Journal of Organometallic Chemistry, 50 (1973) 213–217

SYNTHESIS AND ABNORMAL REACTIONS OF A CHOLESTADIENYLIRON TRICARBONYL CATION

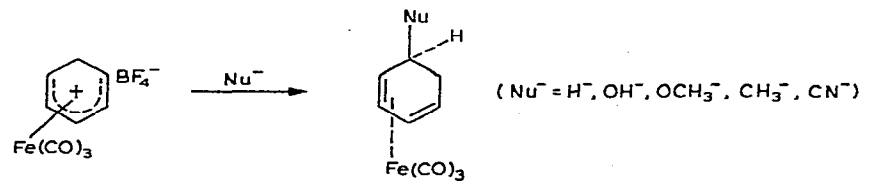
HOWARD ALPER and CHE-CHENG HUANG
Department of Chemistry, State University of New York at Binghamton, Binghamton, New York 13901 *(U.S.A.)*
(Received August 14th, 1972)

SUMMARY

Cholesta-1,3-diene- and cholesta-2,4-dieneiron tricarbonyls each react sluggishly with triphenylmethyl tetrafluoroborate to form the same cationic complex. Treatment of the latter with a variety of nucleophiles results in elimination rather than the normally observed addition reaction.

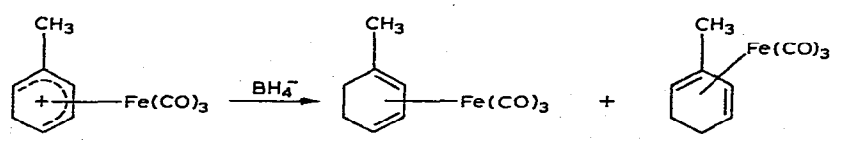
INTRODUCTION

Diene–iron tricarbonyl complexes, such as 1,3-cyclohexadieneiron tricarbonyl, generally undergo a facile hydride-abstraction cation-forming reaction (~30 min reaction time) when treated with triphenylmethyl tetrafluoroborate in methylene chloride at room temperature[1,2]. An X-ray determination of the structure of the (2-methoxycyclohexadienyl)iron tricarbonyl cation[3] reveals a planar five carbon unit with essentially identical carbon–carbon bond distances. The remaining methylene group is too far from the metal to be involved in any direct bonding to it (40.3° dihedral angle). Nucleophilic addition reactions to cations such as (I) give neutral complexes [*e.g.*, (II)][1,2]. While addition to the unsubstituted cation (I) can only give one complex



(I) (II)

of type (II), similar reactions with ring-substituted cyclohexadienyliron tricarbonyl cations may give isomeric mixtures, *e.g.*, cation (III) adds hydride at both terminal



(III) (IV) (V)

positions to give (IV) and (V) in a 1/1 ratio[4]. Stereochemical studies by Birch and coworkers[5] and by Whitesides and Arhart[5] have shown that both the hydride abstraction and the nucleophilic addition reactions occur *exo* to the iron.

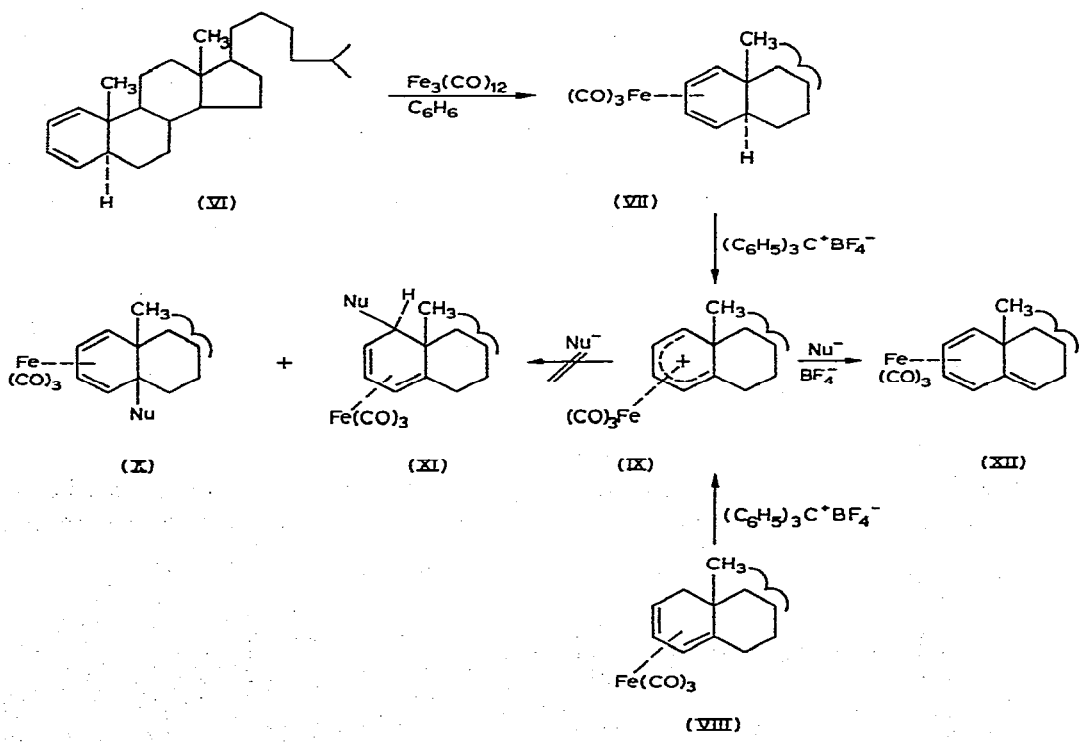
It was planned to apply the hydride abstraction and nucleophilic addition reactions to several cholestadiene complexes. Since diene ligands can be liberated from their iron tricarbonyl complexes by use of oxidizing agents[2], this reaction sequence seemed promising for the synthesis of new steroids of potential biological interest or known compounds not readily prepared by other means.

RESULTS AND DISCUSSION

The isomeric ring A steroid dienes, cholesta-2,4-diene and 5α-cholesta-1,3-diene (VI), were used as starting materials for this study (Scheme 1). The known cholesta-2,4-diene complex (VIII) was obtained in 60% yield from cholesta-2,4-diene and triiron dodecacarbonyl [$Fe_3(CO)_{12}$]. The diene (VI), prepared in five steps from 5α-cholestanol, reacted with $Fe_3(CO)_{12}$ in benzene to give (VII) in 72% yield. The spectral properties for (VII) (Experimental) are similar to those previously reported for other steroid complexes[6].

Treatment of either (VII) or (VIII) with $(C_6H_5)_3C^+BF_4^-$ in methylene chloride at room temperature for 30 min gave recovered starting materials. Hydride abstraction was achieved by conducting the reactions under refluxing conditions for extended

SCHEME 1

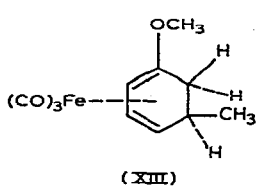


time periods [18 h for (VIII), 72 h for (VII)]. The salt (IX) was obtained in 16% yield from (VIII) and 68% yield from (VII). The IR spectrum of (IX) (KBr disc) displayed carbonyl stretching bands at 2101, 2065, and 2050 cm^{-1}, in accord with literature data for other cation complexes of this type[2].

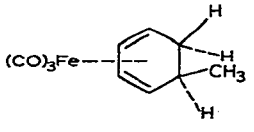
The sluggishness of the hydride abstraction reactions of (VII) and (VIII) is likely due to steric effects. In (VIII), the favored configuration has the iron tricarbonyl group in the "α" position away from the *exo* angular methyl group at C-10. As noted above, hydride abstraction generally occurs *exo* to the metal atom. Hydride abstraction of the *exo* hydrogen at the 1-position would be retarded by the presence of the angular methyl group. The 1,3-diene complex (VII) is also assumed to have the C-10 methyl group *exo* to the $Fe(CO)_3$ fragment. Here, the hydride to be abstracted (at C-5) is *endo* to the $Fe(CO)_3$ group. Consequently, hydride abstraction would be a slow reaction, should it occur at all. It is conceivable that prior to abstraction at C-5, the $Fe(CO)_3$ group flips to the opposite less favored configuration having the methyl group *endo* and the hydrogen at the 5-position *exo* to the iron. Hydride abstraction would now occur *exo* to the iron tricarbonyl group.

It is worthwhile noting that Birch and co-workers[2] reported that no product was detected on reaction of (XIII) or (XIV) (each as part of a mixture) with $(C_6H_5)_3C^+BF_4^-$ for 30 min. If it is assumed that the methyl group in both complexes is *exo* to $Fe(CO)_3$, then abstraction of the sole *exo*-halogen would be hindered by the methyl group in each instance. It is probable that abstraction would occur under the more drastic conditions used to prepare (IX) from (VII) or (VIII).

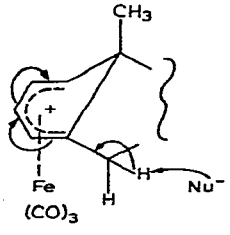
Nucleophilic addition to either of the terminal positions of (IX) should give (X) and/or (XI). However, no such products were obtained on treatment of (IX) with water, sodium methoxide, sodium cyanide, or morpholine. All reactions yielded cholesta-1,3,5-trieneiron tricarbonyl (XII) as the only product. The mass spectrum of (XII) gave a molecular ion peak at *m/e* 506 followed by successive loss of three carbonyls (at *m/e* 478, 450, 422). IR terminal metal carbonyl stretching bands were observed at 2035 s, 1960 s, and 1940 (sh) cm^{-1} (KBr disc). The NMR spectrum (CCl_4) of the complex gave the following pertinent signals: δ 5.33 (m, H-2 and H-3), 5.07 (m, H-6), 3.75 (d, H-4) and 3.34 (d, H-1) ppm.



(XIII)



(XIV)



(IXa)

These novel results can be rationalized as follows: assuming that the salt possesses the configuration (IXa), with the iron tricarbonyl remote from the angular methyl group, then nucleophilic attack at C-1 or C-5 is hindered by the methyl or iron tricarbonyl groups. As a result, proton removal occurs at C-6 to give (XII).

In conclusion, this work demonstrates the importance of steric effects in the hydride abstraction and the nucleophilic addition reactions.

EXPERIMENTAL

General

Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Microanalytical determinations were carried out by Par–Alexander Labs, S. Daytona, Florida, and Meade Microanalytical Laboratory, Amherst, Massachusetts. NMR spectra were recorded on a Varian A-60 spectrometer; TMS was an internal reference. UV spectra were recorded on a Perkin–Elmer 202 spectrophotometer. IR spectra were recorded on Perkin–Elmer 457 or 521 spectrometers. Mass spectra were recorded using an Atlas CH-4 or MS-9 mass spectrometer.

Triiron dodecacarbonyl (Pressure Chemical Co.) was used as received. Solvents were dried and purified by standard techniques. All reactions were run under nitrogen.

5α-Cholesta-1,3-diene

The diene was prepared in five steps from 5α-cholestanol.

(*i*). *5α-Cholestanone.* The ketone, m.p. 126–128° (lit.[7] 125–126°) was prepared from 5α-cholestanol in 85% yield according to the procedure of Bruce[7].

(*ii*). *5α-Cholest-1-en-3-one.* Bromination of 5α-cholestanone with bromine in acetic acid gave the 2-bromo derivative, m.p. 170–171°, in 83% yield[8]. Dehydrohalogenation of the latter with lithium carbonate in *N*,*N*-dimethylformamide gave 5α-cholest-1-en-3-one in 64% yield[9].

(*iii*). *Cholesta-1,3-diene.* Cholesta-1,3-diene (VI) was obtained by first preparing the tosylhydrazone derivative of (*ii*) and then reacting the latter with methyllithium in tetrahydrofuran[10].

5α-Cholesta-1,3-*dieneiron tricarbonyl* (*VII*)

A mixture of (VI) (2.00 g, 5.40 mmol), and $Fe_3(CO)_{12}$ (1.50 g, 3.00 mmol) in benzene (20 ml) was refluxed for 45 h. The solution was cooled, filtered through Celite, and the filtrate concentrated. Chromatography of the residue on basic alumina [activity grade (I)] gave on elution with petroleum ether, 2.29 g of yellow crystals of (VII). Recrystallization from ethanol gave 1.50 g of analytically pure (VII), m.p. 111–113°. IR (CCl_4) ν(CO): 2039 s, 1967 s cm^{-1}; NMR (CCl_4) δ 5.08 (m, H-2 and H-3) and 2.92 (m, H-1 and H-4) ppm; UV spectrum (cyclohexane) λ_{max} 232 nm. Mass spectrum: (*m/e*) 508, 480, 452, 424. (Found: C, 70.25; H, 8.62. $C_{30}H_{44}FeO_3$ calcd.: C, 70.86; H, 8.72%.)

Cholesta-2,4-dieneiron tricarbonyl (*VIII*)

Triiron dodecacarbonyl was used instead of iron pentacarbonyl[6] for preparing (VIII) from cholesta-2,4-diene or cholesta-3,5-diene. A 60% yield of (VIII) was obtained using the procedure described for the preparation of (VII). The m.p. of (VIII) was 48–59° (lit.[6] m.p. 18–20°). The spectral data were in accord with literature results[6].

Reaction of (*VII*) *or* (*VIII*) *with triphenylmethyl tetrafluoroborate*

Triphenylmethyl tetrafluoroborate (4.50 g, 13.6 mmol) in methylene chloride (8 ml) was added dropwise to a methylene chloride (6 ml) solution of the diene complex, and the mixture was stirred and refluxed for 72 h (VII) or 18 h (VIII). The solution was cooled, diluted with ether (10 ml), and the bright yellow solid was filtered, washed

with benzene and/or ether and then dried. The salt (IX), m.p. 185° decomp., was obtained in 68% yield from (VII) and in 16% yield from (VIII). It was insoluble in pentane, benzene, chloroform, and ether but partly soluble in acetone, methanol, and dimethyl sulfoxide. (Found: C, 61.05, 61.07; H, 7.02, 7.11; Fe, 9.72. $C_{30}H_{43}BF_4FeO_3$ calcd.: C, 60.60; H, 7.24; Fe, 9.40%.)

Reaction of (IX) with nucleophiles

(*i*). *Water.* Cation (IX) (0.160 g, 0.30 mmol) was added to a 2 *M* aq. solution of sodium bicarbonate (40 ml) and stirred first at room temperature for 10 min and then heated on a steam bath for the same amount of time. The solution was cooled and the organic product extracted with ethyl ether. The ether extract was dried over $MgSO_4$, then concentrated to a few ml, and chromatographed on neutral alumina [activity grade (I)]. Elution with benzene gave yellow crystalline cholesta-1,3,5-trieneiron tricarbonyl (VII), m.p. 145–147°, in 45% yield. UV spectrum: λ_{max} (hexane) 227.5 nm. See results and discussion for other spectral data. (Found: C, 71.34; H, 8.40. $C_{30}H_{42}FeO_3$ calcd.: C, 71.13; H, 8.36%.)

(*ii*). *Sodium methoxide.* The salt (0.11 g, 0.2 mmol) was added to a methanolic sodium methoxide solution, and the mixture was stirred at room temperature for 0.5 h. Standard work-up gave (XII), m.p. 145–147°.

(*iii*). *Sodium cyanide.* A mixture of cation (IX) (0.15 g, 0.78 mmol) and NaCN (2 g) in acetone (30 ml) was stirred at room temperature for 3 h. Standard work-up gave (XII).

(*iv*). *Morpholine.* A mixture of 0.2 mmol of (IX) and 0.8 mmol of morpholine in acetone (20 ml) was stirred at room temperature for 12 h. Standard work-up gave (XII).

ACKNOWLEDGEMENT

We are grateful to the Research Foundation of the State of New York for support of this research.

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