

CCA-1121

YU ISSN 0011-1643

547.631

Original Scientific Paper

Ferrocene Compounds. VII*. The Stobbe Condensation of Formylferrocene with Diethyl Glutarate

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Received June 5, 1978.

The Stobbe condensation of formylferrocene with diethyl glutarate in the presence of potassium *tert*-butoxide gave (*E*)-1-ethyl hydrogen 2-ferrocenylmethyleneglutarate (I), which was converted by the action of diazomethane to (*E*)-1-ethyl 5-methyl 2-ferrocenylmethyleneglutarate (II). The configurations of compounds I and II are assigned through study of their ¹H-NMR and IR spectra. This stereochemical assignment is supported by the conversion of compound I to cyclopentadienyl(5,6-dihydro-4-oxo-7-ethoxycarbonylazulenyl)iron (III), which was hydrolyzed to the corresponding acid (VI). The same acid VI was obtained from half ester I via the corresponding diacid IV and anhydride V.

The stereoselectivity of the Stobbe condensation is discussed.

INTRODUCTION

Although the Stobbe condensations of aromatic aldehydes and ketones with succinic esters have been thoroughly investigated, only a few examples of the analogous condensation with glutaric esters have been described.

El-Rayyes¹ has reported the formation of the expected (*E*)-half esters in the condensations of some heterocyclic aldehydes with dimethyl glutarate in the presence of sodium hydride. Johnson et al.² have found that diethyl glutarate failed to condense to any appreciable extent with benzophenone under those conditions which promoted condensation with succinate in 90% yield. In the field of ferrocene chemistry only the Stobbe condensations of acetyl- and benzoylferrocene with dimethyl succinate have been described³.

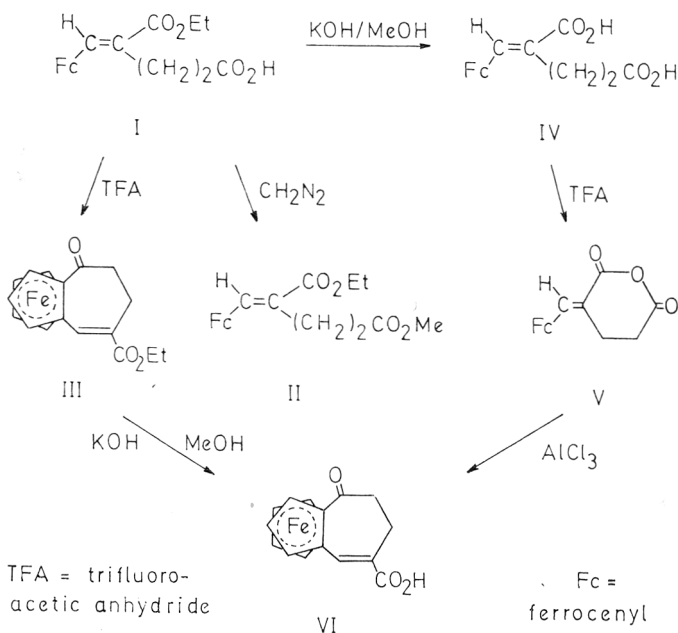
The present paper deals with the condensation of formylferrocene with diethyl glutarate; attempts to condense some ferrocenic ketones with diethyl glutarate have also been made.

RESULTS AND DISCUSSION

The condensation of formylferrocene with diethyl glutarate in the presence of potassium *tert*-butoxide gave the expected (*E*)-half ester I, which was converted by the action of diazomethane to the (*E*)-mixed ester II.

* Part VI: M. Laćan, V. Rapić, and A. Brbot-Šaranović, *Croat. Chem. Acta* 49 (1977) 857.

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The structures of compounds I and II are confirmed by their IR and $^1\text{H-NMR}$ spectra, and by the neutralization equivalent of the compound I. The carbonyl frequencies at 1690 and 1702 cm^{-1} in the IR spectrum of the half ester I can be attributed to the aliphatic acid and the unsaturated ester group [exactly the same carbonyl frequencies are reported for (*E*)-1-methyl hydrogen 2-(1-methyl-2-pyrrolylmethylene)glutarate¹]. The chemical shifts of olefinic and alkoxy carbonyl protons in the condensation products of aldehyde with succinic esters, and their esterification products, resp., depend strongly upon their stereochemical [(*E*)- or (*Z*)-] configuration^{3,4}. The olefinic and methoxycarbonyl protons in the $^1\text{H-NMR}$ spectrum of II were detected as sharp singlets at 7.60 and 3.79 ppm, whereas the analogous signals in the spectrum of (*E*)-1-ethyl 4-methyl 2-ferrocenylmethylenesuccinate⁵ lie at 7.63 and 3.77 ppm, resp.,* indicating the same configuration for the compound II and consequently I.

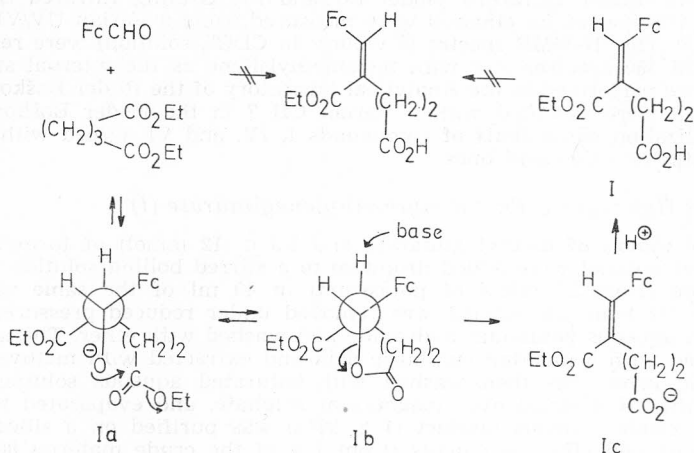
The reaction of acetyl- and benzoylferrocene with diethyl glutarate has failed.

The configuration about the double bond in the class of compounds type I and II can be determined by their intramolecular cyclization, when this reaction is faster than the acid-catalyzed interconversion of the geometrical isomers⁶.

The corresponding keto ester III was obtained by the action of trifluoroacetic anhydride on the half ester I. The precursor of the compound III must be the half ester having the (*E*)-configuration. Alkaline hydrolysis of the compound I gave the corresponding diacid IV, which upon treatment with trifluoroacetic anhydride afforded the anhydride V. The intramolecular Friedel-Crafts reaction of anhydride V gave the keto acid VI, which can be also pre-

* (*Z*)-1-ethyl 4-methyl 2-ferrocenylmethylenesuccinate⁵ gives these signals at 7.53 and 4.08 ppm, resp.

pared by the alkaline hydrolysis of the ester III. Compounds IV and V have presumably the (*E*)-configuration (NMR and IR spectra!), which is necessary for the reaction $V \rightarrow VI$.



In light of Heller's^{4,7} stereochemical observations on the Stobbe reaction of aromatic aldehydes with succinic esters one can interpret the stereoselectivity of the condensation of formylferrocene with diethyl glutarate as follows: in the intermediates Ia and Ib and in the corresponding transition states, the bulky ferrocenyl and ethoxycarbonyl substituents are opposed to each other or nearly so. Such geometry is evidently preferred to the theoretically possible diastereomers having the *gauche* or eclipsed conformations.

The stability of (*E*)-half ester I was demonstrated by the failure of its acid- or base-catalyzed isomerization to the (*Z*)-stereoisomer.

The Stobbe condensation of formylferrocene with diethyl glutarate gave, like the analogous condensation with diethyl succinate⁵, the corresponding half ester I in an almost quantitative yield. This fact could be rationalized in terms of the ease of formation and cleavage of the intermediate γ - and δ -lactonic system (Ib). Keeping in mind the planarity of the lactone group⁸ one can assume from the molecular models that the relative position and the orbital orientation of the reactive atoms in the molecule of Ia are not so favourable as in the analogous precursors to γ -lactone. The unfavourable interactions of the ferrocenyl group with the δ -lactone ring in Ib are more severe than in the analogous γ -lactonic system. On the other hand it is well known⁹ that δ -lactones hydrolyzed far more readily than γ -lactones. From these facts one can assume that (a) the intermediate δ -lactone Ib is more slowly formed, but it cleaves faster to I (by an E2 reaction), and that (b) contrarily, the formation of the analogous intermediate γ -lactonic system is faster, but it cleaves more slowly, so that both reactions [(a) and (b)] could have a similar overall energy profile.

EXPERIMENTAL

General

The experiments were performed under an argon atmosphere, using freshly distilled reactants: methylene chloride or 1,2-dichloroethane was dried over phosphorus pentoxide, and *tert*-butanol was obtained by distillation from sodium *tert*-

-butoxide. The course of reactions was followed by TLC on chromatoplates of silica-gel G (Merck) in benzene : ethanol (v/v) 30 : 1 and 15 : 1.

The melting points were determined by using a Büchi apparatus and are uncorrected. The IR spectra were recorded as KBr pellets, liquid films or CHCl_3 solutions with a Perkin-Elmer Infracord Model 137 and 257 Grating Infrared Spectrophotometer. The UV spectra (in ethanol) were measured using a Varian UV/VIS Model 635 spectrometer. The $^1\text{H-NMR}$ spectra (δ values; in CDCl_3 solution) were recorded using a Varian EM 360 spectrometer with tetramethylsilane as the internal standard. The analyses were performed in the Analytical laboratory of the Ruđer Bošković Institute. Mass spectra were recorded with a Varian CH 7 in the Ruđer Bošković Institute. The neutralization equivalents of compounds I, IV, and VI agreed within the limits of error with the calculated ones.

(E)-1-Ethyl Hydrogen 2-Ferrocenylmethyleneglutarate (I)

3 g (16 mmol) of diethyl glutarate and 2.5 g (12 mmol) of formylferrocene in 15 ml of *tert*-butanol were added dropwise to a stirred boiling solution of potassium *tert*-butoxide (from 17 mmol of potassium) in 40 ml of the same solvent. After heating for 1/2 hour the solvent was removed under reduced pressure, the residue dissolved in aqueous potassium hydroxide and washed with ether. The aqueous layer was acidified with 6 mol/dm³ sulphuric acid and extracted with methylene chloride. The organic layer was then washed with saturated aqueous solution of sodium chloride until pH 4, dried over magnesium sulphate, and evaporated to dryness in vacuo. The crude resinous product (4 g, 97%) was purified on a silica gel column using benzene and ether as eluents (from 1 g of the crude material 800 mg of the crystalline product, m. p. 90–100 °C was obtained) or on preparative TLC plates in benzene: ethanol (30 : 1) (1g of the crude material gave 500 mg of the product with m. p. 106–8 °C). Recrystallization from aqueous ethanol (1 : 1) does not change the m. p. IR spectrum (KBr): 1702 (s), 1690 (s) (ν C=O) and 1631 cm^{-1} (m) (ν C=C); UV spectrum: λ_{max} 248 ($\epsilon = 13,200$) and λ_{max} 295 nm ($\epsilon = 16,400$).

Anal. $\text{C}_{18}\text{H}_{20}\text{FeO}_4$ (356.21) calc'd.: C 60.70; H 5.66%
found: C 60.91; H 5.93%

(E)-1-Ethyl 5-Methyl 2-Ferrocenylmethyleneglutarate (II)

An ethereal solution of 356 mg (1 mmol) of (E)-1-ethyl hydrogen 2-ferrocenylmethyleneglutarate (I) was esterified with diazomethane/ether; after filtering through a short alumina column 360 mg (98%) of an oily product II was obtained. IR spectrum (CHCl_3): 1698 (s) (ν C=O conjugated), 1729 (s) (ν C=O unconjug.) and 1628 cm^{-1} (s) (ν C=C); UV spectrum: λ_{max} 247 ($\epsilon = 12,400$) and λ_{max} 294 nm ($\epsilon = 15,100$); NMR spectrum: 1.30 (t, $\text{CH}_3\text{CH}_2\text{O}$ —), 2.45–3.00 (m, — CH_2CH_2 —), 3.79 (s, CH_3O —), 4.21 (q, $\text{CH}_3\text{CH}_2\text{O}$ —), 7.60 (s, —C=CH), ferrocene protons: 4.21 (s, unsubst. ring), 4.46 (t, H_3, H_4) and 4.58 ppm (t, H_2, H_5).

$\text{C}_{19}\text{H}_{22}\text{FeO}_4$ (370.23) $M^+ = 370$

Cyclopentadienyl(5,6-dihydro-4-oxo-7-ethoxycarbonylazulenyl)iron (III)

(a) To a stirred mixture of 4 ml of trifluoroacetic anhydride and 25 ml of 1,2-dichloroethane a solution of 250 mg (0.7 mmole) of half ester I in the same solvent was added dropwise at the room temperature. The reaction mixture was refluxed for 3 hours dropping an additional amount of 4 ml of trifluoroacetic anhydride in dichloroethane. After cooling it was poured onto crushed ice and water containing some ascorbic acid. The aqueous layer was extracted with ether and the combined organic phases were then washed successively with 10% sodium hydrogencarbonate and water, dried over magnesium sulphate and evaporated to dryness in vacuo; 200 mg of dark pastous material was obtained*. It was purified by TL chromatography (benzene : ethanol 30 : 1) giving 78 mg (33%) of an orange-red oil (which decomposed in a few days). IR spectrum (CHCl_3): 1690 (s) (ν C=O ester), 1658 (s) (ν C=O ketone) and 1631 cm^{-1} (m) (ν C=C); UV spectrum: λ_{max} 269 ($\epsilon = 16,400$) and λ_{max} 294 ($\epsilon = 11,400$);

* A TL chromatogram of this material showed decomposition, while the solution before evaporation showed only a spot of the compound III.

NMR spectrum: 1.37 (t, $\text{CH}_3\text{CH}_2\text{O}-$), 2.53—3.04 (m, $-\text{CH}_2\text{CH}_2-$), 4.31 (q, $\text{CH}_3\text{CH}_2\text{O}-$), 7.65 (s, $-\text{C}=\text{CH}$), ferrocene protons: 4.26 (s, unsubst. ring) 4.73 (m, H_3, H_4) and 5.24 ppm (m, H_5).

$\text{C}_{18}\text{H}_{18}\text{FeO}_3$ (338.17) $M^+ = 338$

(b) A solution of half ester I in a minimum of methylene chloride was added slowly to an excess of trifluoroacetic anhydride and left overnight at 0—4 °C. The reaction mixture was worked up and purified as described under (a) giving keto ester III in a yield of 24%.

The samples described under (a) and (b) showed superimposable IR spectra.

(E)-2-Ferrocenylmethyleneglutaric Acid (IV)

A solution of the half ester I in methanolic potassium hydroxide containing some water was refluxed for 4 hours and the reaction mixture was evaporated under reduced pressure. Water was added to the crude residue and some undissolved material filtered off. The filtrate was washed with ether, acidified with 6 mol/dm³ sulphuric acid and extracted with ether giving 80% of dicarboxylic acid IV; a sample for analysis was crystallized from aqueous ethanol (1 : 1); m. p. 196—8 °C. IR spectrum (KBr): 1690 (sh) ($\nu \text{C}=\text{O}$ unconjug.), 1660 (s) ($\nu \text{C}=\text{O}$ conjug.) and 1633 cm^{-1} (m) ($\nu \text{C}=\text{C}$); UV spectrum: λ_{max} 244 ($\epsilon = 13,800$) and λ_{max} 292 nm ($\epsilon = 14,700$).

Anal. $\text{C}_{16}\text{H}_{16}\text{FeO}_4$ (328.14) calc'd.: C 58.56; H 4.92%
found: C 58.75; H 5.19%

(E)- α -Ferrocenylmethyleneglutaric Anhydride (V)

The conversion of the dicarboxylic acid IV into anhydride V by the action of trifluoroacetic anhydride was performed at room temperature, in a similar manner as described for the preparation of the compound III under (a); yield 98%, m. p. 138—140 °C (the sample hydrolyzed quickly to the starting diacid IV). IR spectrum (KBr): 1783 (s), 1720 (s) ($\nu \text{C}=\text{O}$) and 1590 cm^{-1} ($\nu \text{C}=\text{C}$); NMR spectrum: 2.60—3.00 (m, $-\text{CH}_2\text{CH}_2-$), 7.86 (s, $-\text{C}=\text{CH}$), ferrocene protons: 4.26 (s, unsubst. ring) and 4.45—4.70 ppm (m, H_2-H_5).

Anal. $\text{C}_{16}\text{H}_{14}\text{FeO}_3$ (310.12) calc'd.: C 61.96; H 4.55%
found: C 62.00; H 4.83%

Cyclopentadienyl(5,6-dihydro-4-oxo-7-oxycarbonylazulenyl)iron (VI)

(a) The alkaline hydrolysis of the keto ester III according to the procedure for the preparation of the compound IV gave, after recrystallization from methylene chloride : *n*-heptane, 35% of the air-sensitive acid VI. m. p. IR spectrum (CHCl_3) 1690 (sh) ($\nu \text{C}=\text{O}$ acid), 1660 (s) ($\nu \text{C}=\text{O}$ ketone) and 1630 cm^{-1} (sh) ($\nu \text{C}=\text{C}$); UV spectrum: λ_{max} 223 ($\epsilon = 17,800$), λ_{max} 267 ($\epsilon = 11,100$) and 294_{sh} nm ($\epsilon = 8,100$).

$\text{C}_{16}\text{H}_{14}\text{FeO}_3$ (310.12) $M^+ = 310$

(b) 180 mg (1.3 mmol) of aluminium chloride was added in several portions over a period of 1/2 hour to a stirred solution of 190 mg (0.6 mmol) of the anhydride V in 50 ml of methylene chloride at 0—3 °C. After 2 hr of stirring at room temperature the reaction mixture was hydrolyzed by pouring it onto crushed ice and water containing *ortho*-phosphoric acid and extracted with ether; the ethereal layer was then washed with water until pH 3—4, dried over magnesium sulphate and evaporated to dryness in vacuo; recrystallization as described under (a) gave 40% of the sample, which, as evidenced by the mixed m. p. and IR spectra, was identical to compound VI described above.

Acknowledgment. The authors are indebted to Professor D. E. Sunko, Zagreb, for helpful discussions. Grateful acknowledgement is made to Dr. J. Rolich, Zagreb, for recording the IR spectra, and to B. S. M. Šuprina and Mrs. J. Brcković for taking the UV spectra. Thanks are due to the Council for Scientific Research, Socialist Republic of Croatia, Zagreb, Yugoslavia for partial support by a grant.

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SAŽETAK

Stobbe-ova kondenzacija formilferocena s dietilglutaratom

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Stobbe-ovom kondenzacijom formilferocena s dietilglutaratom u prisutnosti kalij-*terc*-butilata pripremljen je (*E*)-1-etil-hidrogen-2-ferocenilmetilenglutarat (I), koji je djelovanjem diazometana preveden u (*E*)-1-etil-5-metil-2-ferocenilmetilenglutarat (II). Konfiguracije spoja I i II određene su iz njihovih ¹H-NMR i IR-spektara, a potvrđene su i prevođenjem spoja I u ciklopentadienil(5,6-dihidro-4-okso-7-etoksikarbonilazulenil)željezo (III), koje je hidrolizirano u odgovarajuću kiselinu (VI). Ista kiselina VI pripravljena je iz poluetera I preko odgovarajuće dikiseline IV i anhidrida V.

Razmotrena je stereoselektivnost Stobbe-ove kondenzacije.

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Prispjelo 5. lipnja 1978.