CHAPTER-IV
PART - A
CHAPTER IV

Stereoselectivity in Cyclic Enone Reductions with Sodium Borohydride/Nickel Chloride Hexahydrate and Ammonium Formate/Palladium on Carbon (Transfer Hydrogenation)

Reduction with sodium borohydride coupled with transition metal salts and transfer hydrogenation methods are being increasingly used as alternatives for the classical catalytic hydrogenation of organic functional groups, as they offer convenient and simple experimental conditions. Even though functional group selectivity and regioselectivity with these reagents have been well explored, the stereoselectivity involved in such reductions particularly that of cyclic enones is not known. We have studied the stereoselectivity involved in the reduction of bicyclic-enone reductions to the corresponding ketones with these reagents and compared the stereoselectivity with that of conventional catalytic hydrogenation, so as to learn about the mechanisms involved in such reductions. This chapter is divided into two parts, A and B, with Part A dealing with the reductions with sodium borohydride/nickel (II) chloride and Part B dealing with the reductions under transfer hydrogenation conditions with ammonium formate/Pd-C.
IVA. Stereoselectivity in cyclic Enone Reduction with NaBH₄/NiCl₂. 6H₂O.

IVA.1. Introduction

Reduction of functional groups present in organic molecules is an important transformation both in research laboratory and industry. Reductions in organic chemistry is defined as the conversion of a functional group in a molecule from one category of oxidation state to a lower one. The first catalytic hydrogenation recorded in the literature is reduction of acetylene and of ethylene to ethane in the presence of platinum black. The true widespread use of catalytic hydrogenation in 1897 and the reduction with hydrides in 1947 are the two most important milestones in the development of organic chemistry. Both the reagents together account for about half of all the reductions of organic compounds. The reductions with metals and metal salts constitute an important segment of the rest. Even though, an astronomical number of reductions of organic compounds with a variety of reducing agents have been described, there is still a constant demand for new and more selective reducing agents. In the past 45 years metal hydrides particularly NaBH₄ and LiAlH₄ have emerged as the most important reducing agents in organic chemistry. These reagents are
extraordinarily versatile and between them can reduce most of the functional groups. Moreover, with slight modifications of these reagents such as changing organic ligands of Boron and Lithium or changing the metal counterion, the scope, regioselectivity and stereoselectivity of such reductions could be fine tuned.\(^6\)

More recently the transition metal salts were used in conjunction with \(\text{NaBH}_4\) and \(\text{LiAlH}_4\) to modify and enhance the properties of these reagents. The use of transition metal salts with \(\text{NaBH}_4\) has virtually added a new dimension to the versatility of \(\text{NaBH}_4\). Nearly every conceivable transition metal salts have been investigated for the development of new reduction methods.\(^7\) Among the transition metal salts used in conjunction with \(\text{NaBH}_4\), Cobalt, Nickel and Copper salts have emerged as the reagents of choice for the selective reductions. It is to be noted that Nickel catalyzed hydrogenation with molecular hydrogen is a very well known procedure, discovered by Paul Sabatier, for which he won the coveted Noble Prize in 1912\(^4\).

Boron and Aluminum hydrides may combine with transition metal halides in several ways. Most prominent of them is the formation of a boride\(^8\) and an aluminide\(^9\). For e.g., the combination of \(\text{NiCl}_2\) with \(\text{NaBH}_4\) in a protic solvent (methanol) deposits a finely divided black precipitate of nickel boride accompanied by vigorous evolution of Hydrogen.
\(8 \text{NaBH}_4 + \text{NiCl}_2 + 18\text{MeOH} \rightarrow 2\text{Ni}_2\text{B} + 6\text{B}((\text{OMe})_3 + 8\text{NaCl} + 25\text{H}_2 \) 

- (1)

The nickel boride so formed catalyzes further reaction of protic solvents according to Eq. IVA.2.11.

\[
\begin{align*}
\text{Ni}_2\text{B} & \quad \text{etc.} \\
\text{NaBH}_4 + \text{MeOH} & \rightarrow \text{Na} \text{B}((\text{OMe})_3 + \text{H}_2 
\end{align*}
\]

Keeping in view the fact that we have used NaBH\(_4\)/NiCl\(_2\) for reductions, a brief survey of the properties of nickel boride is presented here. Even though the actual structure of the nickel boride is not clear, the formula Ni\(_2\)B is consistent with the elemental composition. It is also known that the nickel boride formed as adsorbed hydrogen on it. On the basis of the metal to boron ratio and the amount of hydrogen evolved, the formula (Ni\(_2\)B)\(_2\)H\(_3\) has been suggested as the reactive species. This adsorbed hydrogen is probably responsible for the reduction of a variety of organic functional groups. Further, the nickel boride activity and the selectivity is highly solvent dependent. For e.g., nickel boride prepared in water is considerably more active and thus, less selective than nickel boride in ethanol. The selectivity of nickel boride prepared in ethanol during the reduction of alkynes to cis-trans alkenes could be improved by the addition of catalyst modifier such as ethylene diamine. Nickel boride is stable in alcohol or
water, but is pyrophoric when exposed to air. This reagent is insoluble in common organic solvents and therefore, reductions involving this reagent are heterogeneous, similar to conventional catalytic hydrogenation. It has been found that the presence of nickel oxide along with nickel boride decreases the ability of the reagent in hydrogenation reactions, for e.g., the boride made from NiCl₂ contains 17% nickel oxide and is a better catalyst for alkene hydrogenation compared to the reagent from nickel formate which contains 85% nickel oxide.¹² Since nickel boride and cobalt boride are easy to prepare and convenient to handle there is a continuing interest in their properties and applications. Most of the reductions using NiCl₂/NaBH₄ were found to be catalytic in nickel species. However, in many reductions either molar equivalent or excess of reagent has been used for speeding the reaction. In the foregoing a brief updated review of the application of sodium borohydride/nickel chloride hexahydrate as a reagent system for the reduction of variety of functional groups is presented. Only selected functional group conversions, and representative examples are given in the form of equations and schemes for the purpose of brevity of presentation.

IVA.1.1. Alkenes, Alkynes and Arenes

NaBH₄/NiCl₂ has found widespread use in the reduction of alkenes and alkynes ¹³ (Eq.IVA.3)
This reagent was found to selectively hydrogenate alkenes in the presence of ketones, alcohols and ethers without concomitant hydrogenolysis\textsuperscript{14}. The reagent has been shown to be more effective when dimethyl formamide/dimethylacetamide were used as a solvent or as co-solvents\textsuperscript{15}. Moreover, this reagent was found to be more reactive than commercial Raney Nickel towards less reactive alkenes such as cyclopentene, cyclohexene etc.\textsuperscript{11,16} It has also been reported that alkynes can be reduced chemoselectively to cis alkenes in high yields\textsuperscript{16}. But, unsaturated nitrils were hydrogenated to saturated primary amines\textsuperscript{17}. Interestingly, $\beta$-sulfenylated $\alpha,\beta$-unsaturated ketones can be converted to the corresponding saturated desulfurized ketones with this reagent\textsuperscript{18}. During the literature survey, we have found that, there was no report on hydrogenation of carbon-carbon double bond in cyclic enones to give the corresponding saturated ketones.

Even though arenes are resistant to reduction with NiCl$_2$/NaBH$_4$ many heteroaromatic compounds can be conveniently hydrogenated (Scheme IVA.1\textsuperscript{19}).

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IVA.1.2. Reduction halides

Ordinarily NaBH₄ doesn't reduce unactivated organic halides, but the combination of NiCl₂ and NaBH₄ reductively dehalogenates several polychlorinated hydrocarbons²⁰ (Scheme IVA.2) and α-halo ketones²¹.

```
  Cl  Cl  Cl
  Cl  Cl  Cl
----> cyclohexane, cyclohexene etc. (6)
```

Scheme IVA.2

IVA.1.3. Reduction of Nitroarenes and Nitroalkanes

Nitro compounds can be conveniently and effectively reduced to the corresponding amines using the combination of NaBH₄ / NiCl₂²⁴,²². It has been shown that the tetra-substituted vicinal di-nitrocompounds can be converted to olefins with this reagent²³. Radical ion mechanism has been postulated for this reduction. Beside nitro compounds and nitriles, oximes²⁴ (Scheme IV.3), azides,²⁵ azo, azoxy,
nitroso compounds and hydroxylaminobenzene\textsuperscript{26} can also be reduced to the corresponding amines with this reagent. Aroyl azides can also be converted to the corresponding benzamides in quantitative yields\textsuperscript{27} (vide, Appendix, Part-A for details of this reaction).

\textbf{IVA.1.4. Deoxygenation reactions}

Nickel boride, prepared in anhydrous diglyme from NiCl\textsubscript{2}/NaBH\textsubscript{4} was found to reductively remove allylic trifluoroacetates, acetates and trimethylsilyl ethers quite effectively. This method can be used for reductive cleavage of allylic alcohols to alkenes in a one pot process via trimethylsilylethers\textsuperscript{28,29} (Scheme IVA.4). Very recently it has been shown that this system generated \textit{in situ} in diglyme can reduce symmetric and mixed anhydrides of carboxylic acids to alcohols in good yields.\textsuperscript{30}

\textbf{IVA.1.5. Desulfurization reactions}

Reductive desulfurization is of great importance in organic chemistry as the sulfur functionality is often used
to manipulate the structure of a molecule. Furthermore, desulfurization process is crucial in the fuel processing industry since oxidized products of sulfur are major pollutants. Traditionally, Raney Nickel has been used for the purpose of desulfurization in organic laboratory. Recently it was found Nickel boride generated from NaBH₄/NiCl₂·6H₂O/methanol-THF (3:1) is an effective reagent for desulfurization. This method is also been employed for stereospecific incorporation of deuterium in the place of sulfur in organosulfur compounds (Scheme IVA.5). Nickel boride has also been used for reductive deselination (Scheme IVA.6).
Even though a wide variety of organic functional group reductions with \( \text{NiCl}_2/\text{NaBH}_4 \) have been described in the literature\(^5\), the stereoselectivity involved in such reductions has largely been ignored. Our efforts directed towards understanding the stereoselectivity involved in cyclic enone hydrogenations in comparison with conventional catalytic hydrogenation is presented in the following section. Traditionally the reduction of cyclic \( \alpha,\beta \)-unsaturated ketones to the corresponding saturated ketones is carried out either with metal in liquid ammonia (or primary amines) or by catalytic hydrogenation. An alternative reagent for this purpose, \( \text{NaBH}_4/\text{NiCl}_2/\text{MeOH} \), has been developed and is discussed in the following.

IVA.2. Results and discussion

In connection with our studies on stereoselectivity of cyclic \( \beta \)-ketoester alkylations a substantial quality of \textit{trans} 7a-methylhydrindan-5-one was required. Literature search revealed that this compound was prepared by Coates et al.\(^3\)\(^3\) from Wieland-Miescher 14 ketone \textit{via} a multistep synthetic sequence (Scheme IVA.7). Stork\(^3\)\(^4\) also reported the synthesis of this scarcely available compound from previously made \(^4\)\(^2\) \textit{trans}-bicyclic dione 15A by multistep sequence as shown in the Scheme IVA.8. Recourse to multistep synthesis for this compound has been necessitated because both catalytic hydrogenation\(^3\)\(^5\) and dissolving metal reductions\(^3\)\(^6\) of 7a-
methylyhydrind-4-ene-5-one (16) result only in cis compound 17, due to its thermodynamic stability over trans isomer 15. In later years, preparation of trans-Hydridanone 15 was reported by conjugate reduction of hydrindenone 16 using reducing agents consisting of dimethyl copper, diisobutyl aluminum hydride (DIBA-H) and hexamethyl phosphoric triamide (Scheme IVA.9). Obviously, this reagent is cumbersome to
use and elaborate set up is required for performing the reaction. Therefore, an alternative and a convenient reagent was required for effecting this reduction.

When hydrindenone 16 was reduced with sodium borohydride/Nickel(II) chloride hexahydrate in methanol at 0°C a mixture of trans and cis hydrindanones 15 and 17 (Scheme IVA.10) were formed respectively in 80% yield within 30 min. A mixture of alcohols derived from the over reduction of the two isomeric ketones 15,17 constituted rest 20%. The ratio of the two isomeric ketones 15, 17 was 41:59 (1H Fig.IVA.1) as determined by the integration of methyl signals in the 1H NMR spectrum of the crude reaction mixture. The yield of the isomeric ketones was quantitative when the crude reduction product mixture was oxidized with pyridineium chlorochromate (PCC). As noted earlier by Tsuda et al.37 trans and cis hydrindanone 15,17 could not be separated satisfactorily by chromatographic techniques. To overcome
this problem a two step procedure was developed for the separation and purification of isomeric ketones 15,17. The mixture of ketones 15,17 were carbomethoxylated with dimethyl carbonate and sodium hydride at 70°C using dry benzene as solvent (Scheme IVA.10). Methoxycarbonylated products 18,19 could now be separated conveniently by column chromatography. Decarbomethoxylation of the purified isomers by refluxing with conc. HCl readily resulted in pure cis 17 (13C NMR, Fig.IVA.2) and trans 15 (13 C NMR, Fig.IVA.3) hydindanones. trans Compound 15 was identified easily from its 1H NMR spectral data. The angular methyl group in trans compound 15 resonated at 0.97 ppm whereas for cis compound 17 the corresponding signal appeared at 1.12 ppm (Fig.IVA.1) in good agreement with reported values 34.

\[
CH_3
\]

\[
16
\]

\[
CH_3
\]

\[
15
\]

\[
CH_3
\]

\[
17
\]

\[
CH_3
\]

\[
18
\]

\[
19
\]

Reagents and conditions (i) NaBH₄ / NiCl₂ · 6H₂O, MeOH, -5°C - 0°C
(ii) PCC, CH₃Cl (iii) (H₂CO)₂CO, NaN, benzene (iv) Separate (v) Conc HCl, reflux

Scheme IVA.10

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FIG. IVA.3. A. $^{13}$C NMR (22.5 MHz) Spectra (inset SEFT of trans-7a-methylhydridan-5-one (15).

FIG. IVA.2. A. $^{13}$C NMR (22.5 MHz) Spectra (inset off-resonance) of cis-7a-methylhydridan-5-one (17).
Authentic cis compound 17 was prepared by the reduction of hydrindenone 16 under H₂/Pd-C, conditions which are known to afford cis ring junction product exclusively 35. ¹³C NMR spectral data was used for confirming structural assignment of product ketones 15,17. The carbon resonance for the angular methyl of trans isomer 15 appeared at 16.30ppm whereas for the cis compound 17 corresponding peak appeared at down field, 22.20ppm. The quaternary carbon, C₇α and the other ring junction carbon C₃α in the trans compound 15 appeared at 40.40 and 48.33ppm respectively where as in the cis hydrindanone 17 the signals appeared at 39.81 (C₇α) and 46.41 (C₃α), the upfield shift in cis compound is due to the r-gauche effect38. These values just noted are in good agreement with the trends seen in the corresponding cis and trans-decalones 27, 2839 and hydrindanones 20, 2139. Complete assignment of all the carbon resonances in ¹³C NMR spectra for the trans-hydrindanone 15 and cis-hydrindanone 17 were done in comparison with data reported for compounds having similar structure 39b,c and are gathered in Table IVA.1.

Hydrogenation of the hydrindenone 16 was very slow when either a catalytic quantity or one molar equivalent of NiCl₂·6H₂O was employed. Best results were obtained when 3 moles of Nickel (II) chloride hexahydrate and 3 moles of sodium borohydride were used for hydrogenation of 1 mole of the hydrindenone 16 (Scheme IVA.10). It is also essential
that NiCl₂·6H₂O and NaBH₄ are added in a sequence and at least in 3 portions with an interval of 5 min. between each addition. It was found that the isomer ratio, cis:trans 59:41, doesn't change after the oxidation of crude product mixture (having ketones 15,17 and the isomeric alcohols) with pyridineium chlorochromate. This result indicates that the reduction of the ketone functionality was taking place on the double bond reduced product rather than on the enone 16.

**TABLE IVA.2**

13C NMR resonances for hydrindanone series

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<tr>
<th>Carbon number</th>
<th>18</th>
<th>16</th>
<th>19</th>
<th>21</th>
<th>17</th>
<th>15</th>
<th>22</th>
<th>23</th>
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<td>C-1</td>
<td>39.94</td>
<td>40.80</td>
<td>37.51</td>
<td>30.64</td>
<td>39.81</td>
<td>39.16</td>
<td>32.84</td>
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<td>C-2</td>
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<td>21.12</td>
<td>21.37</td>
<td>22.17</td>
<td>22.20</td>
<td>22.46</td>
<td>22.36</td>
<td>22.58</td>
</tr>
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<td>C-3</td>
<td>31.91</td>
<td>30.74</td>
<td>31.10</td>
<td>28.17</td>
<td>32.54</td>
<td>28.18</td>
<td>27.56</td>
<td>29.55</td>
</tr>
<tr>
<td>C-3a</td>
<td>174.28</td>
<td>178.84</td>
<td>169.41</td>
<td>42.09</td>
<td>46.41</td>
<td>48.33</td>
<td>48.76</td>
<td>42.52</td>
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<td>121.22</td>
<td>122.53</td>
<td>35.58</td>
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<td>48.76</td>
<td>42.26</td>
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<td>199.74</td>
<td>197.27</td>
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<td>212.79</td>
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<td>32.54</td>
<td>37.36</td>
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<td>38.05</td>
<td>38.17</td>
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<td>C-7</td>
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<td>33.82</td>
<td>37.03</td>
<td>35.74</td>
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<td>C-7a</td>
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<td>39.81</td>
<td>40.40</td>
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<td>C₇a-COOCH₂CH₃</td>
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<tr>
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<tr>
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<td></td>
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<td>14.24</td>
<td>14.29</td>
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itself. Moreover, allylic alcohols derived from the reduction of the keto group present in the hydrindenone 16 were not detected by $^1$H NMR (no olefinic signals). Therefore, we can conclude that NaBH$_4$/NiCl$_2$·6H$_2$O in methanol reduces carbon-carbon double bond present in the enone moiety in preference to carbon oxygen double bond. Once the hydrogenation of the enone to the corresponding ketone has taken place, there is a competitive reduction between the carbon-carbon double bond present in left over enone with NaBH$_4$/NiCl$_2$·6H$_2$O and the carbon-oxygen double bond present in hydrogenated product ketone, with the excess NaBH$_4$ present in the medium.

Mechanism of the hydrogenation of the enone moiety in hydrindenone 16 is consistent with the earlier findings that reductions with hydride reducing agents in conjunction with transition metal salts and protic solvents is more like catalytic hydrogenation involving radical intermediates. However, the fact that cis vs. trans isomer ratio, 59:41, obtained in this reduction is significantly different from conventional hydrogenation (cis vs. trans ratio 100:00) indicates that the actual mechanism involved in this reaction is quite different.

Reduction of hydrindenone 16 with this reagent was carried out at -35°C to find out if there was any effect of temperature on the stereoselectivity. The ratio of the cis
and trans isomeric ketones remained same (56:44) within the experimental error, and there was no change in the product composition (ketone alcohols 4:1).

Encouraged by the result that the stereoselectivity involved in the reduction of cyclic enones are significantly different from the standard hydrogenation, the reduction of enone moiety present in various other hydrindenones 18, 19 (Scheme IVA.11) and decalenones 24, 25, 26 were conducted (Scheme IVA.12).

\[
\text{NaBH}_4/\text{NiCl}_2 \cdot 6\text{H}_2\text{O} \rightarrow \text{MeOH, 0°C, 5-30 min}
\]

18. \( R = \text{H} \)  
16. \( R = \text{CH}_3 \)  
19. \( R = \text{COOC}_2\text{H}_5 \)

15. \( R = \text{CH}_3 \)  
21. \( R = \text{H} \)

17. \( R = \text{CH}_3 \)  
20. \( R = \text{H} \)

22. \( R = \text{COOC}_2\text{H}_5 \)  
23. \( R = \text{COOC}_2\text{H}_5 \)

Scheme IVA.11

Results from these experiments are gathered in the Table IVA.1. For the purpose of comparison the ratios of cis and trans products as obtained by the conventional hydrogenation are given in brackets. It may be noted from the Table IVA.1, that the ratio of cis and trans isomeric ketones formed from the reduction using NaBH\textsubscript{4}/NiCl\textsubscript{2} is quite different from the
conventional hydrogenation with a cross-over occurring for the reduction of hydrindenones (entry 1 substrate 18 Table IVA.1).

\[
\text{NaBH}_4 / \text{NiCl}_2 \cdot 6\text{H}_2\text{O} \rightarrow \text{MeOH, 0°C, 5 - 30min}
\]

\[
\begin{align*}
\text{cis} & \quad \text{trans} \\
24. R = H & \quad 27. R = H & \quad 28. R = H \\
25. R = \text{CH}_3 & \quad 29. R = \text{CH}_3 & \quad 30. R = \text{CH}_3 \\
26. R = \text{COOC}_2\text{H}_5 & \quad 31. R = \text{COOC}_2\text{H}_5 & \quad 32. R = \text{COOC}_2\text{H}_5
\end{align*}
\]

Scheme IVA.12

Reduction of the parent hydrindenone 18 with this reagent system resulted in the formation of cis and trans hydrindanones 20, 21 in 79:21 ratio as determined by GLC. Isomers were separated by column chromatography and were characterized individually on comparison with known \(^1\text{H}\) & \(^{13}\text{C}\) NMR spectra of authentic samples. The authentic cis ketone 20 and trans-ketone 21 (minor product) were made by hydrogenation under standard conditions\(^{41}\) (H\(_2\)/Pd-C).

Reduction of hydrindenone 19 having ethoxycarbonyl group at \(C_{7a}\)-position resulted in cis and trans products 22, 23 in a ratio of 67:33. Isomeric ratio was determined by integration of \(-\text{OCH}_2\) signals in \(^1\text{H}\) NMR of the crude products. Individual isomers were separated and
characterized. Authentic cis compound 22 was made by catalytic hydrogenation\(^4\). Dauben et al.\(^4\) reported that catalytic hydrogenation of the enone 19 results in only cis compound in 83% yield. However, we have found that both cis vs. trans products were formed and the ratio was 87:13, when the reduction was conducted in EtOAc. trans-Ketoester 23 (\(^1\)H, \(^13\)C NMR, Fig.IVA.4) showed -OCH\(_2\)-signal at 4.18 ppm whereas cis compound 22 (\(^1\)H, \(^13\)C NMR, Fig.IVA.5) showed the signal at 4.21 ppm in \(^1\)H NMR spectrum. In \(^13\)C NMR spectrum of the trans-ketoester 23, \(\text{C}_3\) and \(\text{C}_7\) carbon resonance appeared at 42.5 ppm and 50.67 ppm respectively, whereas for the cis-ketoester 22 corresponding signals as expected appeared at down field, at 48.76 (\(\text{C}_3\)) and 52.21 ppm (\(\text{C}_7\)).

Reduction of the parent, decal-4-ene-5-one 24 with NaBH\(_4\)/NiCl\(_2\) in methanol resulted in cis and trans-decal-3-ones 27, 28 in 30:70 ratio. Isomeric ratio was determined by GLC. Authentic cis and trans-decal-3-ones were obtained from Li/NH\(_3\)/t-BuOH reduction of decalenone 24 and subsequent separation of isomers. trans-Decalone 28 showed \(\text{C}_5\), \(\text{C}_{10}\) carbon resonances at 43.10 and 41.22 ppm respectively in agreement with the reported values\(^{39a}\) for this compound. It is to be noted that, similar to earlier cases, the ratio of of the cis and trans-decalones 27, 28 (cis vs. trans, 3:7) obtained from the above reduction is different from conventional hydrogenation\(^43\) (41:59, entry 4, Table IVA.1).
FIG. IV: A. $^1$H NMR (90 MHz) Spectrum B. $^{13}$C NMR (22.5 MHz) Spectrum (inset SEFT, 100 MHz) of trans-7a-ethoxycarbonylhydridan-5-one (23).
FIG.IVA.5. A. $^1$H NMR (90 MHz) Spectrum  B. $^{13}$C NMR (22.5 MHz) Spectrum (inset SEFT, 100 MHz) of cis-7a-ethoxycarbonylhydrindan-5-one (22).
Reduction of 10-methyldecal-4-ene-3-one 25 with the above reagent resulted in cis vs. trans ratio, 58:42. Isomeric ratio was determined by the integration of the angular methyl group signals in $^1$H NMR spectra of the crude reaction mixture. Authentic cis compound 29 was prepared by catalytic hydrogenation$^{44}$ of starting enone 25 and an authentic trans compound 25 was prepared by metal ammonia reduction of the enone 25$^{34}$. The cis isomer 29 showed C$_{10}$-CH$_3$ signal at 1.19 ppm in $^1$H NMR spectrum and the carbon resonances for C$_5$, C$_{10}$, C$_{10}$-CH$_3$ occurred at 39.1, 32.6, 27.5 ppm in carbon-13 NMR spectrum. These values are in good agreement with the reported data$^{44,37}$. trans Decalone 30 showed C$_{10}$-CH$_3$ signal at 1.04 ppm in $^1$H NMR spectrum, upfield compared to the corresponding signal for cis-decalone 29. The carbon-13 NMR spectrum showed signals due to C$_5$, C$_{10}$, C$_{10}$-CH$_3$ at 44.37, 32.78, 14.58 ppm, occurring at downfield compared to the corresponding signals for the cis compound 29. These values are also in good agreement with literature values$^{45,37}$. Similar to other cases, the ratio of cis and trans isomers obtained from this reduction reaction is significantly different from the ratio generated by standard hydrogenation.$^{44}$

Reduction of C$_{10}$-ethoxycarbonyldecal-4-ene-5-one 26 with this reagent led to cis 31 (Fig.IVA.6) and trans 32 (Fig.IVA.7) decalones in the ratio of 42:58. The cis vs. trans ratio was determined by the integration of the salient
FIG. IVA.6. A. $^1$H NMR (90 MHz) Spectrum B. $^{13}$C NMR (22.5 MHz) Spectrum of Cis-10-ethoxycarbonyldecal-3-one (31).
FIG. IVA. 7. A. $^1$H NMR (90 MHz) Spectrum B. $^{13}$C NMR (22.5 MHz) Spectrum of trans-10-ethoxycarbonyldecal-3-one (32).
signals due to the -OCH₂-in the ¹H NMR spectrum. It was found that in cis isomer 31, -OCH₂ group resonates at 4.21ppm whereas in the trans compound 32 corresponding signal occurs at 4.19ppm. The cis and trans isomers were separated and characterized. Authentic trans compound 32 was made by catalytic hydrogenation of the corresponding enone 26 in conditions under which trans isomer predominates in product mixture. Authentic cis isomer 31 was separated from the above reaction mixture. The trans isomer 32 revealed signals at 40.40 and 59.25 ppm due to C₅ and C₁₀ carbons in its carbon-13 NMR spectrum. For the cis compound 31 corresponding signals occurred at 39.06 and 47.24 ppm, in agreement with the known fact that C₅ and C₁₀ carbons resonates upfield in cis isomers compared to trans isomers in these compounds. The ¹³C NMR spectral assignments for all the carbons in the enones 18, 16, 19; 24-26, the cis and trans isomers of hydrindanones 21; 15, 17; 22, 23 and decalones 28, 30, 31, 32 products are gathered in Table IVA.2 & 3 (only for those compounds where lit. data is not available.). The assignment were made on the basis of (a) calculated spectra (b) in comparison with compounds having similar structures such as steroids and terpenoids (c) on the basis of off-resonance decoupling, APT and SEFT experiments (d) accounting for pronounced r-gauche effect (a shift towards a upfield) observable for C-2 carbons in the
### TABLE IVA.2

$^{13}$C NMR Resonances for hydridanone series

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<tr>
<th>Carbon number</th>
<th>18</th>
<th>16</th>
<th>19</th>
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<td>39.94</td>
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<td>C-3</td>
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<td>30.74</td>
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<td>39.81</td>
<td>40.40</td>
<td>52.21</td>
<td>50.67</td>
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| C$_{7a}$-CH$_3$ | 26.79 | 16.30 |
| C$_{7a}$-COOCH$_2$CH$_3$ | 172.39 | 174.50 | 176.37 |
| C$_{7a}$-COOCH$_2$CH$_3$ | 60.51 | 59.95 | 60.51 |
| C$_{7a}$-COOCH$_2$CH$_3$ | 13.30 | 14.24 | 14.29 |

10. $R = H$
16. $R = CH_3$
19. $R = COOC_2H_5$
20. $R = H$
21. $R = CH_3$
22. $R = COOC_2H_5$
23. $R = H$

259
### TABLE IVA.3

$^{13}$C NMR Resonances for decalone series

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24. $R = H$
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26. $R = COOC_2H_5$
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28. $R = CH_3$
29. $R = CH_3$
30. $R = COOC_2H_5$
31. $R = COOC_2H_5$
32. $R = COOC_2H_5$

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$^{13}$C NMR Resonances for decalone series

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<th>28</th>
<th>30</th>
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<td>37.87</td>
<td>47.24</td>
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24. $R = H$
25. $R = CH_3$
26. $R = COOC_2H_5$
27. $R = H$
28. $R = CH_3$
29. $R = CH_3$
30. $R = COOC_2H_5$
31. $R = COOC_2H_5$
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TABLE IV.1

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<td>2</td>
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<td>67 : 33</td>
<td>(100:00; 41)</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>30 : 70</td>
<td>(43:57; 42)</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>58 : 42</td>
<td>(100:00; 21)</td>
</tr>
<tr>
<td>6</td>
<td>26</td>
<td>42 : 58</td>
<td>(05;&gt;95; 45)</td>
</tr>
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</table>

a. Ratios in brackets refer to reported stereoselectivity under conventional hydrogenation conditions with solvent ethanol and a literature reference (b) Ratios were determined by $^1$H NMR or from GLC results (c) the observed stereoselectivity by conventional hydrogenation ($H_2$, 10% Pd-C, rt., 2-3 atm) using EtOAc as solvent was **cis : trans** 12 : 88.
case of hydrindanones having \( C_{7a} - CH_3 \) or \( C_{7a} - COOC_2H_5 \) and \( C_8 \) carbon in the case of decalones having \( C_{10} - CH_3 \) or \( C_{10} - COOC_2H_5 \).

In conclusion, our results show that cyclic \( \alpha, \beta \)-unsaturated carbonyl compounds can be efficiently hydrogenated with \( NaBH_4/\text{NiCl}_2 \cdot 6\text{H}_2\text{O/CH}_3\text{OH} \) under mild conditions. Since the reagent is inexpensive convenient to prepare, easily removed after the completion of the reaction and can be used in the laboratory conditions without the requirement of inert atmosphere and elaborate apparatus, it should be useful for carrying out this transformation. It is particularly noteworthy that the stereoselectivity involved is significantly different from both standard catalytic hydrogenation \(^{40, 31, 41, 42, 21, 45} \) and metal ammonia conditions\(^{36} \), indicating that the actual mechanism involved in this reaction is different. Above results also show that trans-\( C_{7a} \)-methyl hydrindanone \(^15 \) and trans-\( C_{7a} \)-ethoxycarbonylhydrindanone \(^23 \) can easily be prepared in reasonably good yields, which was earlier prepared either by following multistep path way or by using expensive reagents.
For general experimental conditions and substrate molecules synthesis, see Chap.I experimental section.

IVA.3.1. Reduction of cyclic α,β-unsaturated ketones with NaBH₄/NiCl₂.6H₂O General procedure

To the enone (1 mmol) in methanol (20 ml) nickel (II) chloride hexahydrate (3 mmol) was added during 10 min in three portions (1 mmol each time) followed by sodium borohydride (3 mmol) also in three portions (1 mmol each time) at 0°C. After stirring for another 15-30 min at 0°C-rt, the reaction mixture was filtered through a plug of Florosil to remove polar inorganic materials. Filtrate was concentrated under reduced pressure and the residue was taken with water (100ml) and extracted with dichloromethane (25 ml X 6). Organic layer was washed with water (20ml X 2), brine (25 ml) and dried over anhydrous Na₂SO₄ before concentration. Total yields of the mixture of ketones & alcohols was quantitative, and the ¹H NMR spectrum of the crude product was recorded to determine the product ratio through the integration of salient peaks. In cases where the peaks due to isomers were not discernible the ratio was determined by GLC analysis*. The crude product obtained from the reaction mixture was subjected to oxidation with PCC⁴⁰ in dichloromethane for complete conversion of alcohols to ketones (TLC). After due workup isomeric ketones were
obtained in near quantitative yield. The analytical samples were obtained by repeated column chromatography by using different ratios of ethylacetate in hexanes (60°C-80°C boiling mixture) for elution. The products obtained were colorless liquids. Spectral data for individual components were obtained on the purified products and compared with the values of mixture $^1$H NMR. Refer experimental section of Chapter.I for details of spectral data.

*Note: GLC conditions:– Silicone GE.SE 30/10% 2.6/3.2 1D glass spiral support – shimalite, W.AW – DMCS mesh 60/80. Injection temp. 250°C, oven temp. 120-250 (25°C min$^{-1}$) and detection temp. 280°C.
IVA.4. References


4. a. Sabatier, P.; Senderens, J.B. Compt.Rend. 1897, 124, 1358 (1)
   b. Sabatier, P.; Mailhe, A. Compt.Rent. 1907, 144, 784 (92).

5.1. For NaBH₄:
   a. Sodium Borohydride; 1979 product Bulletin; Thiokol/Ventron: Danvers, M.A.;

ii. For LiAlH₄:
   a. Ref. 4b, 4d ;


    b. Ref. 6.


   b. See also, Chaykovsky, M.; Ireland, R.E. J.Org.Chem. 1963, 28, 748.
CHAPTER IV

PART B

Stereoselectivity in Cyclic Enone Reductions with Ammonium Formate/Palladium on Carbon (10%)

IVB.1. Introduction

The discovery of the addition of a molecule of hydrogen across a carbon-carbon double bond in the presence of a noble metal catalyst is probably the most significant development in the field of organic reactions. This reaction commonly referred to as catalytic hydrogenation,¹ is usually performed in the atmosphere of gaseous hydrogen and in the presence of metal catalysts such as Palladium, Platinum, Rhodium, Ruthenium and Iridium. The metal catalyst used may be insoluble in the reaction medium leading to heterogeneous catalytic hydrogenation, or soluble in the reaction medium leading homogeneous catalytic hydrogenation¹. Even though the reduction of organic functional groups under catalytic hydrogenation is very popular, the procedure involved has some difficulty in implementation, for example, the need to maintain an atmosphere of $H_2$ throughout the reaction. Therefore, there was a necessity for the development of procedures which does not require molecular hydrogen gas as a reactant. It was found that some molecules, such as cyclohexadiene, isopropanol and ammonium formate, decompose readily releasing hydrogen in situ to form more stable
products. A method involving the reagents which release $H_2$ in \textit{situ} for hydrogenation of suitable substrates, in the presence of insoluble metal catalysts, is referred to as transfer heterogeneous catalytic hydrogenation$^1$, a concept introduced by Braude$^2$.

Compared with catalytic hydrogenation using molecular hydrogen, transfer hydrogenation using hydrogen donors has many advantages. Molecular hydrogen is a gas of low molecular weight and therefore has a high diffusibility. It is easily ignited and presents considerable hazards, particularly on the large scale. The use of hydrogen donors circumvent these difficulties in that no gas containment is necessary, no pressure vessels are needed and simple stirring of solutions is usually all that is required. In catalytic hydrogenation, possible variations in reaction conditions include change of catalyst, solvent and temperature, but with transfer hydrogenation using hydrogen donors variations in the choice of donors is also possible. With such variations, regio- and chemo-selectivity in the reduction as well as the stereochemistry involved can be different.

Mechanisms involved in transfer hydrogenation are not well understood, particularly because it is not known if the donation of hydrogen atom takes place at a time or sequential transfer of hydride ion and proton takes place. Most of the time decomposition of hydrogen donors have large negative
enthalpy of formation, for e.g., release of CO₂ from formic acid, N₂ from diimide and benzene from cyclohexadiene make them excellent hydrogen donors.

The preparation of Ammonium formate was described in 1941³. It has generally been used in the precipitation of base metals from the salts of the noble metals. The utility of ammonium formate in organic synthesis was first illustrated by Leucart as early as 1885⁴. In this reaction various carbonyl compounds 1 were treated with ammonium formate (2) to afford corresponding amines 3 (Scheme IVB.1).

\[
\begin{align*}
R'\text{-CO-}R'^2 + \text{HCOONH}_4 & \rightarrow R'\text{-CH(NH)}_2R'^2 \\
1 & \quad 2 & \quad 3
\end{align*}
\]

Scheme IVB.1

Ammonium formate when heated decomposes to H₂, CO₂ and NH₃, and in the presence of suitable metal catalysts it can be used for transfer hydrogenation. Ammonium formate is readily available, inexpensive, stable and non-toxic chemical and therefore convenient to handle. Moreover, it can be added to the reaction in a single portion and the organic products can be separated easily from the reaction mixture. An exhaustive review article on the utility of ammonium formate in transfer hydrogenation in organic synthesis has appeared⁵. However,
keeping in view of the research plan on hand a brief account on the use of this reagent for transfer hydrogenation is presented in the following.

IVB.1.1. Reduction of carbon-carbon double bonds

Phenyl conjugated and double bond conjugated carbon-carbon triple bond 4 can be reduced to a cis olefin in good yield with triethyl ammonium formate/Pd-C system\textsuperscript{6} (Scheme IVB.2).

\[
\begin{align*}
\text{n-C}_4\text{H}_9 & \equiv \text{CO}_2\text{Me} \quad \overset{\text{HCO}_2\text{H/ Et}_3\text{N}}{\text{pd-C}} \quad \text{C}_4\text{H}_9\text{-n} \\
4 & \rightarrow 5
\end{align*}
\]

\text{Scheme IVB.2}

This reaction in general leads to the reduction of acetylenic bond and not an isolated double bond\textsuperscript{6}. However, phenyl conjugated \(\alpha,\beta\)-unsaturated ketones can also be reduced to saturated carbonyl groups\textsuperscript{7}. The heterocyclic ring of the quinoline \textsuperscript{6} and isoquinolines can be reduced with this reagent conveniently\textsuperscript{8} (Scheme IVB.3). Reduction of arylalkyl

\[
\begin{align*}
\text{HCO}_2\text{NH}_4/\text{Pd-C} \\
\text{MeOH, reflux}
\end{align*}
\]

\text{Scheme IVB.3}

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Ketones,\textsuperscript{9} diarylketones\textsuperscript{7} (HCOONH\textsubscript{4}/Raney nickel) and the reduction of heterocyclic ring present in hydroxy flavones\textsuperscript{10} and isoflavones\textsuperscript{11} have also been reported. A useful regioselective synthetic method for 1-olefin has been reported in which various terminal allylic compounds \textsuperscript{8} such as allylic esters, phenyl ethers, carbamates, chlorides are reacted with HCOONH\textsubscript{4} in the presence of palladium-tributyl phosphine (Pd [P(C\textsubscript{6}H\textsubscript{5})\textsubscript{3}]\textsubscript{4}) complex as a catalyst to afford the 1-olefin, 9 (Scheme IVB.4)\textsuperscript{12}. It has been demonstrated that the catalyst

\[
\begin{array}{c}
\text{R} \begin{array}{c}{-\text{\textasciitilde}}
\end{array} \text{X} & \text{Pd(O)L/HCO\textsubscript{2}\textsuperscript{-}} & \text{H} \\
\end{array}
\]

\textsuperscript{8} X = OAc, OC\textsubscript{6}H\textsubscript{5}, OCO\textsubscript{2}Me, Cl

\textbf{Scheme IVB.4}

used is specific and critical for this transformation. Further, it was also reported that allylic esters 10 can be converted to the corresponding acids in good yields using ammonium formate/Pd[P(C\textsubscript{6}H\textsubscript{5})\textsubscript{3}]\textsubscript{4} system (Scheme IVB.5)\textsuperscript{13}.

\[
\begin{array}{c}
\text{R} \begin{array}{c}{-\text{\textasciitilde}}
\end{array} \text{CH} & \text{HCO\textsubscript{2}\textsuperscript{-}/Pd/PPh\textsubscript{3}} & \text{R} \begin{array}{c}{-\text{OH}}
\end{array}
\end{array}
\]

\textsuperscript{10} R = CH\textsubscript{3}(CH\textsubscript{2})\textsubscript{2} or C\textsubscript{6}H\textsubscript{5}CH = CH\textsuperscript{-}

\textbf{Scheme IVB.5}
IVB.1.2. Reduction of nitrogenous compounds

$\alpha,\beta$-Unsaturated nitroalkanes 12 can be reduced to the corresponding oximes 13 in excellent yields (Scheme IVB.6)

\[
\begin{align*}
R - \text{NO}_2 & \quad \xrightarrow{\text{HCOO}_2\text{NH}_4/\text{Pd-C}} \quad R' - \text{NO} - \text{OH} \\
\text{R, R'} & = -(\text{CH}_2)_n - \\
\text{a. R, R'} & = -(\text{CH}_2)_4 - \\
\text{b. R} & = \text{Aryl}, \quad R' = \text{Methyl.}
\end{align*}
\]

Scheme IVB.6

with this reagent\textsuperscript{14}. Further, it has been reported that diaryl oximes can be reduced to hydrocarbons\textsuperscript{15}. Aromatic and alicyclic nitro compounds and aromatic nitriles can also be reduced very conveniently in high yields to the corresponding amines\textsuperscript{16} and methyl derivatives\textsuperscript{17}. Hydrazones and azines can be reduced to the corresponding hydrazines using HCOONH\textsubscript{4}/Ni system\textsuperscript{16}. Using this reagent alkyl and aryl azides 14 can be reduced to the corresponding amines 15 in very high yields\textsuperscript{18} (Scheme IVB.7).

\[
\begin{align*}
R - \text{N}_3 & \quad \xrightarrow{\text{HCOO}_2\text{NH}_4/\text{Pd-C}} \quad \text{RNH}_2 \\
R & = \text{alkyl, aryl.}
\end{align*}
\]

Scheme IVB.7
IVB.1.3. Dehalogenation reactions

Mono- and polychlorinated aromatic compounds 16 on treatment with ammonium formate in presence of palladium on carbon at room temperature, afford dehalogenated compounds19 17 (Scheme IVB.8). This reaction is very mild and rapid.

\[
\begin{align*}
\text{Cl} & \quad \text{HCO}_2\text{NH}_4/\text{Pd-C} \\
\text{Cl} & \quad \text{OH} \\
\text{Cl} & \quad \text{OH} \\
\text{Cl} & \quad \text{OH}
\end{align*}
\]

Scheme IVB.8

IVB.1.4. Deprotection of functional groups

One of the most important uses of HCOONH\textsubscript{4}/Pd-C is its utility in deprotection of Q-benzyl group (Scheme IVB.9) and

\[
\begin{align*}
\text{R} & \quad \text{O} \quad \text{C}_6\text{H}_5 \\
\text{HCO}_2\text{NH}_4/\text{Pd-C} & \quad \text{Solvent, } \Delta \\
\text{ROH} & \quad \text{OH}
\end{align*}
\]

Scheme IVB.9

N-benzyloxy carbonyl group. Such deprotections are vital in carbohydrate and peptide chemistry\textsuperscript{20}. In these reactions
glycosidic O-methyl groups are not affected. This reagent can also be used for regioselective hydrogenolysis of benzyl glycosides\textsuperscript{20b}, hydrogenolysis of benzyl glycosides\textsuperscript{20}, hydrogenolysis of dibenzyl uracils\textsuperscript{20d}, reductive cyclization of 2-nitro $\beta$-styrenes to indoles\textsuperscript{21}, and deoxygenation of heteroaromatic N-oxides\textsuperscript{22}.

Literature survey revealed that the utility of HCOONH$_4$/Pd-C (10\%) system for the reduction of cyclic $\alpha,\beta$-unsaturated ketones and stereoselectivity involved in such reductions have not explored. In the foregoing, it will be shown that palladium assisted transfer hydrogenation using ammonium formate is a convenient way of reduction of cyclic $\alpha,\beta$-unsaturated ketones to the corresponding saturated cyclic ketones. The stereoselectivity involved in such reductions are somewhat different from the conventional hydrogenation using H$_2$/Pd-C. An authoritative review on transfer hydrogenation by Johnstone et al.\textsuperscript{1} noted that research in this area is needed not only to unravel the details of mechanism, but also to provide a proper appraisal of the advantages or disadvantages of the application of standard (H$_2$/Pd-C) and transfer hydrogenation methods.

IVB.2. Results and discussion

Since the reduction of cyclic $\alpha,\beta$-unsaturated ketones and stereochemistry involved in these reactions play a vital role in multistep synthetic organic chemistry, we have chosen
C₇a-substituted hydrindenones 20, 21, 22 and C₁₀-substituted decalenones 28, 29, 30 as substrates because of their inherent importance in the field of steroids and terpenoids. These substrates offer convenient handle for direct comparison of the product ratios, resulting from the reduction under standard and transfer hydrogenation. Ammonium formate (5 mmol), 10% palladium-carbon (5% of the substrate by weight) readily reduces cyclic α,β-unsaturated ketones (1 mmol) under reflux in methanol in good yields within 5 min. (Schemes IVB.10 & 11).

\[
\begin{align*}
\text{HCOONH}_2 / 10\% \text{ Pd-C} & \quad \text{MeOH, reflux, 5min} \\
\end{align*}
\]

\begin{align*}
\text{cis} & \quad 23 & \quad 24 \\
\text{trans} & \quad 25 & \quad 26 \\
\end{align*}

\textbf{Scheme IVB.10}

\[
\begin{align*}
\text{HCOONH}_2 / 10\% \text{ Pd-C} & \quad \text{MeOH, reflux, 5min} \\
\end{align*}
\]

\begin{align*}
\text{cis} & \quad 31 & \quad 32 \\
\text{trans} & \quad 33 & \quad 34 \\
\end{align*}

\textbf{Scheme IVB.11}

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The results obtained from this study are presented in Table IVB.1.

**TABLE IVB.1**

![Chemical Reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting enone</th>
<th>Product distribution&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>cis : trans 90 : 10 (100:00)</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>cis : trans 100 : 00 (100:00)</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>cis : trans 100 : 00 (100:00)</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>cis : trans 76 : 24 (43:57)</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>cis : trans 100 : 00 (100:00)</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>cis : trans 77 : 23 (05:95)</td>
<td>76</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ratios were determined by <sup>1</sup>H NMR or from GLC results.

b. Complex mixture of products.
The ratios of \textit{cis} and \textit{trans} products obtained by conventional hydrogenation as reported in the literature are given in brackets in Table IVB.1. It is noteworthy that, for some substrates, the observed stereoselectivity (entry 1, 4, 6) is different from that in conventional hydrogenation. For example, in the reduction of decal-4-ene-3-one (entry 4) to \textit{cis} and \textit{trans} decal-3-ones 31, 32 and C_{10} \textsubscript{-ethoxycarbonyl}decal-4-ene-3-one, saturated ketones 35, 36, there is a cross-over in stereoselectivity (entry 4 and 6). This result indicates that a different mechanism operate in the transfer and the standard hydrogenation\textsuperscript{1}.

Reductions were normally conducted at reflux temperature of methanol. It was found that reductions were slow or did not take place if the reactions were attempted at room temperature or even at 50\textdegree C. Reduction of C\textsubscript{7a} \textsubscript{-ethoxycarbonyl}hydrind-4-ene-5-one resulted in a complex mixture of products (entry 3, Table IVB.1).

Stereoselectivity observed in the reduction of C\textsubscript{7a} \textsubscript{-substituted} hydrindenones 20, 21, 22 and C\textsubscript{10} \textsubscript{-substituted} decalenones 28, 29, 30 under three different conditions viz ammonium formate/Pd-C (10\%)/MeOH/reflux, NaBH\textsubscript{4}/NiCl\textsubscript{2}.6H\textsubscript{2}O/MeOH/0\textdegree C and H\textsubscript{2}/Pd-C/EtOH/rt are gathered in Table IVB.2. This Table allows us to compare readily the ratios of the products obtained from three methods.
It is clear from the Table IVB.2 that the stereoselectivity observed in with three reducing agents are different, indicating that the possibility of an operation of different mechanisms.

Details of the assignment of structures to substrates 20-22; 28-30 as well as cis and trans isomeric cyclic ketones 23-26 31-36, have been described earlier (Chapter IV, Part A) in this thesis. The methods used for determining the product ratios have also been described.

Table IVB.2: Stereoselectivity observed in the hydrogenation of cyclic α,β-unsaturated ketones under

a. NaBH₄/Cl₂/MeOH b. HCOONH₄/Pd-C/MeOH c. H₂/Pd-C/EtOH.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting enone</th>
<th>Product Distribution cis : trans</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NaBH₄/Cl₂.6H₂O₄ MeOH, 60°C</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>21 : 79</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>59 : 41</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>67 : 33</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>30 : 70</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>58 : 42</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>42 : 58</td>
</tr>
</tbody>
</table>

In summary, the results obtained clearly show that cyclic α,β-unsaturated ketones can be reduced to saturated
ketones conveniently with ammonium formate/Pd-C (10%) in good yields with in 5 min. Results obtained from this study have been published.23

IVB.3. Experimental

For general experimental conditions , see Chap.I experimental section.

Reduction of cyclic α,β-unsaturated ketones with ammonium formate/palladium-carbon (10%): General procedure:-

To the enone (1 mmol) in methanol (25 ml) was added catalytic amount of 10% Pd-C (5 mg) and ammonium formate (5 mmol). The mixture was refluxed for 5 min. Reaction progress was monitored by TLC and after completion the reaction, mixture was filtered through a plug of Celite and filtrate was concentrated under reduced pressure. The residue was taken with water (100 ml) and extracted with dichloromethane (25 ml X 6). Organic layer was concentrated after conventional work up and further processing was made following the procedure, described in preceding section (Chapter IV, Part A) to obtain relative product ratio. The analytical samples were obtained by purification by chromatographic techniques which has been described earlier in this thesis.

Details of the experimental procedures, physical and spectral data for substrate molecules 20-22; 28-30 as well as products 23-26; 31-36 are given in the experimental section of Chapters I and II.
IVB.4. References


APPENDIX - A & B
APPENDIX

Part A. Reduction of Aroyl Azides with Sodium Borohydride/Nickel (II) Chloride Hexahydrate

A.1. Introduction:

The study of functional groups and their transformations is of fundamental importance in organic chemistry. Evolution of organic chemistry has been associated with the recognition of functional groups and their interconversions using selective reagents.

Azides are important synthetic intermediates in organic chemistry as they act as a source of primary amino group. Acyl azides, the derivatives of carboxylic acids, are quite different from alkyl azides in their chemistry. For example, unlike alkyl azides, acyl azides undergo facile rearrangement reactions (Curtius rearrangement) via nitrene intermediates with the loss of a nitrogen molecule under thermal and photochemical conditions. The acyl azides derived from many alkyl carboxylic acids are unstable at room temperature and therefore, are difficult to handle. In contrast, aroyl azides are quite stable and can be handled easily under laboratory conditions.

It was found earlier from our laboratory that aroyl azides are reduced to benzyl alcohols predominantly
with sodium borohydride. For example, benzoyl azide (1, X = H) when reacted with NaBH₄ in CH₃OH at 0°C for 1 h resulted in a mixture of benzyl alcohol (2, X = H) and benzamide (3, X = H) in the ratio of 9:1 in 90% yield, (Scheme A.1).

\[
\begin{align*}
4 - X - C₆H₅CON₂ & \overset{\text{NaBH₄/MeOH}}{\underset{0°C \text{ In.}}{\rightleftharpoons}} 4 - X - C₆H₅CH₂OH + 4 - X - C₆H₅CONH₂ \\
X & = H, \text{Cl, CH}_3, \text{OCH}_3 \& \text{NO}_2
\end{align*}
\]

![Scheme A.1]

Substitution of groups with -I effect in the para-position of benzoyl azide viz., NO₂(1 X = NO₂) and Cl(1, X = Cl) resulted in shorter reaction times and almost quantitative formation of the corresponding alcohols 2, indicating their influence on the intermediates formed in the reaction. Further, substitution with groups having +I effect in the para-position viz., CH₃ (1, X = CH₃), OCH₃ (1, X = OCH₃) resulted in longer reaction time as well as lower proportion of substituted benzamide 3. A mechanism has been proposed taking into account of influence of -I and +I effects (Scheme A.2).
Scheme A.2

A.2. Results and discussion

In continuation, during the present work, it was found that in contrast to NaBH₄ reduction of aroylazides to benzylalcohols, benzamide are formed exclusively upon treatment with sodium borohydride/nickel (II) chloride hexahydrate/CH₃OH system at 0°C (Scheme A.3). This reagent has been employed previously for the reduction of alkyl azides to amines. Thus, treatment of benzoyl azide (I) with excess sodium borohydride in dry methanol at 0°C in the presence of nickel (II) chloride hexahydrate resulted in exclusive formation of benzamide (3, 100 % yield) within 5 min. (Scheme A.3). Results of the reduction of the several other aroyl azides with electron-withdrawing groups (4,5,8) or electron donating groups (6,7) are gathered in the Table, and all the reductions were complete in 5 min.
The results indicate that substitution of groups with +I or -I effects in the para-position of the aryl ring doesn't have much effect upon the rate of reduction. As noted earlier, reduction of aryl azides with NaBH₄ led to the formation of the benzyl alcohols predominantly and groups with +I and -I effect had profound influence on the course and rate of reduction. This result supported a mechanism, wherein attack of hydride ion upon the electron deficient carbonyl carbon of the acyl azide was the rate limiting step. On the other hand reduction with sodium borohydride/nickel (II) chloride is more like catalytic hydrogenation, possibly, involving radical intermediates. Thus, in the present case it was not surprising to find that there was little effect on the course or rate of the reaction upon changing substituents from +I to -I as the reaction was not taking place on the carbonyl carbon.

\[ \text{NaBH}_4/\text{NiCl}_2 \cdot 6\text{H}_2\text{O} \rightarrow \text{CONH}_2 \]

CH₃OH, 0°C, 5 min

1. X = H; 4. X = Br
5. X = Cl; 6. X = CH₃
7. X = OCH₃; 8. X = NO₂
9. X = Br
10. X = Cl; 11. X = CH₃
12. X = OCH₃; 13. X = NO₂/NH₂

Scheme A.3
<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a, b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>9</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>10</td>
<td>80&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>11</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>12</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>13</td>
<td>20&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

a. Reaction was conducted at 0°-10°C and monitored by TLC for absence of the azide.
b. Yields are of isolated and purified products.
c. 6% of 4-aminobenzamide (13, X = NH₂) also was isolated.

This piece of work was carried out by Prof. K. Turnbull, Department of Chemistry, Wright State University, Dayton, Ohio 45435, U.S.A., under collaborative programme.

Reduction of the nitro group to the corresponding amine is earlier known with this reagent<sup>8</sup>. Indeed, our collaborator Prof. K. Turnbull found that the attempted reduction of 8 resulted in a mixture of 4-nitrobenzamide (13, X = NO₂), 20%) and 4-ami-no- benzamide (13, X = NH₂, 6%). In another attempt, to effect as complete reduction as possible, excess NaBH₄ (pellets), NiCl₂. 6H₂O was used under ultrasonication for 2h and the reaction, surprisingly, resulted in methyl 4-aminobenzoate (4-NH₂-C₆H₄-COOCH₃). It is curious that under reductive conditions substitution precedes reduction.
Extension of this method to the use of NaBH\textsubscript{4}/cobalt (II) chloride hexahydrate was examined briefly. Thus, using this system 4-chlorobenzoylazide (4) was reduced quantitatively to 4-chlorobenzamide (9).

In conclusion, the present method offers a convenient, mild, high yield route for the reduction of many aroyl azides to the corresponding amides, complementary to the sodium borohydride reduction of aroyl azides to benzyl alcohols. Results from the present study have been published\textsuperscript{9}.

A.3. Experimental

For general methods see experimental section of chapter I

A.3.1. General procedure for the preparation of aroyl azides:

All the starting benzoyl azides were prepared from corresponding freshly distilled benzoyl chlorides by halogen exchange with azide anion (sodium azide/acetone). Aroyl chlorides themselves were prepared fresh from substituted benzoic acids on refluxing with freshly distilled thionyl chloride, following the procedure described in Vogel's Textbook of practical organic chemistry.\textsuperscript{10} Aroyl azides were characterized on the basis of IR (\( \nu_{\text{max}} \approx 2200 \text{ cm}^{-1} \)) and m.p.'s. Benzoyl azide m.p. 31°C (reported 32°C), p-bromo benzoyl azide, 45°C (46-47°C), p-chloro benzoyl azide, 41°C

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(43°C), p-methyl benzoyl azide, 33°C (34-35°C), p-methoxy benzoyl azide, 70°C (70-72°C) and p-nitro benzoyl azide, 68° (71°C).

Substituted benzamides obtained from this study were characterized on the basis of IR m.p. mixed m.p and co-TLC with authentic samples. Benzamide m.p 128°C (reported 127.2°C)\(^\text{11}\), p-bromobenzamide 192°C (193°C), p-chlorobenzamide 171-4°C (172-6°C), p-methylbenzamide 151°C (150-2°C), p-methoxybenzamide 166°C (164-7°C), p-nitrobenzamide 199°C (201°C) and p-aminobenzamide 108°C (110°C).

**A.3.2. General procedure for the reduction of aroyl azides with NaBH\(_4/NiCl_2\cdot6H_2O\).**

Reduction of benzoyl azide (1) is representative of the procedures employed. A mixture of benzoyl azide (1.47g, 10 mmol) and nickel (II) chloride hexahydrate (4.74g, 20mmol) in methanol (100 ml) was cooled to 0-10°C. with stirring, sodium borohydride (0.74g, 20 mmol) was added in one portion. Reaction progress was monitored by TLC using a hexane/ethyl acetate mixture (9:1) as eluant and complete conversion usually occurred with in 5 - 10 min. The mixture was quenched by the addition of saturated brine (20ml) and extracted with dicholoromethane (5 X 20 ml). The combined organic layers were washed with brine (10 ml), dried (Na\(_2\)SO\(_4\)) and evaporated in vacuo to yield benzamide, 1.23 (100%), identical (m.p., IR., TLC) to an authentic sample.
A.4. References


Isoflavones from *Flemingia vestita* (Leguminosae)

B.1. Introduction:

Natural products chemistry, as a distinct branch of organic chemistry, deals with isolation, characterization, synthesis and biosynthesis of secondary metabolites. Primary metabolites viz., proteins, nucleotides, carbohydrates and fatty acids, are responsible for sustenance and propagation of life. On the other hand, secondary metabolites, such as flavonoids, alkaloids, terpenoids and antibiotics are produced by the plants and lower animals for defence, communication and other such varied purposes. They are important for medicinal purposes as even today more than 1/3 of the drugs come from plant sources\(^1\)-\(^5\). Usually, secondary metabolites have complex single unit structures.

Among the secondary metabolites, oxygen containing heterocyclic compounds having phenolic hydroxy groups, e.g., flavonoids and isoflavonoids, are important to plants as they act as phytoalexins\(^6\) and possess oestrogenic activities.\(^7\) These compounds particularly flavonoids\(^8,\(^9\) are present in all vascular plants and therefore commonly used for chemotaxonomy. Flavonoids can be differentiated by the basic structure of their carbon frame work. Various classes of
flavonoids are anthocyanins, lecuoanthocyanidins, flavonols, flavones, glycoflavones, biflavonols, chalcones, aurones, flavanones and isoflavones. Among these, classes isoflavones and biflavonoids are found only in a few specific plant families.

Isoflavonoids are remarkable in that they display an exceedingly diverse range of biological properties. The first isoflavone, ononin, was isolated by Halsiwetz in 1855, but the actual structure of this natural product was available only in 1934. By now over 700 isoflavones have been isolated and structures assigned. Isoflavonoids are prevalent in the family of Leguminosae. Plants belonging to this family are economically important not only due to their products, but also due to their nitrogen fixing properties. *Flemingia vestita* a plant belonging to this family has been chosen for the present study.

*Flemingia vestita* Benth., (Khasi Hills, near Shillong, Meghalaya, India) locally called as Soh-Phlong is a much branched trailing herb with tuberous roots found in practically throughout the Himalays and Khasi hills upto an elevation of 8,000 ft. Stems are 1-3 ft long, hirsute, wiry, leaves trifoliate with abovate-cuneate leaflets. Flowers are bright red, pods sub-cylindrical hairy and 1 seeded.
This Plant is cultivated in Khasi Hills often following potato crop for its tuberous roots. It is sown in Feb-May and harvested in Aug-Nov. About 4 maunds of seed in the form of tubers are sown per acre, and an yield of 40 maunds is obtained. Tubers are nearly elliptical, 1.5-2 inches long and possesses an agreeable nutty flavor. Skin which is somewhat pungent is removed by rubbing under water or by peeling and tubers are eaten raw.

The peels of the tubers are used for its vermifugal properties by local tribals. Keeping in view of the medicinal properties of peels of the tubers, phytochemical investigation of this part has been taken up and is described in the following.

B.2. Results and discussion

Fresh tubers of *Flemingia vestita* were collected from Smit area (elevation 2000 mt) close to Shillong (10km), Meghalaya, India in December 1988. The tubers were peeled immediately. The peels (1.5kg) were extracted in Soxlet apparatus with methanol (2 lit, twice) for 36 h. The dark brown colored solution was filtered through a cotton plug and concentrated under reduced pressure to afford 100g of crude extract. In another batch peels (1 kg) were extracted with ethylacetate as solvent, filtered and concentrated to give 75g residue. Both crude extracts showed 3 major spots on TLC (SiO₂, hexane/ethylacetate 95:5), labeled A, B, C with
increasing Rf values. These three spots were separated by repeated column chromatography using hexane, benzene, ethylacetate in the order of increasing polarity as eluants.

B.2.1. Characterisation of fraction A

Fraction A, a white powder gave red color with Mg-HCl (Shinoda test), characteristic for flavonoids. It gave deep blue under UV and UV/NH₃ light. Rf values of the compound, (0.8, TBA; 0.28, HOAc) indicate that it is an aglycone. The compound showed λmax (MeOH) : 248, 318 nm. With NaOH, a bathochromic shift of 12 nm in band I and 22 nm in band II was noticed. However, there was no bathochromic shift of both bands in presence of AlCl₃, indicating that there is no 5-OH present in the molecule. ¹H NMR spectrum showed characteristic signal for isoflavones, two singlets at 8.33 and 8.55 ppm, indicating that the fraction A is a mixture of two isoflavonoids. A Singlet at 3.77 ppm accounting for 3 protons which could be assigned to a methoxy resonance and signal at 6.2 ppm accounting for 2 protons assigned to -OCH₂O-, resonance, indicating that the fraction A is a mixture of formononentin (1) and pseudobaptigenin (2, Chart IVB.1). EI mass spectrum showing M⁺ peaks at 268 (100 %) and 282 (60%) supported the assignments made for these compounds present in fraction A. NMR integration indicated that 1 and 2 are present in the ratio of 2:1. The mixture could not be separated even by repeated PC or TLC.
B.2.2. Characterisation of fraction B

Solid from fraction B crystallized as colorless needles, during elution from column. It showed deep purple spot under UV and UV/NH₃. It had Rf values 0.85 (TBA) and 0.30 (HOAc). It showed two bands with \( \lambda_{\text{max}} \) (MeOH): 262 and 330 nm (sh). A bathochromic shift of 14 nm from band I was noticed when the spectrum was taken with NaOMe. With AlCl₃ a bathochromic shift of 35 nm in band I, 33.5 nm in band II could be noted. This indicated the presence of OH group at C₅ position. \(^1\)H NMR spectrum (CDCl₃/DMSO-d₆) showed a broad one proton singlet at 8.7 ppm, indicating isoflavone nature of the molecule. All the signals of \(^1\)H NMR spectrum were in aromatic region, showing the the absence of -OCH₃, -OCH₂- groups in the molecule. This compound has been identified as genestein (3) in comparison with authentic sample including co-PC. The carbon-13 NMR spectrum was recorded and assignments are made as shown in structure 3. (Chart IVB.1) EI (70 ev) mass spectrum showed M⁺ peak at 270 (100%) confirming the structural assignment.

B.2.3. Characterization of fraction C

A crystalline solid, appeared deep purple both in UV and UV/NH₃; had characteristic Rf values 0.9 (TBA) and 0.30 (HOAc). It showed two bands: \( \lambda_{\text{max}} \) (MeOH): 255 and 300 nm. The band II showed a bathochromic shift of 34 nm and there
(with no shift in band I) when the spectrum was recorded in NaOMe, indicating phenolic -OH in A-ring. With AlCl3 there was no shift in band I indicating the absence of 5-OH. 1H NMR showed a broad one proton Singlet at 8.75 ppm confirming isoflavone nature of the molecule. Other NMR data fitted quite well for this molecule identified as daidzein (4) structure. EI (70ev) mass spectrum showed M+ peak at 254 (66%) with major peaks at 137 (100%) and 118 (66%), confirming the structure 4 (Chart IVB.1) for this molecule.

In conclusion, four Isoflavones viz., formononetin (1, 0.035%) pseudobaptigenin (2, 0.015%), genestein (3, 0.25%) and daidzein (4, 0.01%) have been isolated from the peels of Flemingia vestita (Chart A.1). Results from the present study have been published14. Genestein (3) seems to be present in rather high concentration and this probably is responsible for the vermifugalt activity. In a related study researchers at North-Eastern Hill University (NEHU), Shillong showed that crude extract of peels from this plant tubers did show significant vermifugal activity against Ascaris suum15. Experimental details are embedded in the results and discussion portion and therefore no separate section has been included, particularly because all compounds isolated are known compounds.
B.3. References


