CHAPTER - 4

Cyclopropanation of Enones Complexed with Tricarbonylchromium

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INTRODUCTION

So far we have discussed two types of reactions: (i) conjugate addition of nitromethane, and, (ii) Lewis acid mediated addition of allylsilane to 2-arylidenec-1-tetralone complexed with Cr(CO)₃. In the former reaction, it was established that the conjugate addition at the β-carbon of the enone was 100% stereospecific. It was also realised that protonation at the epimeric centre was stereoselective even at room temperature, and the major product resulted from protonation from the exo face. The latter reaction described the addition of allyltrimethylsilane in the presence of TiCl₄ at C-3 with complete stereospecificity. This time the proton quench was carried out at low temperature, which ensured total selectivity of protonation at C-2 from the exo face.

Therefore, if a reagent was selected such that the enolate generated by nucleophilic addition could be trapped by an intramolecular electrophile, stereoselectivity at both the centres, C-3 and C-2 could be simultaneously controlled.

It is generally accepted that sulfoxonium ylides react with a double bond activated by an electron withdrawing group in a manner similar to conjugate addition and lead to a cyclopropane by intramolecular displacement of dimethyl sulfoxide. Such cyclopropanation would satisfy the criteria described above.

RESULTS AND DISCUSSION

The cyclopropanation was carried out using dimethylsulfoxonium methylide generated in situ, with 2-arylidenec-1-tetralone-Cr(CO)₃ complexes.

Preparation of the Sulfoxonium salt:
The trimethylsulfoxonium iodide was prepared following a reported procedure\(^2\), by gentle reflux of dimethylsulfoxide and methyl iodide to provide a white solid in 50% yield. The generation of the ylide and cyclopropanation was carried out under PTC conditions\(^3\).

**Reaction of trimethyl sulfoxonium ylide with enones (2a - 2c) (PTC condition):** The complex 2b was dissolved in CH\(_2\)Cl\(_2\) to which trimethylsulfoxonium iodide and tetrabutylammonium bromide (catalytic amount) were added. To this solution, 50% aqueous NaOH (10ml) was added and the mixture was heated under reflux for 16h. The reaction was monitored by TLC. The product was less polar than the starting material. It was observed that even after 16h, trace amount of starting material persisted in the reaction medium. The reaction was stopped at this stage and worked up as usual. The product 23 was separated from the starting material by flash column chromatography and isolated in 87% yield, as orange crystals.

\[ 2b \xrightarrow{} \]

\[
\begin{array}{c}
\text{O} \\
\text{Cr} (\text{CO})_3 \\
\text{23}
\end{array}
\]

The IR spectrum of the complex exhibited bands at 1990, 1920 (Cr-CO) and 1670 (-CO-).

The \(^1\)H NMR spectrum showed the downfield signals which were assigned to the uncomplexed phenyl ring protons at 7.3. The complexed aromatic ring protons appeared as doublet of doublet due to ortho coupling (\(J = 6.8\text{Hz}\)) and meta coupling (1Hz) at 6.2. Unsymmetrical triplets were observed due to two ortho couplings and one meta coupling at 5.6 and 5.3. A doublet with a coupling \(J = 7\text{Hz}\) resonated at 5.1.

The benzylic methylene, the cyclopropane methylene and the benzylic methine appeared as a multiplet between 2.8-2.15. The other methylene protons of the tetralone ring appeared in the region 1.55-1.35.
The $^{13}$C NMR spectrum showed downfield resonances at 230.9 and 195.8 corresponding to Cr-CO and -CO- respectively. The signals of uncomplexed aromatic ring carbon appeared in the region 136.0 to 127.1. The complexed ring carbons resonated between 115.2 to 89.4. The carbon adjacent to ketone appeared at 37.1. The benzylic carbon signal resonated at 33.1. The methylene signals of the tetralone ring appeared at 26.4 and 24.6. The signal at 18.3 was assigned to the methylene of the cyclopropane ring.

From the NMR spectra, it was apparent that a single diastereomer of the product was obtained. The complex 2a under similar reactions provided the product 22 in 84% yield, as orange crystals of a single diastereomer.

The IR spectrum of the complex had characteristic bands. The $^1$HNMR spectrum showed signals in the expected region. The methyl signal appeared at 2.4 as a singlet. In the $^{13}$CNMR spectrum the resonances appeared as expected. The methyl carbon signal resonated at 20.9.

The complex 2c also afforded the product, 24 as orange crystals in 77% yield under similar reaction conditions. Only one diastereoisomer of the product was obtained. The IR spectrum exhibited bands at 1980, 1910 (Cr-CO) and 1660 (-CO-). The resonances in the $^1$HNMR were as expected. The protons of the methoxy group appeared as a singlet at 3.8. The $^{13}$C NMR spectrum of the complex exhibited signals in the expected region. The methoxy signal was observed at 55.1.
The formation of a single diastereomer of the product indicated excellent stereocontrol in the cyclopropanation reaction. Similarity in the $^1$H NMR spectral pattern suggested that the stereochemical relationships in all three products were the same. The stereochemistry of the cyclopropane ring, however, could not be established from the spectral data alone.

Thus, four possible diastereoisomeric products may be formed as depicted in Scheme-1, as a result of exo or endo attack on the enone system.

It can be clearly seen that the pathway leading to the product would determine the stereochemical relationship between the phenyl, carbonyl and methylene groups.

In order to establish such spatial relationship without ambiguity, the structure of the compound 23 was determined by single crystal X-ray diffraction. The X-ray diffraction analysis revealed that the cyclopropane was appended from the same face of the molecule as occupied by the Cr(CO)$_3$ group. The PLUTO diagram of 23 is shown below. The product has resulted from an unusual endo-attack (path c in Scheme 1).
EXO ATTACK

NO C-C ROTATION

WITH C-C ROTATION

ENDO ATTACK

NO C-C ROTATION

WITH C-C ROTATION
Monoclinic space group P2₁/n; a = 7.616(2) Å, b = 10.100(2) Å, c = 22.916(2) Å, β = 95.92(1)° Å, V = 1753.4 Å³. Dc = 1.456 Mg/m³; Z = 4, μ(Mo-Kα) = 0.66 mm⁻¹. 2809 unique reflections, R = 0.038 for 1723 observed reflections.
We may recall that conjugate addition to 2-arylidene-tetralones complexed with Cr(CO)_3 was found to proceed (Chapter-2) with exclusive exo-attack. The reason for the exclusive endo-selectivity in the present case is not obvious.

A possible mechanism can be invoked which would involve participation of the metal in the delivery of the reagent. The sulfoxonium methylide may coordinate with Cr(CO)_3 moiety, which will necessitate ring slippage^4 from \( \eta^6 \) to \( \eta^4 \)-arene in order to maintain 18 electron configuration around the metal. Electron reorganisation could lead to the endo attack at the enone terminus. A fast ring closure would afford the endo cyclopropane.

An alternative explanation for this unusual stereochemical result, which does not involve participation by the metal, may be based on the following two premises: (i) the attack of the sulfur ylide is reversible^3 and (ii) the ring closure of the endo adduct is fast enough to shift the equilibrium in its favour. Thus, the cyclopropanes 22, 23 and 24 could be kinetic products.
The uncomplexed 2-benzylidene-1-tetralone did not undergo any reaction under identical condition.

Reaction of trimethylsulfonium ylide with 2b (Homogeneous conditions):

Following a reported procedure, the ylide was generated in THF, using NaH as base. A solution of the complex 2b in THF was added to the ylide and allowed to react at room temperature overnight. The product was isolated by flash column chromatography in 82.5% yield.

The $^1$H NMR spectrum of this product was found to be identical with that of 23. Thus, no change in stereoselectivity was observed.

Attempted reaction:

Use of triphenylphosphine isopropylidene ylide was investigated as the cyclopropanating reagent for the same substrates. Following a reported procedure, isopropyltriphenylphosphonium bromide was prepared from triphenylphosphine and isopropyl bromide by heating at 150°C in a pressure bottle for one day. The product was recrystallised from a small amount of ethanol and diethyl ether in 89% yield. Isopropylidenetriphenylphosphine was generated from isopropyl triphenylphosphonium bromide (1.1mmol) and n-BuLi (1mmol) in THF at 0°C. A solution of the complex 2a in THF was added dropwise. After addition of the complex, the reaction mixture was allowed to stir overnight at room temperature. The reaction was monitored by TLC. The reaction did not proceed even after 12h and the starting material was recovered in 94% yield.

Summary:

An unprecedented, completely stereospecific endo cyclopropanation of 2-arylidene-1-tetralone Cr(CO)$_3$ complex by dimethylsulfoxonium methylyde has been observed. Although the factors responsible for such reversal of stereoselectivity remain unclear, this result is likely to initiate search for other possible endo-selective transformations.
**EXPERIMENTAL:**

**General procedure for cyclopropanation:**

**Preparation of trimethyl sulfonium iodide:** Following a reported procedure dimethyl sulfoxide (8ml., 1.1 moles) and methyl iodide (16ml.) were refluxed under nitrogen for three days to provide the salt (10g, 45%).

**Phase Transfer Catalysis (PTC) method:** To a solution of the complex 2a-c (0.4 mmol. to 1 mmol), trimethyl sulfonium iodide (0.4 mmol. to 1 mmol.) and tetrabutylammonium bromide (2 mol% of iodide) in deaerated dichloromethane (7 to 10 ml) was added 50% aqueous NaOH (5 to 10 ml). The reaction was heated under reflux for 16h under argon. It was cooled to room temperature and worked up as usual. The residue thus obtained was subjected to flash column chromatography. The starting material and the product could be separated using solvent gradient (10% EtOAc-pet ether to 30% EtOAc-pet ether). The less polar fraction was identified as the starting material. The polar fraction afforded the desired product. The yields were calculated based on consumed starting material.

**Reaction of 2b:** From the complex 2b (369mg, 1 mmol), Trimethyl sulfonium iodide (220mg, 1 mmol) and tetrabutylammonium bromide (4mg) and 50% aqueous NaOH (10ml) in dichloromethane (10ml), a residue was obtained after usual work up. The starting material (60mg) and the product (285mg, 89%) could be separated by flash chromatography using 20% EtOAc-pet ether as eluant.

**m.p.** : 127 - 128°C

**IR** : 1990, 1920, 1670

**¹H NMR** : 1.35 - 1.55 (m, 2H), 2.15 - 2.80 (m, 5H), 5.10 (d, 1H, J = 6Hz), 5.30 (t, 1H, J = 7Hz), 5.60 (dt, 1H, J = 6.1Hz), 6.20 (dd, 1H, J = 6.8Hz), 7.30 (m, 5H).

**¹³C NMR** : 18.3, 24.6, 26.4, 33.3, 37.1, 89.4, 90.2, 90.6, 93.1, 94.0, 115.2, 127.1, 128.2, 128.9, 136.0, 195.8, 230.9.

**Analysis**

<table>
<thead>
<tr>
<th>Comp</th>
<th>Calc</th>
<th>Found</th>
</tr>
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<tbody>
<tr>
<td>C</td>
<td>65.79</td>
<td>65.91</td>
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<tr>
<td>H</td>
<td>4.17</td>
<td>4.25</td>
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</table>
Obs : C = 65.93, H = 4.37

**Reaction of 2a**: From the complex 2a (153mg, 0.4mmol), trimethyl sulfoxonium iodide (88mg, 0.4mmol) and tetrabutylammonium bromide (2mg) and 50% aqueous NaOH (7ml) in dichloromethane (10ml) a crude residue was obtained. Flash column chromatography with 20% EtOAc-pet ether provided the starting material (15mg) and the product (120mg, 84%).

m.p. : 162 - 164°C

IR : 1970, 1900, 1660.

^1H NMR : 1.25 - 1.50 (m, 2H), 2.10 - 2.30 (m, 2H), 2.40 (s, 3H), 2.45 - 2.75 (m, 2H), 5.10 (d, 1H, J = 6Hz), 5.35 (t, 1H, J = 7Hz), 5.60 (t, 1H, J = 7Hz), 6.15 (d, 1H, J = 6Hz), 7.10 (s, 4H).

^13C NMR : 18.2, 20.9, 24.5, 26.4, 37.2, 89.3, 90.2, 90.6, 93.0, 94.1, 115.3, 128.7, 128.9, 132.7, 136.8, 195.9, 230.9.

Analysis : Calc : C = 66.49, H = 4.53

Obs : C = 66.22, H = 4.67

**Reaction of 2c**: Using similar condition as in 2b, the complex 2c (159mg, 0.4mmol) afforded a residue, which on chromatography with 30% EtOAc-pet ether furnished the desired product (116mg, 77%) as well as some starting material (13mg).

m.p. : 134 - 136°C

IR : 1980, 1910, 1660
1H NMR:  1.25 - 1.50 (m, 2H), 2.15 - 2.75 (m, 5H), 3.80 (s, 3H), 5.10 (d, 1H, J = 6Hz), 5.35 (t, 1H, J = 7Hz), 5.60 (t, 1H, J = 7Hz), 6.20 (d, 1H, J = 6Hz), 6.90 (d, 2H, J = 9Hz), 7.15 (d, 2H, J = 9Hz).

13C NMR:  18.5, 24.6, 26.5, 33.3, 37.0, 55.1, 89.4, 90.2, 90.6, 94.0, 94.1, 113.7, 115.2, 127.9, 129.9, 158.8, 195.8, 230.9.

Analysis:  
Calc:  C = 63.92, H = 4.35
Obs:  C = 63.30, H = 4.46

Reaction of 2-benzylidene-1-tetralone: The enone (234 mg, 1mmol) under similar conditions did not yield any product and starting material (216mg, 92%) was recovered.

Homogeneous Condition: NaH (48mg, 50% dispersion in oil, 2mmol) was washed with pet-ether (3 x 10ml) and dried. THF (10ml) and the salt (220mg, 1mmol) was added to the dried NaH and the flask was cooled in an ice bath (15min). The complex 2a (332mg, 0.9mmol) in THF (109ml) was added to it dropwise via siringe. After 16h the reaction was observed to have progressed as usual. With 20% EtOAc - pet ether, starting material (41mg) and product (222mg, 82.5%) could be seperated.

Attempted Reaction: Preparation of isopropyltriphenylphosphonium bromide: Following a reported procedure, triphenylphosphine (13.1g, 0.05mol) and isopropyl bromide (4.7ml, 0.05mol) were taken in a pressure bottle and heated at 150°C for one day. It was recrystallised from a small amount of ethanol and diethyl ether, m.p. 238-239°C (17 gm, 89%).

Triphenylphosphineisopropylidene reagent: The reagent was prepared from isopropyltriphenylphosphonium bromide (423mg, 1.1mmol) and n-BuLi (1ml, 1mmol) in THF (8ml) at 0°C. After stirring for 30min, a solution of the complex 2a (383mg, 1mmol) in THF (7ml) was added at the same
temperature. After 10 min the reaction mixture was allowed to warm to room temperature. The reaction did not proceed even after 16 h. After workup and flash column chromatography with 20\% EtOAc - pet ether, starting material (361 mg, 94\%) was recovered.
References:


