structural properties of ferrocene have caused a growing interest in many areas such as material science, asymmetric catalysis, electrochemistry etc [3]. Owing to the stability and the wealth of methods of its derivatization many ferrocene derivatives have been prepared and studied in the various areas of interest. Among them heteroarylferrocenes attracted the attention of many investigators, since they combine the diverse properties of the heterocyclic residue and the ferrocene moiety. Furthermore several biological activities of these compounds were observed [4].

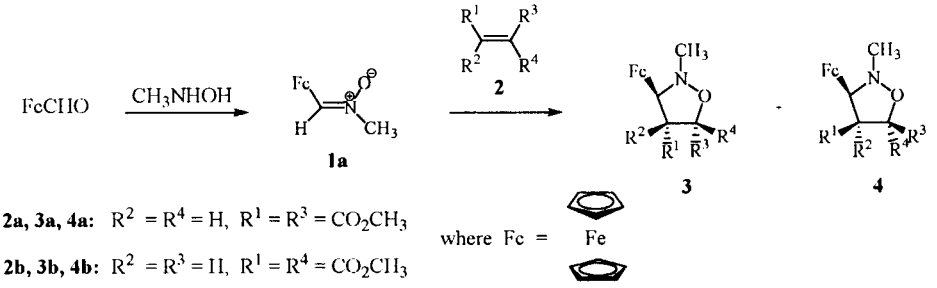
In connection with our earlier studies directed towards various aspects of 1,3-dipolar cycloaddition reactions [5], we examine in this paper the 1,3-dipolar cycloaddition reactions of ferrocenyl nitrones. Our aim is to expand the scope of nitrone cycloadditions to the synthesis of new heteroaryl ferrocenes and also look into the possible effects of the ferrocene group on the regio- and stereoselectivity of the reactions. Nitrone cycloaddition with olefins resulting in isoxazolidines has seen considerable use in organic synthesis and a wide variety of natural products have been synthesized using this reaction [6-8]. The regio- and the stereoselectivity depend on steric effects and the electron-withdrawing ability of the substituents and are often difficult to predict. Recently, satisfactory control of selectivities has been achieved by metal cordination [9,10]. The stereoelectronic properties of ferrocene such as its bulky three dimentional structure and the presence of the transition metal iron bearing lone pairs, suggest that it may affect the regio- and stereoselectivity of reactions.

The *C*-ferrocenyl-*N*-methylnitrone **1a** was prepared from ferrocenecarboxaldehyde by treatment with *N*-methylhydroxylamine. Only one stereoisomer was isolated, which was assigned as the *Z*-isomer. It has been demonstrated that aldonitrones generally exist as the stable *Z*-isomers [11,12], although in some papers nitrone *Z/E* isomerization is invoked to account for the observed selectivities [13,14]. The *Z*-structure of **1a** is supported by NOE experiments. Saturation of the CH_3 signal at δ 3.68 causes significant enhancement (11%) of CH=NO(CH_3) signal at δ 7.11 and saturation of the CH=NO(CH_3) resonance causes 4% enhancement of CH_3 resonance. The ^{1}H nmr spectrum of **1a** was also taken at temperatures up to 80 °C in DMSO-d_6 solution. No new signals or broadenings indicative of *Z/E* interconversion were observed.

Reaction of nitrone **1a** with the symmetrical alkenes **2a** and **2b** afforded mixtures of isoxazolidines **3** and **4** in 40-80% yields. The reactions were performed in refluxing benzene or toluene with an alkene:nitrone ratio of 1.2:1. The reaction with dimethyl maleate in refluxing toluene was found to be highly diastereoselective affording only one stereoisomer, **3a**. However at lower temperature (reflux in benzene) both stereoisomers **3a** and **4a** were isolated in the ratio of 1.6:1. The reaction with dimethyl fumarate afforded both stereoisomers **3b** and **4b** in the ratio of 6:1 in refluxing toluene and 3.5:1 in refluxing benzene. The structural assignment for the adducts **3a**, **4a** and **3b**, **4b** were mainly based on their ^{1}H nmr 4-COOCH$_3$ signals, which are shielded by the vicinal ferrocenyl group in the *cis* configuration. In analogous cycloadducts it has been observed, that C-3 aromatic substituent causes a significant shielding effect on the *cis* C-4 ester substituent, whilst essentially no effect is observed on the C-5 ester substituent [5c]. Thus, the chemical shifts of 4,5-COOCH$_3$ of **3a**, **3b** appear at δ 3.79 (2 x COOCH$_3$) and δ 3.84, 3.87 respectively, whereas that of **4a**, **4b** appear at δ 3.34, 3.73 and 3.48, 3.78. The higher field signals at δ 3.34 and 3.48 are, in both cases, ascribed to the 4-COOCH$_3$ *cis* to the ferrocenyl group. The $J_{3,4}$ values, which are larger for the *cis* arrangement of H-3, H-4, provide further evidence for the proposed structures based on analogy with other nitrone cycloadducts [10b]. Thus the $J_{3,4}$ of stereoisomers **4a** and **3a** from the reaction with dimethyl maleate are 8.2 and 6.8 Hz respectively, whereas that of isomers **4b** and **3b** are 9.1 and 6.7 Hz. It is worth mentioning that some of the ^{1}H nmr and ^{13}C nmr signals are broad. This broadening is attributed to the relatively slow inversion of the isoxazolidine nitrogen atom, a process known for other isoxazolidines [15,16]. With increasing temperature the broadening is usually reduced and some spectra have been measured at 50 °C , as specified in the experimental section. The chemical shift of H-3 either remains broad even at higher temperatures or is overlapped by other peaks, so the $J_{3,4}$ values were found from the multiplicity of H-4.

The diastereoselectivity of the reactions of **1a** with dimethyl fumarate and dimethyl maleate can be

Scheme 1



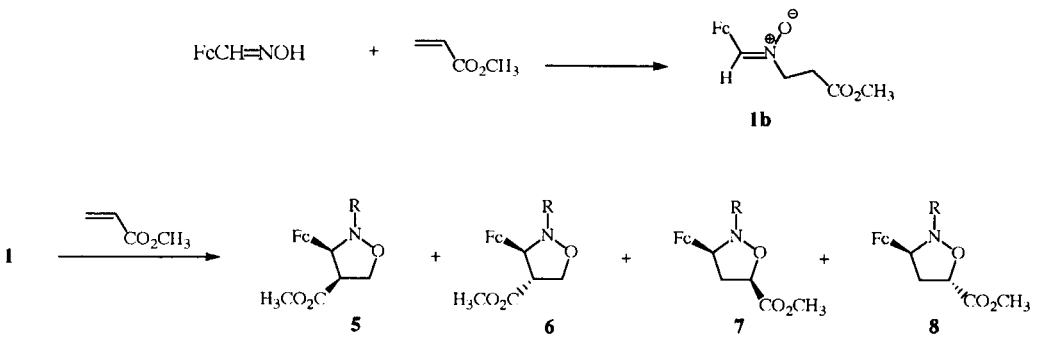
rationalized by examination of the transition states. Since the *Z*-configuration of nitrone **1a** has been found to be stable the cycloaddition is assumed to proceed from this isomer through an *endo* or *exo* transition state. Secondary orbital interactions between the dipolarophile substituents and the nitrone nitrogen favor the *endo*-approach, whereas steric factors favor the *exo*-approach. In the reaction of **1a** with dimethyl fumarate secondary interactions are thought to affect both of the transition states similarly, since in both of them the one $COOCH_3$ is *endo* and the other is *exo*, whereas steric factors are expected to favor the approach with the *endo* $COOCH_3$ located at the less crowded 4-position leading to the major isomer **3b**. In the reaction of **1a** with dimethyl maleate the stereoselectivity is smaller since steric factors compete with secondary interactions. Thus the major isomer **3a** is formed through an *endo*-approach favored by secondary interactions and the minor isomer **4a** through an *exo*-approach favored by steric factors. The observed stereoselectivity is analogous to that of other nitrones with fumarates and maleates [5c,5d,6,15] and the ferrocene moiety does not appear to have any special effects on the stabilization of the transition states. When the reaction is carried out at higher temperatures the formation of the thermodynamically more stable isomers **3a** and **3b** is favored and in the case of **3a** this is the only product, probably as a result of a greater destabilization effect of ferrocene on product **4a**. A retrocycloaddition is invoked in many cases to account for the enrichment of the reaction mixtures of nitrone cycloadditions to the more stable isomers at higher temperatures [6, 7].

The reaction of nitrone **1a** with methyl acrylate afforded four cycloadducts, two diastereomeric 4-methoxycarbonylisoxazolidines **5a** and **6a** and two diastereomeric 5-methoxycarbonylisoxazolidines **7a** and **8a** in 74% total yield and in the ratio of 1:1.5:1.1:5.6, as estimated from the ^1H nmr spectra of their mixtures. Only the major isomer **8a** was isolated in a pure state, whilst the diastereoisomers **5a** and **6a** were isolated as a mixture and **7a** was assigned from its mixture with **8a**. The structure of the isomers was assigned on the basis of their ^1H nmr and ^{13}C nmr chemical shifts by analogy to other isoxazolidines [5c,5d]. The 5-methoxycarbonyl regioisomers **7a** and **8a** exhibit characteristic downfield signals for 5-H at δ 4.59 and 4.63 and for C-5 at δ 74.2 and 74.6 respectively. The distinction between the stereoisomeric 4-methoxycarbonylisoxazolidines **5a** and **6a** was easily made on the basis of 4-$COOCH_3$ proton signal, which in the *cis* configuration is shifted upfield. Thus the **5a** isomer exhibits its $COOCH_3$ proton signal at δ 3.39 whereas in **6a** it is at δ 3.82. The distinction between stereoisomers **7a** and **8a** was not obvious from their spectra. The structure **8a** was assigned to the major isomer on the basis of its reduction product **10a**.

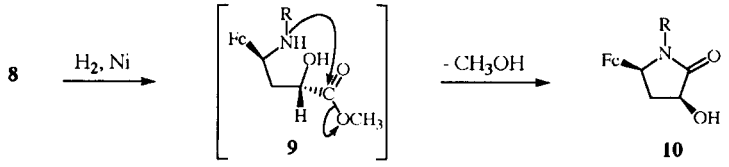
As an alternative path to ferrocenyl isoxazolidines the reaction of ferrocenecarboxaldehyde oxime with methyl acrylate was examined. Over the past few years oximes have been proved to be precursors of isoxazolidines in a wide range of tandem nitrone-cycloaddition processes [17,18]. Nitrone generation from oximes is allowed *via* a 1,2-prototropic process or the 1,3-azaprotiocyclotransfer reaction. The latter is invariably preferred when electron deficient alkenes are involved. Thus the reaction of ferrocenecarboxaldehyde oxime with methyl acrylate is assumed to proceed *via* the intermediate nitrone **1b** and subsequent cycloaddition. The reaction was performed by boiling ferrocenecarboxaldehyde oxime in excess methyl acrylate and afforded a mixture of the four isomeric isoxazolidines **5b**, **6b**, **7b** and **8b** in the ratio of 1:1.1:1.2:3.8 and in 84% total yield. Also in this case only the major isomer **8b** was isolated in a pure state, whilst the diastereoisomers **5b** and **6b** were isolated as mixture and the isomer **7b** was assigned from its mixture with **8b**. The structure assignment of the isomers was made as in the case of the reaction products with **1a**. In the ^1H nmr spectrum of 5-substituted isomers **7b** and **8b** the 5-H appears at δ 4.58 and 4.61, whilst in the ^{13}C nmr the C-5 appears at δ 74.3 and 75.0 respectively. In the ^1H nmr spectrum of the mixture of **5b** and **6b** there are four signals for the $COOCH_3$ hydrogens at δ 3.39, 3.64, 3.72 and 3.80. The upfield signal at δ 3.39, indicative of a *cis* methoxycarbonyl-ferrocenyl configuration, permits the distinction of stereoisomer **5b** from **6b**. The assignment of stereoisomers **7b, 8b** was made on the basis of the reduction product of **8b**, as described below.

The regio- and stereoselectivity of the reactions of **1a** and **1b** with methyl acrylate is rather low as in most reactions of nitrones with unsymmetrical electron deficient dipolarophiles [6-8]. The formation of 5-substituted regioisomers favored by a LUMO-dipole interaction predomi-

Scheme 2



Scheme 3



nates. The ratios of 5- to 4-substituted isomers in the reactions of **1a** and **1b** are 2.7:1 and 2.4 :1 respectively. The process to 5-substituted regioisomers is quite regioselective leading preferentially to the *trans*-isomer probably *via* an *endo* transition state favored by secondary interactions. The process to the 4-substituted regioisomers lacks almost any selectivity, a fact rationalized by an *endo* transition state, in which the methoxycarbonyl group is more crowded and steric factors compete with secondary interactions. Compared with the cycloaddition of other aryl nitrones to methyl acrylate [5c,5d] reactions of **1a** and **1b** show an increased selectivity for the formation of products **8a** and **8b** respectively. However this fact cannot be attributed to a definite effect of the ferrocene moiety.

We have previously shown [5d] that reduction of 5-methoxycarbonylisoxazolidines leads stereospecifically to 3-hydroxypyrrolidinones, in which the initial 5-H of the isoxazolidine ring comes to the opposite site of the new ring. Following the same procedure upon reduction with hydrogen over Raney Nickel isoxazolidines **8a** and **8b** were transformed, *via* intermediate **9**, to pyrrolidinones **10a** and **10b** respectively. The stereochemistry of pyrrolidinone **10a** was assigned on the basis of the chemical shifts of the 4-H protons, which are largely differentiated and appear as multiplets centered at δ 2.16 and 2.94. These values are very close to those of analogous hydroxypyrrolidinones with the same stereochemisty confirmed by NOE experiments [5d]. In a *cis* arrangement both the ferrocenyl and the hydroxy groups exhibit a shielding effect to the same 4-H causing this large difference. The assignment of 4-H in the spectrum of **10b** was not obvious, since, besides the 4-H protons, the diastereotopic protons of the chain methylene groups exhibit also separate multiplets, as given in the experimental part. The interpretation of the spectrum and the assignment of 4-H was possible with decoupling experiments. Irradiation of the overlapped 3-H and 5-H multiplet centered at δ 4.35 disturbs the multiplets centered at δ 2.16 and 2.93, irradiation of the signal at δ 2.93 disturbs the signals at δ 4.35 and 2.16, whilst irradiation of the signal at δ 2.16 disturbs those at δ 4.35 and 2.93 as well as all the other multiplets corresponding to the chain methylene protons. So the signal at δ 2.93 is attributed to one of the 4-H and the signal at δ 2.16 to the other overlapped with one of the chain methylene protons. The observed 4-H chemical shifts of **10b** are almost the same as that of **10a** suggesting the same stereochemistry. Unfortunately, due to the overlapping of 3-H with 5-H in **10b** or with the cyclopentadiene protons in **10a**, it was not possible to perform useful NOE experiments to further support the proposed stereochemistry.

On the basis of the above results we conclude, that ferrocenyl nitrones exhibit the same behavior as other aryl nitrones and show almost similar selectivities in reactions

with electron deficient alkenes. The observed small differences cannot be attributed to a definite effect of the ferrocene moiety. Thus, ferrocenyl nitrones prepared from aldehydes or derived as intermediates from oximes, are useful building blocks for the synthesis of ferrocenylisoxazolidines, which suitably substituted can be further transformed to other heteroarylferrocenes.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The ir spectra were obtained with a Perkin-Elmer Model 297 spectrometer. ^{1}H nmr spectra were recorded on a 300 Bruker AM spectrometer at 300 MHz and ^{13}C nmr spectra on the same spectrometer at 75.7 MHz, in deuteriochloroform solutions and are quoted relative to tetramethylsilane as internal standard, unless otherwise specified. Mass spectra were determined on a VG-250 spectrometer with ionization energy maintained at 70 eV. Microanalyses were performed on a Perkin-Ermer Model 2400-II analyser. Column chromatography was carried out on Merck Kieselgel (particle size 0.063-0.200).

Ferrocenecarboxaldehyde Oxime.

This compound was prepared according to the literature method [19]. It was obtained as a mixture of *Z* and *E* isomers as determined by ^{1}H nmr and was used as a mixture.

C-Ferrocenyl-*N*-methyl-nitrone (**1a**).

This compound was prepared from ferrocenecarboxaldehyde and *N*-methylhydroxylamine. The latter was used in excess in order to consume all the ferrocenecarboxaldehyde. Thus, a solution of *N*-methylhydroxylamine hydrochloride (752 mg, 9 mmoles) and sodium carbonate (636 mg, 6 mmoles) in water (3 ml) was added to a solution of ferrocenecarboxaldehyde (856 mg, 4 mmoles) in ethanol (4 ml) and the reaction mixture was stirred under argon at room temperature for 24 hours. The ethanol was evaporated under *vacuum* and the residue was extracted with methylene chloride (3 x 20 ml). The organic layer was dried with sodium sulfate (Na_2SO_4) and evaporated. Trituration of the residue with diethyl ether gave nitrone **1a** (780 mg, 80%) as an orange-brown solid mp 96-98 °C; ir (nujol): ν 1600 (C=N) cm^{-1}; ^{1}H nmr: δ 3.68 (s, 3H, *N*-CH_3), 4.19 (s, 5H, Cp), 4.36-4.40 (m, H, Cp), 4.98-5.02 (m, 2H, Cp), 7.11 [s, 1H, C*H*=N(O)CH_3]; ^{13}C nmr: δ 53.0 (N-CH_3), 69.1, 69.8, 70.4 (CH in Cp), 84.0 (quaternary C in Cp), 136.1 [*C*H=N(O)CH_3]; ms: m/z: 243 (M^+, 45%).

Anal. Calcd. for $C_{12}H_{13}FeNO$: C, 59.29; H, 5.39; N, 5.76. Found: C, 58.96, H, 5.35; N, 5.63.

Reaction of Nitrone **1a** With Dimethyl Maleate.

A solution of nitrone **1a** (1 mmole) and dimethyl maleate (1.2 mmoles) in dry benzene (5 ml) was heated to reflux under argon for 8 hours. After evaporation of the solvent from column chromatography with hexane/ethyl acetate 5:1 as eluent there were obtained in order of elution **3a** and **4a** in the of ratio 1.6:1 and a total yield of 55%. Repeat of the reaction by heating to reflux in toluene for 4 hours gave only the isomer **4a** in yield 40%. The yield was not improved by increasing the reaction duration.

(3*R**,4*S**,5*R**)-3-Ferrocenyl-4,5-bis(methoxycarbonyl)-2-methylisoxazolidine (**3a**).

This compound was obtained as an orange solid, mp 78-79 °C; ir (nujol): ν 1725 (CO) cm^{-1}; ^{1}H nmr (50 °C): δ 2.80 (s, 3H, *N*-CH_3), 3.79 (s, 6H, $COOCH_3$), 3.85 (dd, ΣJ = 15.7Hz, 1H, 4-H), 3.97 (broad, 1H, 3-H), 4.15 and 4.10-4.30 (superimposed s and m, 9H, H-Cp), 4.83 (d, J = 8.9 Hz, 1H, 5-H); ^{13}C nmr (50 °C): δ 43.0 (broad, *N*-CH_3), 52.3 ($COOCH_3$), 58.0 (C-4), 65.9, 68.3, 68.6, 68.7 and 68.8 (CH in Cp), 70.8 (broad, C-3), 77.4 (C-5), 83.5 (quaternary C in Cp), 168.8 and 171.3 (CO): ms: m/z 387 (M^+, 66%).

Anal. Calcd for $C_{18}H_{21}FeNO_5$: C, 55.83; H, 5.47; N, 3.62. Found: C, 56.20; H, 5.59; N, 3.81.

(3*S**,4*S**,5*R**)-3-Ferrocenyl-4,5-bis(methoxycarbonyl)-2-methylisoxazolidine (**4a**).

This compound was obtained as an orange solid, mp 138-140 °C (from ethanol); ir (nujol): ν 1725 (CO) cm^{-1}; ^{1}H nmr: δ 3.05 (s, 3H, *N*-CH_3), 3.34 (s, 3H, $COOCH_3$), 3.73 (s, 3H, $COOCH_3$), 3.89 (broad, 1H, 3-H), 4.04 (t, ΣJ = 16.5 Hz, 1H, 4-H), 4.16 and 4.10-4.29 (superimposed s and m, 9H H-Cp), 4.82 (d, J = 8.3 Hz, 1H, 5-H); ^{13}C nmr: δ 45.2 (*N*-CH_3), 51.8 ($COOCH_3$), 52.3 ($COOCH_3$), 58.1 (C-4), 67.0, 67.4, 67.6, 67.8 and 68.9 (CH in Cp), 71.1 (C-3), 75.4 (C-5), 81.8 (quaternary C in Cp), 170.3 (CO); ms: m/z 387 (M^+, 7%).

Anal. Calcd for $C_{18}H_{21}FeNO_5$: C, 55.83; H, 5.47; N, 3.62. Found: C, 55.44; H, 5.43; N, 3.49.

Reaction of Nitrone **1a** With Dimethyl Fumarate.

A solution of nitrone **1a** (1 mmole) and dimethyl fumarate (1.2 mmoles) in dry benzene (5 ml) was heated to reflux under argon for 8 hours. After evaporation of the solvent from column chromatography with hexane/ethyl acetate 5:1 as eluent the two isomers **3b**, **4b** were obtained as an oily mixture in the ratio of 3.5:1 (nmr integration) and 65% total yield. Repeat of the reaction by heating to reflux in toluene for 4 hours afforded the two isomers **3b**, **4b** in the ratio of 6:1 and 80% total yield. From the reaction mixture a part of isomer **4b** was crystallized from ethanol by refrigerated cooling, but after the filtration at room temperature it was transformed to oil again. After the removal of ethanol the filtrates were subjected to a second column chromatography with hexane/ethyl acetate 10:1 as eluent from which a small fraction of pure **3b** was isolated.

(3*R**,4*S**,5*S**)-3-Ferrocenyl-4,5-bis(methoxycarbonyl)-2-methylisoxazolidine (**3b**).

This compound was isolated as an oil; ir (neat): ν 1730 (CO) cm^{-1}; ^{1}H nmr (50 °C): δ 2.73 (s, 3H, *N*-CH_3), 3.84 (s, 3H, $COOCH_3$), 3.87 (s, 3H, $COOCH_3$), 4.07 (dd, J = 6.7, 4.1 Hz, 1H, 4-H), 4.15 and 4.12-4.30 (superimposed s and m, 10H 3-H and H-Cp), 4.71 (d, J = 4.1 Hz, 1H, 5-H); ^{13}C nmr: δ 43.1 (*N*-CH_3), 52.7 ($COOCH_3$), 52.8 ($COOCH_3$), 57.2 (C-4), 66.1, 67.3, 68.3, 68.7 and 68.9 (CH in Cp), 71.1 (C-3), 78.2 (C-5), 83.4 (quaternary C in Cp), 172.6 (CO); ms: m/z 387 (M^+, 83%).

Anal. Calcd for $C_{18}H_{21}FeNO_5$: C, 55.83; H, 5.47; N, 3.62. Found: C, 55.92; H, 5.56; N, 3.90.

(3*S**,4*S**,5*S**)-3-Ferrocenyl-4,5-bis(methoxycarbonyl)-2-methylisoxazoli-dine (**4b**).

This compound was isolated as an oil; ir (neat): ν 1730 (CO) cm^{-1}; ^1H nmr: δ 2.98 (s, 3H, *N*-CH_3), 3.48 (s, 3H, $COOCH_3$), 3.78 (s, 3H, $COOCH_3$), 3.94 (t, ΣJ = 16.3 Hz, 1H, 4-H), 4.17 and 4.03-4.29 (superimposed s and m, 10H 3-H and H-Cp), 4.87 (d, J = 7.2 Hz, 1H, 5-H); ^{13}C nmr: δ 46.1 (*N*-CH_3), 52.0 ($COOCH_3$), 52.7 ($COOCH_3$), 56.4 (C-4), 67.2, 67.3, 67.5, 68.0 and 68.9 (CH in Cp), 70.0 (C-3), 77.6 (C-5), 84.3 (quaternary C in Cp), 169.3 and 171.2 (CO); ms: m/z 387 (M^+, 42%).

Anal. Calcd for $C_{18}H_{21}FeNO_5$: C, 55.83; H, 5.47; N, 3.62. Found: C, 55.63; H, 5.53; N, 3.97.

Reaction of Nitrone **1a** with Methyl Acrylate.

A solution of the nitrone **1a** (1 mmole) in methyl acrylate (2ml) was heated to reflux under argon for 1 hour. After evaporation of the excess methyl acrylate the residue was subjected to column chromatography with hexane/ethyl acetate as eluent to give isomers **5a**, **6a**, **7a** and **8a** in the ratio of 1:1.5:1.1:5.6 and 74% total yield. From the column there were obtained in order of elution: a) 65 mg mixture of **5a**, **6a** in the ratio of 1:1.5 (nmr integration), 44 mg mixture of **7a** and **8a** in the ratio of 2:1 c) 133 mg of **8a**. Further chromatographic separation of the isomers was not possible, so stereoisomers **5a** and **6a** were assigned as a mixture, whereas **7a** was assigned from its nmr specrta of its mixture with **8a**.

Mixture of the stereoisomers (3*R**, 4*S**)- and (3*R**, 4*R**)-3-ferrocenyl-4-methoxycarbonyl-2-methylisoxazolidines (**5a**) and (**6a**).

The mixture of stereoisomers **5a** and **6a** was obtained as a solid mp 90-140 °C ; ir (nujol): ν 1730 (CO) cm^{-1}; ^1H nmr: δ 2.71 (s broad, *N*-CH_3), 2.90 (s, *N*-CH_3), 3.39 (s, $COOCH_3$), 3.55-3.75 (m, 4-H), 3.82 (s, $COOCH_3$), 4.14, 4.15 and 3.99-4.29 (superimposed s and m, 3-H, 5-H and Cp-H); ^{13}C nmr: δ 43.4 and 45.2 (broad, *N*-CH_3), 51.5, 52.3, 53.0 and 55.4 ($COOCH_3$ and C-4), 65.8 and 70.6 (broad C-3 and C-5), 66.9, 67.0, 67.2, 67.4, 67.6, 68.1, 68.5, 68.7, 68.8 and 69.5 (CH in Cp), 84.9 and 85.7 (quaternary C in Cp), 170.6 and 173.6 (CO); ms: m/z 329 (M^+, 18%), 243 (100%).

Anal. Calcd for $C_{16}H_{19}FeNO_3$: C, 58.38; H, 5.82; N, 4.26. Found: C, 58.32; H, 6.02; N, 4.09.

(3*R**,5*S**)-3-Ferrocenyl-5-methoxycarbonyl-2-methylisoxazolidine (**7a**).

^1H nmr (50 °C): δ 2.62 (s *N*-CH_3), 2.75-3.02 (m, 4-H), 3.79 (s, $COOCH_3$), 4.17 and 4.05-4.30 (superimposed s and m, 3-H and Cp-H), 4.59 (dd, J = 9.6, 5.4 Hz, 5-H); ^{13}C nmr: δ 40.2 (C-4), 42.9 (*N*-CH_3), 52.3 ($COOCH_3$), 66.3 (C-3), 68.2, 68.4, 68.5, 68.8 and 68.9 (CH in Cp), 74.2 (C-5), 82.8 (quaternary C in Cp), 173.0 (CO).

(3*R**,5*R**)-3-Ferrocenyl-5-methoxycarbonyl-2-methylisoxazolidine (**8a**).

This compound was obtained as a yellow solid mp 95-96 °C; ir (nujol): ν 1760 (CO) cm^{-1}; ^1H nmr (50 °C): δ 2.62 (s broad, 3H, *N*-CH_3), 2.74-2.86 (m, 2H, 4-H), 3.80 (s, 3H, $COOCH_3$), 4.17 and 4.00-4.28 (superimposed s and m, 10H, 3-H and Cp-H), 4.63 (t, J = 7.1 Hz, 1H, 5-H); ^{13}C nmr: δ 40.8 (C-4), 43.3 (*N*-CH_3), 52.3 ($COOCH_3$), 65.9 (C-3), 68.1, 68.3, 68.5, 68.7 and 69.3 (CH in Cp), 74.6 (C-5), 83.2 (quaternary C in Cp), 171.7 (CO); ms: m/z 329 (M^+, 90%), 243 (100%).

Anal. Calcd for $C_{16}H_{19}FeNO_3$: C, 58.38; H, 5.82; N, 4.26. Found: C, 58.10; H, 5.81; N, 4.24.

Reaction of Ferrocenecarboxaldehyde Oxime with Methyl Acrylate.

A suspension of ferrocene carboxaldehyde oxime (1 mmole) in methyl acrylate was heated to reflux for 2 hours. After evaporation of the excess methyl acrylate the residue was subjected to column chromatography with hexane/ethyl acetate (5:1) as eluent to give the four isomers **5b**, **6b**, **7b** and **8b** in the ratio of 1:1.1:1.2:3.8 and 84% total yield. From the column there were obtained in order of elution: a) 78 mg mixture of **5b** and **6b** in the ratio of 1:1.4; b) 54 mg mixture of **5b**, **6b**, **7b** and **8b** in the ratio of 2.1:1:2.2:2.2 c) 124 mg mixture of **7b** and **8b** in the ratio of 1:2.1 and d) 80 mg of **8b**. Further separation of the isomers by column chromatography or by crystallization was not possible, so stereoisomers **5b** and **6b** were assigned as **a** mixture, whereas **7b** was assigned from nmr spectra of its mixture with **8b**.

Mixture of the stereoisomers (3*R**, 4*S**)- and (3*R**, 4*R**)-3-ferrocenyl-4-methoxycarbonyl-2-(2-methoxycarbonylethyl)isoxazolidines **5b** and **6b**.

This mixture was obtained as an oil; ir (neat): ν 1735 (CO) cm^{-1}; ^1H nmr: δ 2.60 (t broad, CH_2COOCH_3), 2.64-2.82 (m, CH_2COOCH_3), 2.87-3.13 (superimposed broad and m, NCH_2), 3.39 (s, $COOCH_3$), 3.64, 3.72, 3.80 and 3.50-380 (superimposed s and m, $COOCH_3$ and 4-H), 3.94-4.31 (superimposed s and m, 3-H, 5-H and Cp-H); ^{13}C nmr: δ 32.9 and 33.1 (CH_2COOCH_3), 51.4, 51.5, 51,6, 52.3, 52.5, 52.7 and 55.0 (NCH_2, $COOCH_3$ and C-4), 65.9, 66.3, 67.0, 67.1, 67.5, 67.6, 68.0, 68.1, 68.3, 68.4, 68.5 and 68.6 (C-3 , C-5 and CH in Cp), 85.5 (quaternary C in Cp), 170.1, 172.5, 172.6 and 173.3 (CO); ms: m/z 401 (M^+, 33%), 315 (56%), 229 (45%), 121 (100%).

Anal. Calcd for $C_{19}H_{23}FeNO_5$: C, 56.88; H, 5.78; N, 3.49. Found: C, 57.10; H, 5.81; N, 3.34.

(3*R**,5*S**)-3-Ferrocenyl-5-methoxycarbonyl-2-(2-methoxycarbonylethyl)isoxazolidine (**7b**).

^1H nmr: δ 2.50-3.35 (m, NCH_2, CH_2COOCH_3, 4-H), 3.62 (s, $COOCH_3$), 3.76 (s, $COOCH_3$), 4.07-4.26 (superimposed s and m, 3-H and Cp-H), 4.58 (t, J = 7.3 Hz, 5-H); ^{13}C nmr (50 °C), δ : 32.7 (CH_2COOCH_3), 39.9 (C-4), 50.8, 51.3 and 52.0 (NCH_2 and $COOCH_3$), 65.7 (C-3), 66.5, 68.4, 68.6 and 69.3 (CH in Cp), 74.3 (C-5), 83.7 (quaternary C in Cp), 172,3 (CO).

(3*R**,5*R**)-3-Ferrocenyl-5-methoxycarbonyl-2-(2-methoxycarbonylethyl)isoxazolidine (**8b**).

This compound was obtained as an oil; ir (neat): ν 1735 (CO) cm^{-1}; ^1H nmr, δ : 2.50-3.35 (m, NCH_2, CH_2COOCH_3, 4-H), 3.63 (s, $COOCH_3$), 3.78 (s, $COOCH_3$), 4.14 and 4.05-4.25 (superimposed s and m, 3-H and Cp-H), 4.61 (t, J = 7.3 Hz, 5-H); ^{13}C nmr (50 °C), δ : 32.8 (CH_2COOCH_3), 40.2 (C-4), 51.2, 51.4 and 51.9 (NCH_2 and $COOCH_3$), 65.1 (C-3), 66.1, 67.4, 68.3 68.5 and 69.0 (CH in Cp), 75.0 (C-5), 84.3 (quaternary C in Cp), 171.9, 172.4 (CO); ms: m/z 401 (M^+, 89%), 315 (56%), 229 (45%), 121 (100%).

Anal. Calcd for $C_{19}H_{23}FeNO_5$: C, 56.88; H, 5.78; N, 3.49. Found: C, 56.58; H, 5.61; N, 3.77.

Reduction of Isoxazolidine **8a**.

To a solution of isoxazolidine **8a** (0.5 mmole) in methanol (5 ml) a catalytic amount of W-2 Raney nickel was added. A balloon , filled with hydrogen was adapted to the reaction flask by means of a three way stopcock. After flushing three times with hydrogen gas, the reaction mixture was stirred under hydrogen atmosphere for 2 hours at room temperature. Nickel was separated by filtration through Celite and washed several times with methanol and methylene chloride. The combined filtrate and washings were concentrated under *vacuo* and the residue was subjected to column chromatography with hexane/ethyl acetate as eluent to give compound **10a** in 95% yield. For analytical purposes compound **10a** was further purified with a second column chromatography.

(3*S**, 5*S**)-5-Ferrocenyl-3-hydroxy-1-methylpyrrolidin-2-one (**10a**).

This compound was obtained as yellow needles, mp 220-223 °C; ir (nujol): ν 3300 (OH), 1660 (CO) cm^{-1}; ^1H nmr: δ 2.08-2.24 (m, 1H, 4α-H), 2.55 (s, 3H, *N*-CH_3), 2.78 (broad removed with D_2O, 1H, OH), 2.86-3.00 (m, 1H, 4β-H), 4.19 and 4.13-4.28 (superimposed s and m, 10H, 3-H and Cp-H), 4.42 (t, J = 8.1 Hz, 1H, 5-H); ^{13}C nmr, δ : 27.4 and 35.5 (*N*-CH_3 and C-4), 56.2 (C-5), 66.1 (C-3), 68.3, 68.6, 68.7, 69.4 and 69.5 (CH in Cp), 84.9 (quaternary C in Cp), 174.2 (CO); ms: m/z 299 (M^+, 97%).

Anal. Calcd for $C_{15}H_{17}FeNO_2$: C, 60.23; H, 5.73; N, 4.68. Found: C, 59.91; H, 6.02; N, 4.51.

Reduction of Isoxazolidine **8b**.

The same procedure with the above reaction was followed. Compound **10b** was obtained in 70% yield from the column. For analytical purposes it was further purified by recrystallization from methanol/diethyl ether.

(3*S**,5*S**)-5-Ferrocenyl-3-hydroxy-1-(2-methoxycarbonylethyl) pyrrolidin-2-one (**10b**).

This compound was obtained as a yellow solid, mp 138-139 °C; ir (nujol): ν 3290 (OH), 1660 (CO) cm^{-1}; ^1H nmr, δ : 2.08-2.23 (m, 2H, one of CH_2COOCH_3 and 4α-H), 2.43 (m, 1H, one of CH_2COOCH_3), 2.87-2.99 (m, 1H, 4β-H), 3.07-3.19 (m, 1H, one of NCH_2), 3.53 and 3.38-3.58 (superimposed broad and m, 2H, OH and one of CH_2COOCH_3), 3.63 (s, 3H, $COOCH_3$), 4.19 (s, 7H, H-Cp), 4.24 (s, 2H, Cp-H), 4.29-4.41 (m, 2H, 3-H, 5-H); ^{13}C nmr, δ : 32.0, 35.8 and 36.5 (CH_2), 51.7 and 54.8 (C-5 and $COOCH_3$), 66.3 (C-3), 68.6, 68.7, 68.8, 69.4 and 69.6 (CH in Cp), 88.0 (quaternary C in Cp), 171.8 and 174.2 (CO); ms: m/z 371 (M^+, 100%).

Anal. Calcd for $C_{18}H_{21}FeNO_4$: C, 58.24; H, 5.70; N, 3.77. Found: C, 58.53; H, 5.74; N, 3.82.

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