Synthesis and structure of some (*E*)-ferrocene-methylenecycloalkanones and their benzylidene analogues[1]

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Dedicated to Professor Gábor Bernáth on his 70th birthday

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Abstract

E-2-ferrocenemethylene- and *E*,*E*-diferrocenemethylenecycloalkanones as well as partial benzylidene analogues of the latter were synthesized by base-catalyzed Claisen-Schmidt condensation of ferrocenecarboxaldehyde with cyclopentanone, cyclohexanone, cycloheptanone and *E*-2-(4'-X-benzylidene)cycloalkanones. The stereostructure (configuration and conformation) and the electronic properties (conjugation of the enone moiety and the aromatic rings) of the compounds were studied by IR, ^{1}H and ^{13}C NMR methods. The spectroscopic properties of the ferrocene derivatives were compared with those of the respective benzylidene analogues**.**

Keywords: Ferrocene, cyclic enones, synthesis, spectroscopy

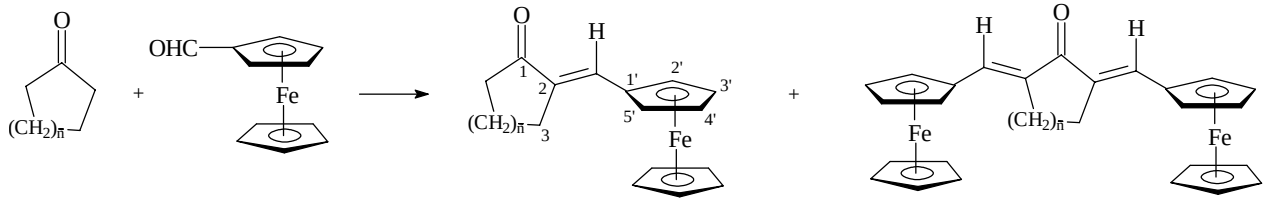
Introduction

Arylidenecycloalkanones are versatile starting materials for the synthesis of saturated and partially saturated heterocyclic ring systems.[1] Previously, we described the preparation of saturated and partially saturated 1,3-thiazines using *E*-2-arylidenecycloalkanones as starting materials.[2,3] Some diarylidenecycloalkanones have been reported to possess cytoprotective[4,5] as well as HIV-1 integrase[6] and factor Xa inhibitor activities[7]. These effects were found to depend on the ring size (stereochemistry) and the substituents of the aromatic rings.

[1]Study on ferrocenes, Part 11

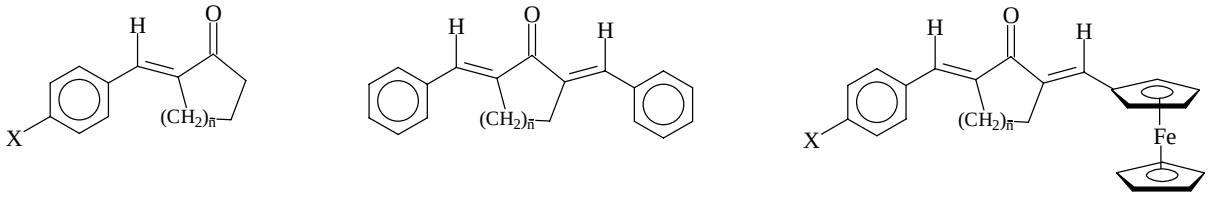
*Correspondance in relation to syntheses.

Replacement of a benzene ring by a ferrocene moiety influences significantly both the chemical and the biological properties of aromatic compounds.[8,9] Recently, we have synthesized some *E*-2-ferrocenemethylenebenzocyclanones and compared their electronic and stereochemical characteristics with the respective benzylidene analogues.[10,11] As a continuation of this work here we report on the synthesis and the spectroscopic investigation of some *E*-2-ferrocenemethylene- **3** and *E,E*-diferrocenemethylenecycloalkanones **4** as well as their complete **5**,**6** and partial **7**-**11** benzylidene analogues (Figure 1).



1 **2** **3** **4**

n = 1 (**a**), 2 (**b**), 3 (**c**)



5 **6** **7-11**

n = 1 (**a**), 2 (**b**), 3 (**c**); X = H (**7**), CH_3 (**8**), OCH_3 (**9**), NO_2 (**10**), $N(CH_3)_2$ (**11**).

Figure 1

Experimental Section

General Procedures. Cycloalkanones **1a-c**, ferrocenecarboxaldehyde (**2**) were obtained from Sigma-Aldrich, Hungary. Compounds **5a-c** (and their substituted derivatives) and **6a-c** were prepared according to the methods described in the literature.[12,13,14] The isolated **4a** and **4b** had the melting points (250 ^{o}C (decomp.) and 179-181 ^{o}C, respectively) corresponding to the previously reported values.[15] All the compounds were purified by column chromatography over Kieselgel 60 (Merck, 0.063-0.2 mm) using toluene or toluene/methanol (99/1)- as eluents. Melting points were determined on a Boetius apparatus at a heating rate of 4 ^{o}C/min and are uncorrected.

The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at RT, on a Bruker DRX-500 spectrometer at 500.13 (^{1}H) and 125.76 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The standard Bruker microprogram NOEMULT to generate NOE[16] and to get DIFFNOE spectra[17a,18] was used with a selective pre-irradiation time. DEPT spectra[19] were run in a standard manner,[20] using only a $\Theta=135^{\circ}$ pulse to separate the CH/CH_3 and CH_2 lines phased 'up' and 'down,' respectively. The 2D-COSY,[21a,22a] HMQC[21b,22b] and HMBC[23,24] spectra were obtained by using the standard Bruker pulse programs COSY-45, INV4GSSW and INV4GSLRNDSW, respectively. IR spectra were run in KBr disks on a Bruker IFS-55 FT-spectrometer controlled by Opus 3.0 software.

Reaction of ferrocenecarboxaldehyde (2) with cycloalkanones (1a-c). 1 mmol ferrocenecarboxaldehyde (**2**) and 5 mmol cycloalkanone (**1a-c**) were dissolved in 5 mL of MeOH and the solution was saturated with O_2-free N_2-gas for 5 min. In 5 mL MeOH saturated with O_2-free N_2, 1 mmol KOH was dissolved and the solution was added to the MeOH solution of **2** and the respective **1a-c**. The flask was sealed and kept at RT for 3-5 days. Then the mixture was placed in a refrigerator overnight and the resulting crystals (**4a**, **4b**) were filtered and purified by column chromatography. The filtrate (or the homogeneous reaction mixture) was evaporated at 40 $^{\circ}$C, the residue was dissolved in 100 mL $CHCl_3$, washed with distilled water (to remove all KOH), dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue, as well as the separated crystals, were subjected to column chromatography on Kieselgel 60 (Merck, 0.063-0.2 mm) adsorbent using toluene followed by toluene/MeOH (99/1) as eluent. The purity of the collected fractions were checked by TLC (Merck, Kieselgel 60 F_{254} aluminum sheets; developing solvents: dichloromethane and/or toluene/EtOH (4/1). The combined chromatographically pure fractions were evaporated to yield **3a**, **3b**, **3c**, **4a**, and **4b** as red or deep-red (**4a**,**4b**) crystals. The products obtained were further purified by crystallization from hexane or toluene-hexane (**4a**,**4b**) mixtures. The physical and analytical data of the previously unpublished compounds follow:

3a: 71-72 ºC; Yield 25%, Analysis: Found: C 68.47, H 5.68, Calculated ($C_{16}H_{16}FeO$, MW: 280.15) C 68.60, H 5.76%.

3b: 115-116 ºC; Yield 51%, Analysis: Found: C 69.32, H 6.23, Calculated ($C_{17}H_{18}FeO$, MW: 294.18) C 69.41, H 6.17%.

3c: 64-66 ºC; Yield 16%, Analysis: Found: C 69.98, H 6.31, Calculated ($C_{18}H_{20}FeO$, MW: 308.20) C 70.15, H 6.54%.

Reaction of ferrocenecarboxaldehyde (2) with *E*-2-benzylidenecycloalkanones (5a-c, X=H) and their substituted derivatives. 1 mmol ferrocenecarboxaldehyde (**2**) and 1.2 mmol *E*-2-benzylidenecycloalkanone (**5a-c,** X=H) were dissolved in 10 mL of MeOH and the solution was saturated with O_2-free N_2-gas for 5 min. In 5-mL MeOH saturated with O_2-free N_2, 1 mmol KOH was dissolved and the solution was added to the MeOH solution of **2** and the respective **5a-c**. The flask was sealed and kept at RT for 2 days (**5a**), or heated at reflux for 2 hours (**5b**) or 8 hours (**5c**) under an argon atmosphere. (Similar conditions were applied when the corresponding *E*-2-(4'-X-benzylidene)cycloalkanones [**5a**: X = H, CH_3, OCH_3, $N(CH_3)_2$; **5b**: X= H, CH_3,

OCH_3, NO_2; **5c**: X= H, CH_3, OCH_3, $N(CH_3)_2$] were used instead of the unsubstituted **5a-c**.). Then the mixture was placed in a refrigerator overnight and any resulting crystals (**7a**, **8a**, **9a**, **11a**) were filtered and purified by column chromatography. The filtrate (or the homogeneous reaction mixture) was evaporated at 40 °C and the residue was treated as described above. Column chromatography of the hydroxide-free residues and the separated crystals yielded **7a**, **8a**, **9a**, **11a**, **7b**, **8b**, **9b**, and **10b** as deep-red crystals. The products obtained were further purified by crystallization from hexane (**7b**, **8b, 9b**) or toluene-hexane mixtures. The physical and analytical data of the obtained compounds follow:

7a: M.p. 173-176 °C, Yield 67%, Analysis: Found: C 74.93, H 5.38, Calculated ($C_{23}H_{20}FeO$, MW: 368.26) C 75.02, H 5.47%.
8a: M.p. 198-199 °C, Yield 81%, Analysis: Found: C 75.18, H 5.83, Calculated ($C_{24}H_{22}FeO$, MW: 382.29) C 75.41, H 5.80%.
9a: M.p. 226-228 °C, Yield 73%, Analysis: Found: C 72.41, H 5.41, Calculated ($C_{24}H_{22}FeO_2$, MW: 398.28) C 72.38, H 5.57%.
11a: M.p. 212-215 °C; Yield 85%, Analysis: Found: C 72.86, H 5.93, Calculated ($C_{25}H_{25}FeNO$, MW: 411.33) C 73.00, H 6.13%.
7b: M.p. 128-130 ºC; Yield 58%, Analysis: Found: C 75,24, H 5,77, Calculated ($C_{24}H_{22}FeO$, MW: 382.29) C 75,41, H 5,80%.
8b: M.p. 153-155 ºC; Yield 64%, Analysis: Found: C 75,65, H 6,01, Calculated ($C_{25}H_{24}FeO$, MW: 396.31) C 75.77, H 6.10%.
9b: M.p. 181-183 ºC; Yield 62%, Analysis: Found: C 72,78, H 5,92, Calculated ($C_{25}H_{24}FeO_2$, MW: 412.31) C 72.83, H 5,87%.
10b: M.p. 182-184 ºC. Yield 78%, Analysis: Found: C 67.24, H 4.81, Calculated ($C_{24}H_{21}FeNO_3$, MW: 427.28) C 67.46, H 4.95%.

Results and Discussion

Reaction of ferrocenecarboxaldehyde (**2**) with cycloalkanones **1a-c** yielded the respective mixtures of *E*-ferrocenemethylenecycloalkanones **3a-c** and *E,E*-diferrocenemethyelene- cycloalkanones **4a** and **4b**. While most of the formed **4a** separated from the reaction mixture, no precipitate formation was observed in the other two reactions. The soluble mixtures of unreacted **2**, **3** and **4** could be separated by column chromatography on Kieselgel 60 using toluene and toluene/MeOH (99/1) as eluent. Contrary to the reactions with cyclopentanone (**1a**) and cyclohexanone (**1b**), in which two products (**3a,b** and **4a,b**) could be isolated, reaction of **2** with cycloheptanone (**1c**) resulted in the formation of only the respective monoferrocenemethylene derivative **3c** in a rather low yield. TLC analysis of the reaction mixture showed the formation of a second product as well; however, the amount of the formed compound was insufficient for its isolation and structural characterization.

The reason for the low yield is supposed to be the relatively high stability of the intermediate cycloheptanolate, which results in a less reactive intermediate to give a good yield in an aldolic reaction.[25] For spectroscopic comparisons we have also prepared the corresponding *E*-2-benzylidenecycloalkanones (**5a-c**)[12,13,14] and *E,E*-dibenzylidenecycloalkanones (**6a-c**).[12]

In order to synthesize ferrocene analogues (**7**-**11**) of *E,E*-dibenzylidenecyclanones **6a-c** we treated *E*-2-benzylidenecycloalkanones (**5a-c**) with ferrocenecarboxaldehyde (**2**) in the presence of KOH as a catalyst. Since the expected compounds (**7a-c**) are of interest from both chemical and biological points of view, we performed the reactions with some substituted *E*-2-(4'-X-benzylidene)cycloalkanones as well. In these reactions the expected mixed type ferrocene analogues of **6a** and **6b** were formed (Figure 1). In case of the reactions of **2** with **5c** and its substituted derivatives, low quantities of product were formed even after prolonged heating of the reaction mixtures, although formation of a new product could be detected on TLC. Also, no structural characterization of the products could be performed.

Because of the biological interest in the seven-membered ring derivatives, we are planning to develop modified reaction conditions that provide the expected compounds in higher yields in order to perform spectroscopic investigations and biological testing.

The ^{1}H and ^{13}C NMR data and characteristic IR frequencies of the new compounds are given in Tables 1 and 2 and they prove the expected structures straightforwardly. Only a few additional remarks are necessary.

The expected *E*-configuration of the compounds was based on comparisons of their ^{1}H and ^{13}C NMR data with previously published data of **5** and **6**[5,13] and those of the respective *E*-2-benzylidene- and *E*-2-ferrocenmethylenebenzocyclanones.[10,11] The stereohomogeneous *E,E*-configuration of **4a** and **6a-c** is proved by the symmetrical pattern of their NMR spectra. The change in substituents bonded to the cyclanone ring (arylmethylene or ferrocenylmethylene) has no significant influence on the structures and spectral characteristics in the new compounds.

In accordance with our earlier investigations the stereostructure (conformation) of *E*-2-benzylidene- and *E*-2-ferrocenmethylenebenzocyclanones depend on the size of the cyclanone ring.[10,11] Similar to the respective benzocyclanones, in the series **6** (dibenzylidenecyclanones) the molecule with 5-membered ring (**6a**) is almost fully planar: in the solid state the two benzylidene moieties subtend an angle of 10°.[26] In the cyclohexanone (**6b**) and the cycloheptanone (**6c**) derivatives the molecules are more distorted and the conformers with out of plane aryl group to the C=C double bonds are preferred.[27,6] The stereostructure is practically the same in the **4** and the **7-11**-type dienones.

In the monosubstituted cyclanones **5** the cinnamoyl moiety is distorted even in the molecules of **5a** with 5-membered ring: in the solid state the plane of the aryl ring deviates from that of the C=C double bond by 23°.[28] Similar conclusions could be drawn from the ^{13}C NMR investigation of a series of *E*-(4'-X-benzylidene)cyclohexanones.[13] The similar spectral characteristics of **5** and **3** reflect a similar stereostructure for the corresponding **3**.

In all the molecules the chemical equivalence of H/C–2',5' and H/C–3',4' atom pairs of the substituted Cp rings as well as the H/C–2,6 and H/C–3,5 atom pairs in the aryl groups proves a

fast interchange of coplanar conformations – the free internal rotation around the C–C bond binding the cyclic enone moiety to the ferrocenyl or aryl substituent.

The electron-reservoir character of the ferrocenyl moiety compensates the electron deficiency due to enone-polarisation around the C-β atom, and as a consequence, the chemical shift of =**C**(Fc) atom is higher in **b**- and **c**-type compounds where this effect is not present in the non-planar conformations.

In accordance with our previous results with the respective benzocylanones,[10,11] the characteristic higher C=O IR frequency[29] and ^{13}C NMR chemical shift[17b] of the cyclopentanones are observed in the series **a** (see Tables 1 and 2).

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