# Intramolecular Oxidative Coupling of 2,2′-Ethylenedi-1,3-cyclohexanediones with Iron(III) Hexacyanoferrate(III)

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2,2′-Ethylenedi(5,5-dimethyl)-1,3-cyclohexanedione (*1a*) on treatment with a slight excess of iron(III) hexacyanoferrate(III) gives several products, two of which have so far been isolated in low yields, the carbon-oxygen coupling product *2* and the spirane γ-lactone *4a*. Under similar conditions using a larger excess of oxidizing agent, a homologue of *1a*, compound *1b*, gives the spirane γ-lactone *4b* as major product. There was no sign of carbon-carbon coupling products. The iron(III) hexacyanoferrate(III) reagent has been shown to produce hydroxy radicals.

Previous work [1,2] on intramolecular oxidative coupling of cyclic β-diketones with iron(III) hexacyanoferrate(III) has shown that it is possible to obtain carbon-carbon as well as carbon-oxygen coupling. We now report on the coupling reactions of 2,2′-ethylenedi-1,3-cyclohexanedione derivatives of type *1*, using the same dehydrogenating agent.

1a R = H, *1b* R = C₂H₅   *2*   *3*

4a R = R′ = H
4b R = C₂H₅, R′ = H
4c R = H, R′ = C₂H₅
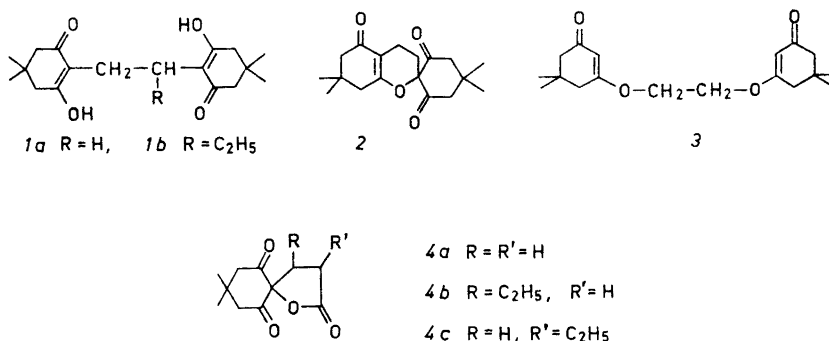
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Synthesis of the dimedone derivative *1a* was made according to a modified procedure originally described by Stetter and Dierichs.[3] The potassium salt of dimedone was allowed to react with 1,2-dibromoethane in refluxing methanol solution. The crude reaction mixture consisted of the desired compound *1a* (15 %), $C_{18}H_{26}O_4$, m.p. 239—240°C; a neutral substance *3* (66 %), isomer of *1a*, m.p. 139—140°C, identified as the di-*O*-alkylated derivative, and starting material. Several variations in the alkylation procedure were tried in unsuccessful attempts to increase the yield of *1a*.

Compound *1a* when treated for 2 h in aqueous ethanol with a slight excess of iron(III) hexacyanoferrate(III) gave a complex mixture of products. On addition of ethanol a neutral compound A (15 %), $C_{18}H_{24}O_4$, m.p. 209—210°C, crystallized. The IR spectrum of A, which has strong bands at 1735, 1705, 1625, and 1225 cm^{-1}, shows striking similarities with those of earlier isolated carbon-oxygen coupling products,[1,2,4] strongly suggesting structure *2* for compound A. The structure is supported by the UV (λ_{max} 260 nm, ε 14 200) and the NMR spectra (CDCl$_3$). The gem-dimethyl protons appear as three singlets at δ 0.92 (3H), δ 1.08 (6H), and δ 1.20 (3H).[2] Two singlets (somewhat broadened) at δ 2.23 (6H) and δ 2.48 (2H) are assigned to the methylene protons adjacent to the carbonyl groups and the allylic methylene protons of the cyclohexenone ring, respectively.[5] The four methylene protons in the dihydropyran ring give rise to a multiplet centered at δ 2.70 (4H).

The mass spectra of this as well as of most other compounds described here have been presented elsewhere.[6]

Examination by TLC of the mother liquor from the isolation of *2* showed only one well-defined spot which did not absorb at 250 nm, but reacted with 2,4-dinitrophenyl hydrazine. Isolation with preparative TLC on silica gave a compound B, $C_{11}H_{14}O_4$, m.p. 206—207°C. The IR spectrum of B shows three bands in the carbonyl region at 1790, 1740, and 1710 cm^{-1} ($\varepsilon_{1710}/\varepsilon_{1740}$ $\sim$2) indicating the presence of a γ-lactone structure and a 2,2-disubstituted dimedone ring,[2,7-9] which suggests structure *4a* for compound B. Support for the proposed structure is given by the mass spectrum [6] and the NMR spectrum of B (CDCl$_3$). The gem-dimethyl protons give rise to two singlets at δ 1.05 (3H) and δ 1.09 (3H). A singlet at δ 2.53 (4H) is assigned to the methylene protons of the dimedone ring. The four protons of the γ-lactone ring give rise to an A_2B_2 spectrum centered at δ 2.76 (4H).

It is reasonable to assume that *4a* is formed in a multi-step process involving initial oxidation of one dimedone ring to 3,3-dimethylglutaric acid and a monoacid *5* (Fig. 1). In the final step intramolecular carbon-oxygen bond formation between the carboxylic acid group and the 2-position of the dimedone ring leads to *4a*. Although the presence of 3,3-dimethylglutaric acid has not been demonstrated in this case, it has been shown to be one of the products from the reaction between dimedone and iron(III) hexacyanoferrate(III).[10]

There are at least three formally possible mechanisms for the last reaction step. The first route involving radical coupling between a carboxylate and an enolate radical is rejected for two reasons. Firstly it is known that carboxylate radicals are only rarely formed, *e.g.* in Kolbe synthesis, due to the high oxida-
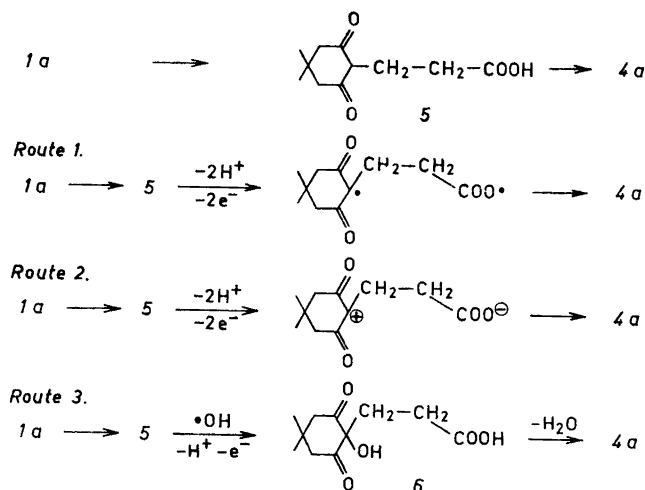
$$1a \longrightarrow \begin{array}{c} O \\ \diagup\!\!\!\diagdown \\ -CH_2-CH_2-COOH \\ \diagup\!\!\!\diagdown \\ O \end{array} \longrightarrow 4a$$

5

Route 1.

$$1a \longrightarrow 5 \xrightarrow[-2e^-]{-2H^+} \begin{array}{c} O \\ /CH_2-CH_2 \\ \cdot \quad \diagdown COO\cdot \\ O \end{array} \longrightarrow 4a$$

Route 2.

$$1a \longrightarrow 5 \xrightarrow[-2e^-]{-2H^+} \begin{array}{c} O \\ /CH_2-CH_2 \\ \oplus \quad \diagdown COO^\ominus \\ O \end{array} \longrightarrow 4a$$

Route 3.

$$1a \longrightarrow 5 \xrightarrow[-H^+-e^-]{\cdot OH} \begin{array}{c} O \\ /CH_2-CH_2 \\ \diagdown OH \quad \diagdown COOH \\ O \end{array} \xrightarrow{-H_2O} 4a$$

6

Fig. 1.

tion potential required $[E^0(\mathrm{RCH_2COO}\cdot/\mathrm{RCH_2COO^-}) > 2.2 \; \mathrm{V}]$.[11] Secondly iron(III) hexacyanoferrate(III) has not been observed to react with aliphatic carboxylic acids.

In the second route two electrons are abstracted by the reagent from the enolate system giving rise to a carbonium ion, which would be readily attacked by the carboxylate anion to give *4a*. Most probably, however, the oxidation potential of iron(III) hexacyanoferrate(III) is not sufficiently high to permit the abstraction of the second electron from a carbon atom surrounded by two carbonyl groups.

In the third, preferred mechanism the enolate radical initially formed from *5* couples with a hydroxy radical leading to a hydroxyketoacid *6*, which undergoes ring closure to *4a*. Although the oxidation potential of the iron(III) hexacyanoferrate(III) system has not been determined, it has been shown to oxidize chloride $[E^0(\mathrm{Cl_2/Cl^-}) = 1.36 \; \mathrm{V}]$. Heckner and Landsberg [12] and Stein [13] have independently and in different ways determined $E^0(\cdot\mathrm{OH/OH^-})$ to be $1.4 \pm 0.1 \; \mathrm{V}$ and $1.25 \; \mathrm{V}$, respectively. These measurements strongly suggest that it is within the scope of the iron(III) hexacyanoferrate(III) reagent to oxidize hydroxyl ions. This assumption is supported by the observation that an orsellinic acid derivative has been hydroxylated and converted into the corresponding quinone using iron(III) hexacyanoferrate(III).[10]

So far no obvious mechanism for the breakdown of the dimedone ring can be suggested. It should, however, be noted that the formation of the spirane γ-lactone *4a* formally requires eight equivalents of iron(III) hexacyanoferrate(III) (six equivalents of hydroxy radicals). Somewhat similar oxidative couplings of phenolic acids with formation of γ-lactones have been observed in a few cases.[14]

A substance closely related to *1a*, compound *1b* [15] was, on the basis of the indications given above, treated with excess of iron(III) hexacyanoferrate(III) (1:5). The crude reaction mixture, containing several products, showed one major well-defined spot on TLC without absorption at 250 nm which reacted with 2,4-dinitrophenyl hydrazine. On addition of isopropanol to the mixture a neutral compound C (31 %), $C_{13}H_{18}O_4$, m.p. 162—163°C, crystallized. It did not absorb UV-light above 220 nm. On the basis of its IR-spectrum, which shows strong bands at 1795, 1740, and 1712 cm^{-1}, compound C was assigned structure *4b* or *4c*. In the NMR spectrum (CDCl$_3$) the gem-dimethyl protons appear as two singlets at δ 0.92 (3H) and δ 1.22 (3H). The methylene protons of the dimedone ring give rise to a singlet at δ 2.68 (4H). The remaining protons are found as poorly resolved multiplets in the regions δ 0.8—1.6 (5H) and δ 2.4—2.9 (3H). At present it cannot be established which of the two structures, *4b* or *4c*, is the correct one.

No attempts were made to isolate homologues of *2* which are evidently formed as shown by TLC.

The results presented show that it is possible to obtain carbon-oxygen coupling products of dihydropyran type using iron(III) hexacyanoferrate(III) when the active rings are two carbon atoms apart. The absence of carbon-carbon coupling products is noteworthy. Russell and Lokensgard [16] have shown that the highest spin density of the enolate radical is found at the carbon atom, which would favour carbon-carbon coupling. However, framework models of the postulated cyclobutane derivatives show that they are highly crowded and steric hindrance seems to be the main reason why they are not formed.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. IR spectra were recorded on a Perkin-Elmer No. 221 or a 257 instrument. UV spectra were measured in 99.5 % ethanol with a Beckman DK 2 spectrophotometer. The NMR spectra were obtained on a Varian A-60 spectrometer using 10 % solutions with tetramethylsilane as internal standard. Chemical shifts are given in δ (ppm) units. The microanalyses were made by Dr. A. Bernhardt, Mühlheim, Ruhr, West Germany.

Chromatographic investigations. All reactions were followed by TLC on polyamide (Merck) or silica gel HF plates with 1,2-dichloroethane-methanol in different proportions as solvents. The spots were detected by examining the plates under UV and by spraying with 2,4-dinitrophenyl hydrazine (0.25 M) in 85 % phosphoric acid-ethanol (3:2) or with a solution of iron(III) hexacyanoferrate(III) in water-methanol (3:2).

2,2'-Ethylenedi(5,5-dimethyl)-1,3-cyclohexanedione (1a). To a stirred solution of potassium methoxide (3.90 g potassium, 100 mmoles) in methanol (50 ml) was added dimedone (14.0 g, 100 mmoles). and 1,2-dibromoethane (9.5 g, 50 mmoles). The solution was refluxed for 100 h. Evaporation at reduced pressure gave 25 ml of residue. Water was added, the organic layer was removed and dissolved in the minimum amount of methanol. A 4 % NaOH solution (100 ml) was added. The alkaline solution was extracted with ether (3 × 40 ml) and cautiously acidified with 2 M HCl to pH 5.* The oil thus obtained crystallised on the addition of methanol. Repeated crystallisation from methanol gave *1a* (1.0 g, 15 %) as plates, m.p. 239—240°C, λ_{max} (EtOH) in acidic solution 261 nm (ε 24 500), λ_{max} (EtOH) in basic solution 288 nm, (ε 40 000),

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* On further acidification of the aqueous solution after separation of the oil, appreciable quantities of starting material was recovered.

ν_{max}(KBr) 2900 (br), 1575, 1374, 1232 cm^{-1}, NMR (CDCl$_3$) δ 1.10 (s, 12H), δ 2.34 (s, 4H), δ 2.42 (s, 8H). (Found: C 70.5; H 8.38. C$_{18}$H$_{26}$O$_4$ requires C 70.6; H 8.55).

3,3'-Ethylenedioxydi(5,5-dimethyl)-cyclohex-2-en-1-one (3). The ether extract from the isolation of *1a* was dried and evaporated to dryness *in vacuo*. The residue was recrystallised from ethyl acetate giving *3* (4.4 g, 66 %) as prisms, m.p. 139–140°C, λ_{max}(EtOH) 251 nm (ε 33 800), ν_{max}(KBr) 1650, 1600, 1355, 1218, 1145 cm^{-1}, NMR (CDCl$_3$) δ 1.02 (s, 12H), δ 2.13 (s, 4H), δ 2.25 (s, 4H), δ 4.06 (s, 4H), δ 5.27 (s, 2H). (Found: C 70.5; H 8.56. C$_{18}$H$_{26}$O$_4$ requires C 70.6; H 8.55).

Oxidative coupling of compound 1a. To a solution of *1a* (1.84 g, 6 mmoles) in ethanol-water (3:2) (560 ml) was added dropwise and with stirring an aqueous solution (160 ml) containing iron(III) hexacyanoferrate(III) freshly made from iron(III) chloride (4.86 g, 18 mmoles) and potassium hexacyanoferrate(III) (5.94 g, 18 mmoles). After 2 h the mixture was extracted with ether (10 × 80 ml). The extract was dried and the solvent was evaporated. Addition of ethanol to the remaining oil yielded crystals (0.27 g, 15 %). Repeated crystallisation from isopropanol gave *2* as plates, m.p. 209–210°C, λ_{max}(EtOH) 260 nm (ε 14 200), ν_{max}(KBr) 1735, 1705, 1625, 1375, 1225, 1120 cm^{-1}. (Found: C 71.1; H 8.05. C$_{18}$H$_{24}$O$_4$ requires C 71.0; H 7.95).

Preparative TLC on silica of the mother liquor from isolation of *2* gave *4a*, m. p. 206–207°, λ_{max}(CHCl$_3$) 1790, 1740, 1710, 1180, 1075 cm^{-1}. High resolution mass spectrum on an Atlas high resolution instrument gave M$^+$ 210.0899. C$_{11}$H$_{14}$O$_4$ requires 210.0892.

Oxidative coupling of compound 1b. To a solution of *1b* [15] (668 mg, 2 mmoles) in 50 % aqueous ethanol (800 ml) was added dropwise a freshly made aqueous solution of iron(III) hexacyanoferrate(III) (100 ml, 0.05 M). After 30 min another portion of the reagent (100 ml, 0.05 M) was added and the reaction was continued for half an hour. The reaction mixture was extracted with chloroform (5 × 70 ml), dried, filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in boiling isopropanol. On cooling, needles were formed which were recrystallized from isopropanol to give *4b* or *4c* (145 mg, 31 %), m.p. 162–163°C, ν_{max}(KBr) 1795, 1740, 1712, 1455, 1180, 1135 cm^{-1}. (Found: C 65.4; H 7.59. C$_{13}$H$_{18}$O$_4$ requires C 65.5; H 7.62).

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