THE KINETICS AND MECHANISM OF METHOXIDE ION CATALYZED
E TO Z ISOMERIZATION OF
O-METHYLBENZOHYDROXIMOYL CYANIDE

A THESIS
SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE
DEGREE OF MASTER OF SCIENCE IN CHEMISTRY
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COLLEGE OF
ARTS AND SCIENCES
BY
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DENTON, TEXAS
AUGUST 1998
To the Associate Vice President for Research and Dean of the Graduate School:

I am submitting herewith a thesis written by Bing Yao entitled "The Kinetics and Mechanism of Methoxide Ion Catalyzed E to Z Isomerization of O-Methylbenzohydroximoyl Cyanide". I have examined this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Chemistry.

Dr. James E. Johnson, Major Professor

We have read this thesis and recommend its acceptance:

J. E. Hardcastle
Department Chair

Dean of College

Accepted

Associate Vice President for Research and Dean of the Graduate School
DEDICATION

With deep love and unspeakable gratitude, I am dedicating this little piece of work to my parents and my wife whose love, compassion, strength and wisdom inspired me. I am thankful to have been blessed with them.
ACKNOWLEDGMENTS

I wish to thank first and foremost my advisor, Dr. James Elver Johnson, for being one of the most influential persons in my life. His encouragement, patience, understanding, and thoughtfulness have made this research possible.

Sincere gratitude and appreciation are extended to my committee members, Dr. Carlton T. Wendel and Dr. James E. Hardcastle, for their understanding and continuous support during my studies at Texas Woman's University.

I wish to give special thanks to Debra D. Dolliver, Isabelle Okuda, Nora Morales, Aaron Bolton, Mei Hou, Longchun Yu, Qingxian Zhou, Vilma Garza, and Martha Hotema for their kindness, friendship, and cooperation throughout the course of this research.
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ABSTRACT

Several new pairs of Z- and E-O-methylbenzohydroximoyl cyanides have been synthesized, and the rates of E to Z isomerization have been measured in 9:1 DMSO/MeOH solution at 44.6°C. The Hammett $\rho$-value for the isomerization is $+2.34$, which is consistent with an isomerization mechanism involving nucleophilic attack by methoxide ion at the carbon atom of the carbon-nitrogen double bond. The activation parameters for the isomerization of E-O-methyl-p-methoxybenzohydroximoyl cyanide have been determined ($\Delta H^* = 16.9$ kcal/mol and $\Delta S^* = -17.5$ cal/°K-mol). In the case of isomerization of the E-O-methyl-p-nitrobenzohydroximoyl cyanide there is a competing reaction, in which the nitro group at the aromatic ring is substituted by methoxide ion to give E-O-methyl-p-methoxybenzohydroximoyl cyanide. It has been found that substitution with methoxide ion on Z-O-methyl-p-nitrobenzohydroximoyl cyanide gives only Z-O-methyl-p-methoxybenzohydroximoyl cyanide.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEDICATION</td>
<td>iii</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>iv</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>v</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>viii</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>ix</td>
</tr>
<tr>
<td>CHAPTER I: INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>CHAPTER II: RESULTS AND DISCUSSION</td>
<td>13</td>
</tr>
<tr>
<td>A. Synthesis of the Z and E Isomers of O-Methylbenzo-hydroximoyl Cyanide and Substituted Compounds</td>
<td>13</td>
</tr>
<tr>
<td>B. Kinetics and Mechanism</td>
<td>16</td>
</tr>
<tr>
<td>CHAPTER III: EXPERIMENTANAL</td>
<td>43</td>
</tr>
<tr>
<td>A. General Procedures</td>
<td>43</td>
</tr>
<tr>
<td>1. The Column Chromatographic Method</td>
<td>43</td>
</tr>
<tr>
<td>2. The Kinetic Method</td>
<td>44</td>
</tr>
<tr>
<td>3. Preparation of Solvents and Solutions Used for Kinetics</td>
<td>45</td>
</tr>
<tr>
<td>B. Synthesis of Substituted Z-Oximinophenylacetonitrile</td>
<td>46</td>
</tr>
</tbody>
</table>
Z-p-methylbenzohydroximoyl Cyanide ...................... .46
Z-p-methoxybenzohydroximoyl Cyanide ..................... 47
Z- and E-O-Methyl-p-chlorobenzohydroximoyl Cyanide. ..... 48
Z- and E-O-Methyl-p-methylbenzohydroximoyl Cyanide. ..... 49
Z- and E-O-Methyl-p-methoxybenzohydroximoyl Cyanide. ..... 51
Z-O-Methylloxime of 1-Keto-p-chlorophenylacetamide. ..... 52
Z-O-Methylloxime of 1-Keto-p-methylphenylacetamide. ..... 52
Z-O-Methylloxime of 1-Keto-p-methoxylphenylacetamide. ..... 53
Z-O-Methylloxime of 1-Keto-p-nitrophenylacetamide. ..... 54

REFERENCES ........................................................ 55
LIST OF TABLES

1. Product distributions for nucleophilic substitution in \( R_1C_6H_4(X)C=NR_2 \) .... 9

2. Data from a typical kinetic run of methoxide ion-catalyzed isomerization of
   5Ea to 5Za in 90:10 DMSO:MeOH at 44.6°C ......................................... 17

3. Rate constants for the isomerization of 5E to 5Z .................................. 19

4. Data from a typical run of methoxide ion catalyzed isomerization of 5Ee to
   5Ze competing with substitution to form 5Ed in 90:10 DMSO:MeOH ........ 22

5. Second-order rate constants for the reaction of 5Ee with methoxide ion .... 25

6. Average rate constants for the methoxide ion-catalyzed isomerization
   reaction of 5E to 5Z ................................................................. 26

7. Second-order rate constants for the reactions of 5Zd and 5Zb with methoxide
   ion in 90:10 DMSO:MeOH ................................................................. 30

8. Average second-order rate constants for the reactions of 5Zd and 5Zb with
   methoxide ion in 90:10 DMSO:MeOH ............................................... 31

9. Activation parameters for the reactions of 5Ed \( \rightarrow \) 5Zd, 5Zd \( \rightarrow \) 5Ed, 5Zd \( \rightarrow \)
   6Zd and 5Zd \( \rightarrow \) 4Zd ................................................................. 32

10. Calculated second-order rate constants for isomerization and substitution
    reactions at 25°C and at 44.6°C .................................................. 36
LIST OF FIGURES

1. Typical first-order plot of the reaction of 5Ee with methoxide ion. ............18

2a. Plot of ln(Bo-Eo+E)/E vs time for 5Ee. ........................................23

2b. Plot of [5Ed] vs [5Ze]. ..................................................24

3. Hammett plot for the methoxide ion-catalyzed isomerization
   of 5E to 5Z at 44.6 °C. ..................................................33

4. Hammett plot for hydrolysis and substitution reactions of 5Z
   with methoxide ion at 44.6 °C ...........................................37
CHAPTER 1
INTRODUCTION

Nucleophilic substitutions belong to the most important and most thoroughly studied reactions in organic chemistry. A vinylic system substituted by an appropriate leaving group (LG) and β-substituents Y and Y' (1a) is an ambident electrophile, and three general mechanistic routes shown in Scheme 1 are available for the substitution reactions by the nucleophile (Nu). Depending upon the nucleophile, the solvent, the β-substituents, and the leaving group, the reaction can take place by the different processes outlined in Scheme 1. Some of the following experimental methods have been used to determine the mechanisms of these reactions: 1) common ion rate effects; 2) element effects (especially \(k_{Br}/k_{Cl}\)); 3) isotopic effects; 4) substituent effects; Hammett \(\rho\)-values with \(\sigma\) or \(\sigma^+\); 5) activation parameters \((\Delta H^*\) and \(\Delta S^*)\); and 6) solvent effects.

Pathway A is very limited and can be deduced by obtaining evidence that a vinyl cation\(^1,6\) is formed. Generally, this pathway would be expected to result in partial or complete stereoconvergence. When this pathway is being followed, the Hammett \(\rho\)-value is negative and a common ion rate effect is observed.

In the most thoroughly investigated nucleophilic reactions, numerous
SCHEME I

PATHWAY A (S_N1):

\[ \text{R}C\equiv\text{C}^{Y'} \text{Y} \quad \text{LG} \quad 1a \]
\[ \rightarrow \quad \text{R}C\equiv\text{C}^{Y'} \quad + \quad \text{Nu}^{-} \]

PATHWAY B (S_N2):

\[ \text{R}C\equiv\text{C}^{Y'} \quad \text{LG} \quad 1a \]
\[ \rightarrow \quad \text{R}C\equiv\text{C}^{Y'} \quad \text{Nu}^{-} \]

PATHWAY C (A_N + D_N):

\[ \text{Nu} \quad \text{k}_{\text{rot}}(180\degree) \quad \text{R} \quad \text{k}_{\text{rot}}(120\degree) \quad \text{Y'} \quad \text{Nu} \quad \text{k}_{\text{rot}}(180\degree) \quad \text{2a} \]
\[ \rightarrow \quad \text{Nu} \quad \text{k}_{\text{rot}}(120\degree) \quad \text{k}_{\text{rot}}(60\degree) \quad \text{Nu} \quad \text{k}_{\text{rot}}(180\degree) \quad \text{2a} \]
\[ \rightarrow \quad \text{Nu} \quad \text{k}_{\text{el}}(-\text{Nu}) \quad \text{Y'} \quad \text{Nu} \quad \text{k}_{\text{el}}(-\text{LG}) \quad \text{2b} \]
By pathway B (direct displacement), the reaction should give only product with
retained stereochemistry. For the pathway C, perpendicular attack on the
substrate (1a) by the nucleophile gives carbanion 3A. In order to form product,
rotation of 3A is necessary. Rotation of the intermediate will give inverted
product, and/or retained product, and/or cause isomerization of the starting
material. For good nucleofuges, i.e., LG = Cl, Br, and OSO₂R, the intermediate’s
lifetime is so short that the reaction may give only retained products. The k₄/[kᵢ] element effect¹⁷ can be used to prove whether the cleavage of the carbon-
halogen bond is in the rate-determining step or not. Rappoport⁸ attempted to
develop the k₄/[kᵢ] ratio as a mechanistic tool for the addition-elimination route
in nucleophilic vinylic substitution, but he was unsuccessful. By observing the
stereochemistry of the substitution of activated halo-substituted olefins¹³,
Rappoport concluded that for the addition-elimination process (Scheme I,
Pathway C) the following factors are important: 1) k₄ is affected both by
hyperconjugation and by steric effects; 2) a change from a good to a poor
nucleofuge will increase the lifetime of carbanion 3A and will lead to a higher
extent of stereoconvergence; 3) when k₄(-LG) > k₄, the k₄(60°)/k₄(120°) ratio
determines the product ratios (2a/2b); when k₄(60°) >> k₄(120°), only retained
products were obtained; and 4) when k₄(-LG) ≪ k₄, expulsion of the Nu⁺ after
180° rotation would be possible and isomerization of starting material occurs.
A mechanistic study on the base-catalyzed isomerization of $Z$- to $E$-substituted chalcones was reported by Bowden, Duah and Ranson$^9$. The Hammett $\rho$-values for the $\beta$-phenyl and benzoyl group were +1.99 and +1.93 respectively, which indicated the assistance of electron withdrawing groups in stabilizing the developing negative charge on the $\alpha$-carbon atom of the double bond. The ratio of the $\rho$-values for substitution in the benzoyl group to that in the $\beta$-phenyl group is ca. 0.97. This demonstrates consistent stabilization of the developing anionic center. The activation parameters, $\Delta H^*$ and $\Delta S^*$, of 14.2 kcal mol$^{-1}$ and -14 e.u., respectively, are typical of a bimolecular reaction. The mechanism of this isomerization is believed to involve rate-limiting attack of methoxide ion on the $\beta$-carbon atom of the substrates to form a carbanion in which free rotation can occur. Elimination of methoxide ion results in formation of the trans-isomer. The alkoxide-catalyzed isomerization of $\alpha$-cyano-$cis$-stilbenes observed by Kroeger and Stewart$^{10}$ and the amine-catalyzed $Z$ to $E$ isomerization of MeOC$_6$H$_4$CH=C(CN)CO$_2$Et by Rappoport$^{11}$ are all consistent with this mechanism. In the case of poor nucleofuges, i.e., cyanide ion, Chalchat and coworkers$^{12}$ reported the formation of the $Z$ and $E$ substitution products and the isomerization in the starting materials during the reaction of CH$_3$CX=CHY with nucleophiles (C$_2$H$_5$O$^-$, C$_2$H$_5$S$^-$).
In the $E$ to $Z$ (or $Z$ to $E$) isomerization of a vinylic system that is undergoing nucleophilic substitution, the intermediate formed by nucleophilic attack undergoes rotation to another conformation of the intermediate, which loses the nucleophile to form isomeric starting material. Stereoconvergence of products is also concluded to be good evidence for the addition-elimination mechanism.

In analogy with vinylic systems, there are three general mechanisms of displacement of a leaving group (LG) attached to the carbon atom of a carbon-nitrogen double bond by a nucleophile (Nu) in basic or neutral solution as shown in Scheme II. The experimental methods used to prove the mechanism are similar to the vinylic system.

Some of the mechanistic work reported by Ta-Shma and Rappoport on the reaction of imidoyl chlorides $[\text{ArC(Cl)=NR}]$ with nucleophiles led to the conclusion that the reactions proceed either by the $S_{N1}$ or the $A_N + D_N$ pathway depending on the nature of the substituents and the solvent for the reaction. In benzene solution with electron-donating substituents, imidoyl chlorides reacted by $S_{N1}$ mechanisms. When imidoyl chlorides substituted with electron-withdrawing groups were reacted with secondary amines, the substitution reactions proceeded by the $A_N + D_N$ pathway with rate-limiting addition ($A_N + D_N$). In acetonitrile solution, imidoyl chlorides reacted by rate-determining ionization to nitrilium ions ($S_{N1}, D_{N\#} + A_N$) regardless of the nature of substituents. Nucleophilic substitution on imidoyl cyanides with amines and
PATHWAY A (S_N1):

\[
\begin{align*}
X & \quad C = N \quad R_2 \\
R_1 & \quad \quad Z
\end{align*}
\]

\[-X^- \rightarrow \left\{ \begin{array}{l}
R_1 - C = N - R_2 \\
R_1 - C = N^+ - R_2 
\end{array} \right\}
\]

\[
\begin{align*}
& \quad Nu^- \\
& \quad \quad \quad Nu \\
& \quad \quad \quad E
\end{align*}
\]

PATHWAY B (S_N2):

\[
\begin{align*}
X & \quad C = N \quad R_2 \\
R_1 & \quad \quad Z
\end{align*}
\]

\[Nu^- \rightarrow \left[ \begin{array}{l}
Nu \\
R_1 \\
R_2 \\
X
\end{array} \right] \rightarrow -X^- \rightarrow \left[ \begin{array}{l}
Nu \\
R_1 \\
R_2 \\
X
\end{array} \right] \rightarrow -X^- \rightarrow \left[ \begin{array}{l}
Nu \\
R_1 \\
R_2 \\
X
\end{array} \right]
\]

PATHWAY C (A_N + D_N):

\[
\begin{align*}
X & \quad C = N \quad R_2 \\
R_1 & \quad \quad Z
\end{align*}
\]

\[k_1(Nu^-) \quad k_{-1}(-Nu^-) \quad k_{rot}(120^\circ) \quad k_{rot}(-120^\circ) \]

\[Nu \quad E \]

\[\begin{align*}
& \quad Nu \\
& \quad R_1 \\
& \quad R_2 \\
& \quad X
\end{align*}
\]

\[k_{rot}(120^\circ) \quad k_{rot}(120^\circ) \]

\[Nu \quad E \]

\[\begin{align*}
& \quad Nu \\
& \quad R_1 \\
& \quad R_2 \\
& \quad X
\end{align*}
\]
alkoxides proceeded by the $A_N + D_N$ mechanism with rate-limiting elimination ($A_N + D_N$). Rowe and Hegarty$^{16,17}$ found that in polar solvents and in the absence of good nucleophiles, benzohydrazonyl chlorides reacted by the ionization mechanism. In solvents of low ionizing power with good nucleophiles, these reactions proceeded by the $A_N + D_N$ mechanism with rate-limiting addition$^{18,19}$ ($A_{N*} + D_N$). Johnson, et al$^{20-24}$, found hydroximoyl chlorides react with methoxide ion, pyrrolidine, azetidine and pyrrolidide ion by an $A_N + D_N$ mechanism. Nucleophilic substitution on hydroximoyl chlorides with a weak nucleophile ($H_2O$) investigated by Johnson, et al$^{25,26}$ proceeded by rate-determining ionization to a nitrilium ion ($D_{N*} + A_N$).

Rowe$^{16}$ suggested that the role of the nitrogen in the transition state was the crucial difference between the $S_N1$, $S_N2$ and the $A_N + D_N$ mechanisms. During the addition-elimination mechanism the double bond begins to cleave and the nitrogen must bear a partial negative charge. In the $S_N1$ or $S_N2$ mechanism, the nitrogen must bear part of the positive charge as it assists the direct expulsion of the leaving group. Rogne$^{27}$ suggested that the Hammett $\rho$-value, which is a measure of the change in charge at the reaction center, is related to the extent of bond formation and bond breaking in the transition state. The more positive the $\rho$-value is, the more bond making will have proceeded relative to bond breaking. A large Hammett positive $\rho$-value is a good indicator that the
reactions are proceeding by an $A_N + D_N$ mechanism. A low $k_{Br}/k_{Cl}$ ratio$^{28}$ (less than 30) also provides strong evidence that the carbon-halogen bond is not being broken in the rate-determining step and is a powerful tool for distinguishing between the $S_N2$ and the $A_{N+} + D_N$ mechanisms. The observations of common-ion rate depression and a negative Hammett $\rho$-value for the reaction are indicative of the $S_N1$ mechanism.

Similar product distributions (Table 1) were observed by Rowe and Hegarty$^{18,19}$ for the nucleophilic reaction of hydrazonyl chlorides and hydrazonates and by Johnson, et al.$^{22,23,24,28}$ for oxime derivatives. The stereochemistry of these reactions have been rationalized in terms of Deslongchamps' theory$^{29}$ of stereoelectronic control. The tetrahedral intermediate (A) (Scheme II) formed from the $Z$ starting materials is in a suitable conformation to give elimination of $X$, leading to $Z$ products. The tetrahedral intermediate (B) formed from the $E$ starting materials would have to undergo rotation to either A or C before elimination of the leaving group can occur, leading to a mixture of $Z$ and $E$ products. Therefore, the $Z$ substrates give either exclusive or a high degree of retention of the $Z$ configuration. The leaving group effects for the $Z$ substrates are generally small. The $E$ isomer, reflecting the need for stereomutation of the tetrahedral intermediate before elimination, shows a variety of behaviors depending on the nucleophile and the leaving
Table 1. Product distributions of the nucleophilic substitution in $R_1C_6H_4(X)C=NR_2$

<table>
<thead>
<tr>
<th>$R_1$</th>
<th>$R_2$</th>
<th>X</th>
<th>Nu</th>
<th>Solvent</th>
<th>geometry</th>
<th>E/Z (prod)</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>OCH$_3$</td>
<td>Cl</td>
<td>MeO$^-$</td>
<td>DMSO/MeOH</td>
<td>Z/E</td>
<td>2/98, 77/23</td>
<td>22</td>
</tr>
<tr>
<td>p-OCH$_3$</td>
<td>OCH$_3$</td>
<td>Cl</td>
<td>MeO$^-$</td>
<td>DMSO/MeOH</td>
<td>Z/E</td>
<td>2/98, 95/5</td>
<td>22</td>
</tr>
<tr>
<td>p-NO$_2$</td>
<td>OCH$_3$</td>
<td>Cl</td>
<td>MeO$^-$</td>
<td>DMSO/MeOH</td>
<td>Z/E</td>
<td>2/98, 84/16</td>
<td>22</td>
</tr>
<tr>
<td>H</td>
<td>OCH$_3$</td>
<td>OEt</td>
<td>MeO$^-$</td>
<td>DMSO/MeOH</td>
<td>E</td>
<td>8.7/91.3</td>
<td>22</td>
</tr>
<tr>
<td>H</td>
<td>OCH$_3$</td>
<td>Cl</td>
<td>EtO$^-$</td>
<td>DMSO/MeOH</td>
<td>Z/E</td>
<td>5/95, 86/14</td>
<td>22</td>
</tr>
<tr>
<td>p-OCH$_3$</td>
<td>OCH$_3$</td>
<td>Br</td>
<td>MeO$^-$</td>
<td>DMSO/MeOH</td>
<td>Z/E</td>
<td>0/100, 70.6/29.4</td>
<td>28</td>
</tr>
<tr>
<td>H</td>
<td>OCH$_3$</td>
<td>CN</td>
<td>MeO$^-$</td>
<td>DMSO/MeOH</td>
<td>Z/E</td>
<td>0/100, 10/90</td>
<td>23</td>
</tr>
<tr>
<td>p-NO$_2$</td>
<td>OCH$_3$</td>
<td>Cl</td>
<td>Azetidine</td>
<td>MeCN</td>
<td>E</td>
<td>98/2</td>
<td>24</td>
</tr>
<tr>
<td>p-OCH$_3$</td>
<td>N(Me)-2,4(NO$_2$)$_2$Ph</td>
<td>Cl</td>
<td>MeO$^-$</td>
<td>MeOH</td>
<td>Z</td>
<td>1/99</td>
<td>18</td>
</tr>
<tr>
<td>p-NO$_2$</td>
<td>N(Me)-2,4(NO$_2$)$_2$Ph</td>
<td>Cl</td>
<td>MeO$^-$</td>
<td>MeOH</td>
<td>Z</td>
<td>2/98</td>
<td>18</td>
</tr>
<tr>
<td>p-OCH$_3$</td>
<td>N(Me)-2,4(NO$_2$)$_2$Ph</td>
<td>S-Ph(p-NO$_2$)</td>
<td>MeO$^-$</td>
<td>MeOH</td>
<td>E</td>
<td>16/84, 49/51</td>
<td>18</td>
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<tr>
<td>p-NO$_2$</td>
<td>N(Me)-2,4(NO$_2$)$_2$Ph</td>
<td>S-Ph(p-NO$_2$)</td>
<td>MeO$^-$</td>
<td>MeOH</td>
<td>Z/E</td>
<td>10/90, 62/38</td>
<td>18</td>
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<td>p-NO$_2$</td>
<td>N(Me)-2,4(NO$_2$)$_2$Ph</td>
<td>O-Ph(p-NO$_2$)</td>
<td>MeO$^-$</td>
<td>MeOH</td>
<td>Z</td>
<td>16/84</td>
<td>18</td>
</tr>
<tr>
<td>m-NO$_2$</td>
<td>N(Me)-2,4(NO$_2$)$_2$Ph</td>
<td>Cl</td>
<td>Pyrrolidine</td>
<td>MeCN</td>
<td>Z</td>
<td>3/97</td>
<td>19</td>
</tr>
<tr>
<td>m-Cl</td>
<td>N(Me)-2,4(NO$_2$)$_2$Ph</td>
<td>Cl</td>
<td>Pyrrolidine</td>
<td>MeCN</td>
<td>Z</td>
<td>15/85</td>
<td>19</td>
</tr>
<tr>
<td>m-NO$_2$</td>
<td>N(Me)-2,4(NO$_2$)$_2$Ph</td>
<td>Cl</td>
<td>Butan-1-amine</td>
<td>MeCN</td>
<td>Z</td>
<td>10/90</td>
<td>19</td>
</tr>
</tbody>
</table>

a. Isomerization reaction only.
group, particularly when a poor leaving group is involved. For a good nucleofuge, the short lifetime of the tetrahedral intermediate may permit the tetrahedral intermediate to maintain its stereochemical integrity. The ratio of \( Z \) and \( E \) products depends on the substituent on the benzene ring, leaving group, nucleophile and solvent. The isomerization between \( Z \) and \( E \) products would affect the product ratio depending on the reaction time\(^{18,22}\). Isomerization of the product takes place after long reaction times.

In more recent work shown in Scheme III, Johnson, et al.\(^{23}\) found that the reaction of the \((Z)\)-hydroximoyl cyanide \((5Za)\) with sodium methoxide in DMSO-methanol \((9:1)\) solution at 44.8°C gives a mixture of methyl \((Z)\)-O-methylbenzohydroximate \((4Za)\) and the O-methyloxime of \(\alpha\)-ketophenyl acetamide \((6a)\). The \((E)\)-hydroximoyl cyanide \((5Ea)\) undergoes methoxide ion-catalyzed isomerization to the \(Z\)-isomer faster than it undergoes nucleophilic substitution. These observations were interpreted in terms of an addition-elimination mechanism \((A_N + D_{Nw})\) in which the rate-limiting step is loss of a poor nucleofuge, cyanide ion, from the tetrahedral intermediate. Recently, Johnson, Jano and McAllister\(^{30}\) calculated the energy of the tetrahedral intermediates formed in this reaction by methoxide attack at the carbon-nitrogen double bond using the AM1 method. They found that the staggered conformations at a torsional angle corresponding approximately to conformations 7A and 7B (\(Ar = Ph\)) represent minima in the potential energy diagram. The other staggered
comformation, which corresponds approximately to conformation 7C, has a conformational energy 5.25 kcal/mol higher than conformation 7B. This may indicate why conformation 7C does not form the product 4E.

This research consists of an investigation of the substituent effects on the isomerization of the E-hydroximoyl cyanide (5E) with sodium methoxide in DMSO-methanol (9:1) solution.

**SCHEME III**

![Scheme III](image)

- a. Y = H
- b. Y = Cl
- c. Y = CH₃
- d. Y = OCH₃
- e. Y = NO₂
SCHEME IV

5Z

5E

7A

7B

7C

4Z

4E

Ar = \[ \text{Ar} = \begin{array}{c}
\text{Ar} = \end{array} \]

a. Y = H
b. Y = Cl
c. Y = CH₃
d. Y = OCH₃
e. Y = NO₂
CHAPTER II
RESULTS AND DISCUSSION

A. Synthesis of the Z and E Isomers of O-Methyl-p-(substituted)-benzohydroximoyl Cyanide and Some Substituted Compounds.

Two different synthetic methods have been previously described\textsuperscript{31-33} to prepare the Z-O-methylbenzohydroximoyl cyanides (Schemes V and VI). Several new Z and E isomers of O-methyl-p-(substituted)benzohydroximoyl cyanides (5Zb, 5Eb, 5Zc, 5Ec, 5Zd, 5Ed) and their substitution compounds were synthesized according to the procedure outlined in Scheme V.

The method shown in Scheme VI was used for the synthesis of the Z and E isomers of O-methyl-p-(substituted)benzohydroximate (4Zb, 4Zc, 4Ec, 4Ze and 4Ee).

A convenient method shown in Scheme V was used for the synthesis of the Z-O-methyloxime of 1-keto-p-(substituted)phenyl acetamide (6Zb, 6Zc, 6Zd, 6Ze). In some cases\textsuperscript{34} the hydrolysis of nitriles can be stopped at the amide stage. Under basic conditions, O-methyl-p-(substituted)benzohydroximoyl cyanide (5Z) was reacted with hydrogen peroxide to obtain the Z-O-methyloxime of 1-keto-p-(substituted)phenyl acetamide (6Z). The amide was extracted with ether from the aqueous solution and purified by recrystallization.
from methanol-chloroform solution.

All of these compounds were purified by column chromatography. Their purities were checked by GC/MS and were all above 99% purity based on the ratio of peak areas.

**SCHEME V**

![Scheme V](image)
SCHEME VI

10

NH₃OCH₃⁺Cl⁻
Na₂CO₃

11

PCl₅

5Z

C₄H₄N=C=O

C₄H₄N=C=O

C₄H₄N=C=O

C₄H₄N=C=O

4E

4Z

Δ

NaOCH₃

DMSO/MeOH

Δ

Acetic Acid

a: Y= H
b: Y= Cl
c: Y= CH₃
d: Y=OCH₃
e: Y= NO₂
B. Kinetics and Mechanism of Isomerization and Substitution of Z and E Isomers of O-Methyl-p-(substituted)benzohydroximoyl Cyanide by Methoxide Ion Attack

The reaction rates of $E$ (5Ea-c) to $Z$ (5Za-c) isomerization in 9:1 dimethylsulfoxide-methanol at 44.6°C were measured under pseudo-first-order conditions (excess methoxide ion). The reaction rates of 5Ed to 5Zd at four different temperatures (60.0°C, 44.6°C, 30.0°C, 23.6°C) were studied. All reactions were found to follow second order kinetics (first-order in methoxide ion and first-order in the cyanide). Samples of data for typical kinetic runs of these compounds were shown in Table 2. Plots of $\ln E_0/E$ (where $E_0$ is equal to the initial concentration of the $E$ isomer and $E$ is equal to the correction concentration of the $E$ isomer a time $t$) versus time yielded straight lines in all cases using a linear regression program Cricket Graph (Figure 1). The slopes of the lines correspond to the observed first-order rate constants ($k_{obs}$) of these reactions. The second-order rate constants were calculated by dividing the rate constants ($k_{obs}$) by methoxide ion concentration (Table 3). In the absence of methoxide ion, compound 5Ed in DMSO-MeOH solution remained unchanged for at least one month.

In the reaction of 5Ee with methoxide ion (Scheme VII), it was found that 5Ee underwent a displacement reaction of the para-nitro group much faster
Table 2. Data from a typical kinetic run for methoxide ion-catalyzed isomerization of 5Ea to 5Za in 90:10 DMSO:MeOH at 44.6°C

<table>
<thead>
<tr>
<th>time (s)</th>
<th>%(5Ea)</th>
<th>In E₀/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>96.86</td>
<td>0</td>
</tr>
<tr>
<td>272.9</td>
<td>79.05</td>
<td>0.2032</td>
</tr>
<tr>
<td>373.4</td>
<td>73.45</td>
<td>0.2767</td>
</tr>
<tr>
<td>518.0</td>
<td>67.31</td>
<td>0.3640</td>
</tr>
<tr>
<td>653.1</td>
<td>61.30</td>
<td>0.4575</td>
</tr>
<tr>
<td>740.1</td>
<td>57.98</td>
<td>0.5132</td>
</tr>
<tr>
<td>874.8</td>
<td>54.69</td>
<td>0.5716</td>
</tr>
<tr>
<td>980.5</td>
<td>51.46</td>
<td>0.6325</td>
</tr>
<tr>
<td>1185.6</td>
<td>44.87</td>
<td>0.7695</td>
</tr>
<tr>
<td>1341.8</td>
<td>39.28</td>
<td>0.9026</td>
</tr>
<tr>
<td>1520.7</td>
<td>36.27</td>
<td>0.9823</td>
</tr>
<tr>
<td>1693.3</td>
<td>32.80</td>
<td>1.083</td>
</tr>
<tr>
<td>1856.6</td>
<td>30.26</td>
<td>1.163</td>
</tr>
<tr>
<td>2017.7</td>
<td>26.04</td>
<td>1.314</td>
</tr>
<tr>
<td>2332.6</td>
<td>21.26</td>
<td>1.516</td>
</tr>
</tbody>
</table>
Figure 1. Typical first-order plot of the reaction of \( E-O \)-methylbenzohydroximoyl cyanide with methoxide ion at 44.6°C \(([\text{MeO}^-] = 5.35 \times 10^{-2} \text{M}, [\text{Eo}] = 2.65 \times 10^{-3} \text{M})\)

\[
y = 6.314E-04x + 2.789E-02 \quad r = 9.991E-01
\]
Table 3. Rate constants for the isomerization of 5E to 5Z

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Temp. (°C)</th>
<th>[OCH₃] (M)</th>
<th>[cyanide] (M)</th>
<th>pseudo 1st-order rate constant (s⁻¹)</th>
<th>2nd-order rate constant (s⁻¹ M⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5Ea</td>
<td>44.6</td>
<td>0.0535</td>
<td>0.00265</td>
<td>6.31x10⁻⁴</td>
<td>1.18x10⁻²</td>
</tr>
<tr>
<td>5Ea</td>
<td>44.6</td>
<td>0.0535</td>
<td>0.00283</td>
<td>5.71x10⁻⁴</td>
<td>1.07x10⁻²</td>
</tr>
<tr>
<td>5Eb</td>
<td>44.6</td>
<td>0.0535</td>
<td>0.00286</td>
<td>2.32x10⁻³</td>
<td>4.34x10⁻²</td>
</tr>
<tr>
<td>5Eb</td>
<td>44.6</td>
<td>0.0535</td>
<td>0.00262</td>
<td>2.36x10⁻³</td>
<td>4.41x10⁻²</td>
</tr>
<tr>
<td>5Ec</td>
<td>44.6</td>
<td>0.0535</td>
<td>0.00240</td>
<td>2.67x10⁻⁴</td>
<td>4.99x10⁻³</td>
</tr>
<tr>
<td>5Ec</td>
<td>44.6</td>
<td>0.0535</td>
<td>0.00259</td>
<td>2.69x10⁻⁴</td>
<td>5.03x10⁻³</td>
</tr>
<tr>
<td>5Ed</td>
<td>44.6</td>
<td>0.0535</td>
<td>0.00227</td>
<td>1.29x10⁻⁴</td>
<td>2.41x10⁻³</td>
</tr>
<tr>
<td>5Ed</td>
<td>44.6</td>
<td>0.0535</td>
<td>0.00263</td>
<td>1.24x10⁻⁴</td>
<td>2.32x10⁻³</td>
</tr>
<tr>
<td>5Ed</td>
<td>30.0</td>
<td>0.0535</td>
<td>0.00272</td>
<td>3.36x10⁻⁵</td>
<td>6.28x10⁻⁴</td>
</tr>
<tr>
<td>5Ed</td>
<td>30.0</td>
<td>0.0535</td>
<td>0.00253</td>
<td>3.22x10⁻⁵</td>
<td>6.02x10⁻⁴</td>
</tr>
<tr>
<td>5Ed</td>
<td>60.0</td>
<td>0.0535</td>
<td>0.00235</td>
<td>4.00x10⁻⁴</td>
<td>7.48x10⁻³</td>
</tr>
<tr>
<td>5Ed</td>
<td>60.0</td>
<td>0.0535</td>
<td>0.00267</td>
<td>4.04x10⁻⁴</td>
<td>7.55x10⁻³</td>
</tr>
<tr>
<td>5Ed</td>
<td>23.6</td>
<td>0.0571</td>
<td>0.00269</td>
<td>1.57x10⁻⁵</td>
<td>2.75x10⁻⁴</td>
</tr>
<tr>
<td>5Ed</td>
<td>23.6</td>
<td>0.0571</td>
<td>0.00271</td>
<td>1.62x10⁻⁵</td>
<td>2.84x10⁻⁴</td>
</tr>
<tr>
<td>5Ze⁺</td>
<td>44.6</td>
<td>0.0571</td>
<td>0.00188</td>
<td>1.08x10⁻²</td>
<td>1.89x10⁻¹</td>
</tr>
<tr>
<td>5Ze⁺</td>
<td>44.6</td>
<td>0.0571</td>
<td>0.00174</td>
<td>1.09x10⁻²</td>
<td>1.91x10⁻¹</td>
</tr>
</tbody>
</table>

* the reaction of 5Ze to 5Zd.
than it underwent isomerization to 5Ze. The kinetic runs were carried out under second-order reaction conditions at six different concentration ratios of the methoxide ion and hydroximoyl cyanide. The rate data for these reactions were dealt with using the procedure for parallel second-order reactions\textsuperscript{35} (Scheme VIII). The kinetic results are shown in Table 4 which are plotted in Figures 2a and 2b. The observed second-order rate constants are shown in Table 5.
SCHEME VIII

Parallel 2nd-order reactions:

\[ \begin{align*}
E + B & \xrightarrow{k_s} S \\
E + B & \xrightarrow{k_z} Z
\end{align*} \]

Then,

\[ \begin{align*}
\frac{-dE}{dt} &= (k_s + k_z)E \cdot B \\
\frac{dS}{dt} &= k_sE \cdot B \\
\frac{dZ}{dt} &= k_zE \cdot B
\end{align*} \] (1) (2) (3)

From the stoichiometric equation \( dE = dB \), and integration gives

\[ \begin{align*}
E_0 - E &= B_0 - B \\
B &= B_0 - E_0 + E
\end{align*} \] (4)

Entering this into equation (1), gives

\[ \frac{-dE}{E (B_0-E_0+E)} = (k_s + k_z) \frac{dt}{E_0-B_0} \]

Integration gives

\[ \begin{align*}
\frac{1}{B_0-E_0} \ln \frac{E_0}{E} + \frac{1}{B_0-E_0} \ln \frac{B_0-E_0+E}{B_0} &= (k_s + k_z) t \\
\frac{1}{B_0-E_0} \ln \frac{E_0(B_0-E_0+E)}{B_0E} &= (k_s + k_z) t
\end{align*} \] (5)

The slope of a plot of \( \ln(B_0-E_0+E)/E \) vs \( t \) is \( (k_s + k_z)(B_0-E_0) \) (6)

From equations (2) and (3), one obtains

\[ \frac{dS}{dZ} = \frac{k_s}{k_z} \] (7)

The slope of a plot of \( S \) over \( Z \) is \( k_s/k_z \) (8)

From (6) and (8), one can obtain the 2nd-order rate constants \( k_s \) and \( k_z \).
Table 4. Data from a typical run of methoxide ion catalyzed isomerization of 5Ee to 5Ze competing with substitution to form 5Ed in 90:10 DMSO:MeOH at 44.6°C ([MeO\textsuperscript{-}] = 4.57\times10^{-3}M (Bo), Eo = 1.81\times10^{-3}M)

<table>
<thead>
<tr>
<th>time(s)</th>
<th>% (5Ee)</th>
<th>%(5Ze)</th>
<th>% (5Ed)</th>
<th>ln(Bo-Eo+E)/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>81.08</td>
<td>8.91</td>
<td>10.01</td>
<td>1.05</td>
</tr>
<tr>
<td>8.1</td>
<td>72.25</td>
<td>11.50</td>
<td>16.24</td>
<td>1.13</td>
</tr>
<tr>
<td>19.6</td>
<td>67.93</td>
<td>13.40</td>
<td>18.67</td>
<td>1.18</td>
</tr>
<tr>
<td>29.1</td>
<td>63.11</td>
<td>14.95</td>
<td>21.94</td>
<td>1.23</td>
</tr>
<tr>
<td>39.1</td>
<td>56.56</td>
<td>16.91</td>
<td>26.53</td>
<td>1.31</td>
</tr>
<tr>
<td>52.0</td>
<td>52.31</td>
<td>18.60</td>
<td>29.09</td>
<td>1.36</td>
</tr>
<tr>
<td>65.2</td>
<td>47.35</td>
<td>20.17</td>
<td>32.49</td>
<td>1.44</td>
</tr>
<tr>
<td>79.6</td>
<td>42.33</td>
<td>21.83</td>
<td>35.84</td>
<td>1.52</td>
</tr>
<tr>
<td>93.8</td>
<td>38.36</td>
<td>23.02</td>
<td>38.63</td>
<td>1.60</td>
</tr>
<tr>
<td>107.9</td>
<td>34.03</td>
<td>24.25</td>
<td>41.72</td>
<td>1.70</td>
</tr>
<tr>
<td>121.6</td>
<td>31.74</td>
<td>25.09</td>
<td>43.17</td>
<td>1.76</td>
</tr>
<tr>
<td>135.8</td>
<td>27.40</td>
<td>25.93</td>
<td>46.67</td>
<td>1.88</td>
</tr>
</tbody>
</table>
Figure 2a. Plot of \( \ln \left( \frac{B_0 - E_0 + E}{E} \right) \) vs time for 5Ee (\([\text{MeO}'] = 4.57 \times 10^{-3} \text{M}, [5\text{Ee}] = 1.81 \times 10^{-3} \text{M})\)

\[
y = 5.847E-03x + 1.064E+00 \quad r = 9.988E-01
\]

\( k_{\text{seq}} + k_{\text{dis}} = k_{\text{trp}} / (B_0 - E_0) \)
Figure 2b. Plot of [5Ed] vs [5Ze], the slope is $k_{5Ed}/k_{5Ze}$. 

The line equation is $y = 2.072x - 8.698$ with a $r$ value of 0.998.
Table 5. Second-order rate constants for the reaction of 5Ee with methoxide ion at 44.6°C

<table>
<thead>
<tr>
<th>compd.</th>
<th>[OCH₃] (M)</th>
<th>[cyanide] (M)</th>
<th>prod.</th>
<th>2nd-order rate constant (s⁻¹ M⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5Ee</td>
<td>2.14 × 10⁻³</td>
<td>1.94 × 10⁻³</td>
<td>5Ze</td>
<td>0.782</td>
</tr>
<tr>
<td>5Ee</td>
<td>3.43 × 10⁻³</td>
<td>1.83 × 10⁻³</td>
<td>5Ze</td>
<td>0.707</td>
</tr>
<tr>
<td>5Ee</td>
<td>3.43 × 10⁻³</td>
<td>1.77 × 10⁻³</td>
<td>5Ze</td>
<td>0.729</td>
</tr>
<tr>
<td>5Ee</td>
<td>4.57 × 10⁻³</td>
<td>1.81 × 10⁻³</td>
<td>5Ze</td>
<td>0.691</td>
</tr>
<tr>
<td>5Ee</td>
<td>4.57 × 10⁻³</td>
<td>1.65 × 10⁻³</td>
<td>5Ze</td>
<td>0.724</td>
</tr>
<tr>
<td>5Ee</td>
<td>5.35 × 10⁻³</td>
<td>1.98 × 10⁻³</td>
<td>5Ze</td>
<td>0.721</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5Ed</td>
<td>1.43</td>
</tr>
</tbody>
</table>
Furthermore, it was found that the reaction of 5Ze with methoxide ion at 9:1 DMSO-methanol solution at 44.6°C only underwent the displacement of the para-nitro group to give 5Zd. The rate data for this reaction were obtained under pseudo-first-order reaction conditions, and the rate constants are shown in Table 3. The average second-order rate constants for these reactions are in Table 6.

**Table 6. Average rate constants for the methoxide ion-catalyzed isomerization reactions of 5E to 5Z**

<table>
<thead>
<tr>
<th>compound</th>
<th>Temperature (°C)</th>
<th>2nd-order rate constant (s⁻¹ M⁻¹)</th>
<th>dev,%&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>5Ea</td>
<td>44.6</td>
<td>$1.13 \times 10^2$</td>
<td>4.42</td>
</tr>
<tr>
<td>5Eb</td>
<td>44.6</td>
<td>$4.38 \times 10^2$</td>
<td>0.91</td>
</tr>
<tr>
<td>5Ec</td>
<td>44.6</td>
<td>$5.01 \times 10^3$</td>
<td>0.40</td>
</tr>
<tr>
<td>5Ed</td>
<td>44.6</td>
<td>$2.37 \times 10^3$</td>
<td>2.11</td>
</tr>
<tr>
<td>5Ed</td>
<td>30.0</td>
<td>$6.15 \times 10^4$</td>
<td>2.44</td>
</tr>
<tr>
<td>5Ed</td>
<td>60.0</td>
<td>$7.52 \times 10^3$</td>
<td>0.53</td>
</tr>
<tr>
<td>5Ed</td>
<td>23.6</td>
<td>$2.80 \times 10^4$</td>
<td>1.42</td>
</tr>
<tr>
<td>5Eea</td>
<td>44.6</td>
<td>(to 5Ze) $7.26 \times 10^1$</td>
<td>3.09</td>
</tr>
<tr>
<td>5Zeb</td>
<td>44.6</td>
<td>(to 5Ed) 1.42</td>
<td>3.25</td>
</tr>
<tr>
<td>5Ze&lt;sup&gt;b&lt;/sup&gt;</td>
<td>44.6</td>
<td>(to 5Zd) $1.90 \times 10^1$</td>
<td>1.05</td>
</tr>
</tbody>
</table>

a. Two competing reactions.  
b. The displacement of the p-nitro group by methoxide ion.  
c. Deviation from average of two results for all reactions except for 5Ee where the deviation is the relative standard deviation of all six results.
The reaction of Z-\(\text{O-}\)methyl-\(p\)-methoxybenzohydroximoyl cyanide (5Zd) with methoxide ion was investigated. It was found that three products were formed competitively in this reaction (Scheme IX): substitution at the carbon-nitrogen double bond (4Zd), nucleophilic attack at the carbon atom of the carbon-nitrogen triple bond (6d), and isomerization (5Ed). The equations used to calculate the rate constants for these reactions are derived in Scheme X. The
SCHEME X*

\[
\begin{align*}
\frac{dA}{dt} &= (k_1 + k_2 + k_3) A - k_4 D & \text{(1)} \\
\frac{dD}{dt} &= k_3 A - k_4 D & \text{(2)} \\
\frac{dC}{dt} &= k_2 A - k_5 C & \text{(3)} \\
\frac{dE}{dt} &= k_5 C & \\
\frac{dB}{dt} &= k_1 A & \text{(4)}
\end{align*}
\]

* See Scheme IX

**Method I**

The observed \( K_{eq} \) for the isomerization reaction of A to D is approximately 0.1.

We assume: when \( D < 2\% \) and \( A > 90\% \), \( k_3 A >> k_4 D \), then,

\[
\frac{dD}{dt} = k_3 A
\]

From equation 1, one obtains

\[
- \frac{dA}{dt} = (k_1 + k_2 + k_3) A
\]

\( k_{obs} = k_1 + k_2 + k_3 \) \( (k_{obs} \) was obtained from the plot of \( \ln A \) against \( t) \)

By combining the equations 3 and 4, one obtains

\[
\frac{dB}{dt} = k_1/k_2 \frac{d(C+E)}{dt}
\]

\( k_1/k_2 \) is obtained from the slope of the plot of \( B \) vs \( (C+E) \)

By combining the equations 2 and 4, one obtains

\[
\frac{dB}{dt} = k_1/k_3 \frac{dD}{dt}
\]

\( k_1/k_3 \) is obtained from the slope of the plot of \( B \) vs \( D \)

From equations 5, 6 and 7, one obtains \( k_1 \), \( k_2 \), and \( k_3 \)

\( k_4 \) is obtained from a separate kinetic measurement for the isomerization of \( D \) to \( A \);

\( K_{eq} \) for the isomerization of \( A \) to \( D \) is \( k_2/k_4 \).
Method II

When isomerization reaction reaches equilibrium,

\[ \frac{dD}{dt} = 0, \]

and, \( k_3 \ A = k_4 \ D \) (from equation 2).

When D reaches its highest point, the isomerization reaction is at equilibrium.

At that point,

\[ \frac{D}{A} = K_{eq} = k_3/k_4 \]

When the reaction is close to equilibrium,

\[ \frac{dD}{dt} = k_3 \ A - k_4 \ D = 0, \]

From equation 1,

\[ \frac{dA}{dt} = (k_1 + k_2) \ A \]

\[ k_{obs} = k_1 + k_2 \]

\( k_{obs} \) is obtained from the slope of the plot of \( \ln A \) vs \( t \) \quad \text{--------- 9}

By combining equations 3 and 4, one obtains

\[ dB = k_1/k_2 \ d(C+E) \]

\[ k_1/k_2 \] is the slope of the plot of B vs (C+E) \quad \text{--------- 10}

From equations 9 and 10, one obtains \( k_1 \) and \( k_2 \).

\( k_4 \) is obtained from a separate kinetic measurement for the isomerization of D to A.

\( K_{eq} \) for the isomerization of A to D (from equation 8) is equal to \( k_3/k_4 \).

Therefore,

\[ k_3 = K_{eq} \ k_4. \]
rates of reaction of methoxide ion with 5Zd were measured at four different temperatures (44.6°C, 50.0°C, 54.6°C, 60.0°C). The reaction of Z-O-methyl-p-chlorobenzohydroximoyl cyanide (5Zb) with methoxide ion (44.6°C) was observed and the rate constants were calculated using Method I outlined in Scheme X. The rate constants are in Tables 7 and 8.

Table 7. Second-order rate constants for the reactions of 5Zb and 5Zd with methoxide ion (0.0571M) in 90:10 DMSO:MeOH

<table>
<thead>
<tr>
<th>Temp. (°C)</th>
<th>$10^3 [5Zd]$ M</th>
<th>$10^4 k$, M$^{-1}$ s$^{-1}$ (to 6d)</th>
<th>$10^4 k$,M$^{-1}$ s$^{-1}$ (to 4Zd)</th>
<th>$10^4 k$,M$^{-1}$ s$^{-1}$ (to 5Ed)</th>
<th>$K_{eq}$ (to 5Ed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>44.6$^a$</td>
<td>1.54</td>
<td>1.88</td>
<td>1.15</td>
<td>1.43</td>
<td></td>
</tr>
<tr>
<td>44.6$^a$</td>
<td>1.62</td>
<td>2.02</td>
<td>1.15</td>
<td>1.75</td>
<td></td>
</tr>
<tr>
<td>44.6$^b$</td>
<td>1.81</td>
<td>2.32</td>
<td>1.19</td>
<td></td>
<td>0.08096</td>
</tr>
<tr>
<td>44.6$^b$</td>
<td>1.78</td>
<td>2.30</td>
<td>1.10</td>
<td></td>
<td>0.07701</td>
</tr>
<tr>
<td>50.0$^b$</td>
<td>1.73</td>
<td>4.23</td>
<td>2.15</td>
<td></td>
<td>0.09275</td>
</tr>
<tr>
<td>50.0$^b$</td>
<td>1.75</td>
<td>4.53</td>
<td>2.32</td>
<td></td>
<td>0.09495</td>
</tr>
<tr>
<td>54.6$^b$</td>
<td>1.90</td>
<td>8.02</td>
<td>3.78</td>
<td></td>
<td>0.09763</td>
</tr>
<tr>
<td>54.6$^b$</td>
<td>1.89</td>
<td>8.24</td>
<td>4.06</td>
<td></td>
<td>0.09150</td>
</tr>
<tr>
<td>60.0$^b$</td>
<td>1.83</td>
<td>11.6</td>
<td>7.69</td>
<td></td>
<td>0.1083</td>
</tr>
<tr>
<td>60.0$^b$</td>
<td>1.73</td>
<td>13.4</td>
<td>7.43</td>
<td></td>
<td>0.09587</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temp. (°C)</th>
<th>$10^3 [5Zb]$ M</th>
<th>$10^3 k$, M$^{-1}$ s$^{-1}$ (to 6b)</th>
<th>$10^3 k$,M$^{-1}$ s$^{-1}$ (to 4Zb)</th>
<th>$10^3 k$,M$^{-1}$ s$^{-1}$ (to 5Eb)</th>
<th>$K_{eq}$ (to 5Eb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>44.6$^a$</td>
<td>2.20</td>
<td>2.04</td>
<td>1.99</td>
<td>1.24</td>
<td></td>
</tr>
<tr>
<td>44.6$^a$</td>
<td>2.14</td>
<td>2.41</td>
<td>2.19</td>
<td>1.60</td>
<td></td>
</tr>
</tbody>
</table>

a. Method I  
b. Method II
Table 8. Average second-order rate constants for the reactions of 5Zd and 5Zb with methoxide ion in 90:10 DMSO:MeOH ([MeO⁻] = 5.71 × 10⁻²M)

<table>
<thead>
<tr>
<th>Temp. (°C)</th>
<th>10⁴ k M⁻¹ s⁻¹</th>
<th>dev %</th>
<th>10⁴ k M⁻¹ s⁻¹</th>
<th>dev %</th>
<th>10⁴ k M⁻¹ s⁻¹</th>
<th>dev %</th>
<th>10³ k M⁻¹ s⁻¹</th>
<th>dev %</th>
<th>Keq (5Zd to 5Zd)</th>
<th>dev %</th>
</tr>
</thead>
<tbody>
<tr>
<td>44.6⁰</td>
<td>1.95</td>
<td>3.6</td>
<td>1.15</td>
<td>0.0</td>
<td>1.59</td>
<td>1.0</td>
<td>2.37</td>
<td>d</td>
<td>0.0671</td>
<td>g</td>
</tr>
<tr>
<td>44.6⁰</td>
<td>2.31</td>
<td>0.4</td>
<td>1.15</td>
<td>3.5</td>
<td>1.87</td>
<td>c</td>
<td>2.37</td>
<td>d</td>
<td>0.0789</td>
<td>2.4</td>
</tr>
<tr>
<td>50.0⁰</td>
<td>4.38</td>
<td>3.4</td>
<td>2.24</td>
<td>4.0</td>
<td>3.26</td>
<td>c</td>
<td>3.47</td>
<td>d</td>
<td>0.0939</td>
<td>1.2</td>
</tr>
<tr>
<td>54.6⁰</td>
<td>8.13</td>
<td>1.4</td>
<td>3.92</td>
<td>3.6</td>
<td>4.81</td>
<td>c</td>
<td>5.09</td>
<td>d</td>
<td>0.0946</td>
<td>3.2</td>
</tr>
<tr>
<td>60.0⁰</td>
<td>12.5</td>
<td>7.2</td>
<td>7.56</td>
<td>1.7</td>
<td>7.68</td>
<td>c</td>
<td>7.52</td>
<td>d</td>
<td>0.102</td>
<td>5.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temp. (°C)</th>
<th>10³ k M⁻¹ s⁻¹</th>
<th>dev %</th>
<th>10³ k M⁻¹ s⁻¹</th>
<th>dev %</th>
<th>10² k M⁻¹ s⁻¹</th>
<th>dev %</th>
<th>10² k M⁻¹ s⁻¹</th>
<th>dev %</th>
<th>Keq (5Zb to 5Zb)</th>
<th>dev %</th>
</tr>
</thead>
<tbody>
<tr>
<td>44.6⁰</td>
<td>2.23</td>
<td>8.1</td>
<td>2.09</td>
<td>4.8</td>
<td>1.42</td>
<td>3.2</td>
<td>4.38</td>
<td>g</td>
<td>0.0324</td>
<td>e</td>
</tr>
</tbody>
</table>

a. Method I.
b. Method II.
c. Calculated from the experimentally measured Keq.
d. From Arrhenius plot for the isomerization of 5Ed to 5Zd.
e. Calculated from Keq = K_{(5Z to 5E)} / K_{(5E to 5Z)}.
f. Deviation from average of two results.
g. From Table 6.
The Hammett plot for the isomerization of E-hydroximoyl cyanide (5E) is shown in Figure 3. The sign and magnitude of the ρ-value of +2.34 is consistent with a mechanism in which the rate-determining step is nucleophilic attack by methoxide ion on the carbon atom of the carbon-nitrogen double bond to form a negatively charged tetrahedral intermediate (Scheme IV). The activation parameters for the isomerization of 5Ed have been determined (ΔH* = 16.9 kcal/mol and ΔS* = -17.5 cal/°K·mol, Table 9) and are similar to the values reported by Johnson22 for the substitution reactions of Z-O-methylbenzohydroximoyl chlorides with methoxide ion which proceed by an $A_N + D_N$ mechanism. The negative entropy of activation for isomerization of 5Ed is consistent with a bimolecular reaction. It was found that E-hydroximoyl cyanide (5E) isomerizes to the Z-isomer under reaction conditions that eventually lead to substitution in the Z-isomer.

Table 9. Activation parameters for the reactions 5Ed→5Zd, 5Zd→5Ed, 5Zd→6Zd and 5Zd→4Zd

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Ea (kcal/mol)</th>
<th>ΔH* (kcal/mol)</th>
<th>ΔS* (eu)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5Ed→5Zd</td>
<td>17.5</td>
<td>16.9</td>
<td>-17.5</td>
</tr>
<tr>
<td>5Zd→5Ed</td>
<td>19.1</td>
<td>17.8</td>
<td>-19.7</td>
</tr>
<tr>
<td>5Zd→6Zd</td>
<td>23.4</td>
<td>22.3</td>
<td>-5.17</td>
</tr>
<tr>
<td>5Zd→4Zd</td>
<td>25.6</td>
<td>24.7</td>
<td>1.19</td>
</tr>
</tbody>
</table>
Figure 3. Hammett plot for the methoxide ion catalyzed isomerization of 5E to 5Z at 44.6°C

\[ y = 2.341x + 0.007 \quad r = 0.999 \]
In the reaction of 5Zd with methoxide ion, it was found that 5Zd isomerized to 5Ed. When the concentration of 5Ed reaches its highest point, it decreased again. This may indicate the reaction of 5Zd to 5Ed is at an equilibrium at that point, and the concentration ratio of 5Zd and 5Ed is equal to the equilibrium constant. Using the equation $K_{eq} = k_t/k_1$, the rate constants at different temperatures for the reaction of 5Zd to 5Ed can be calculated (Table 8). The similarity of the activation parameters for the reaction of 5Zd to 5Ed (Table 9) with the isomerization of 5Ed indicates that the reverse reaction is also consistent with an $A_{NH} + D_N$ mechanism.

Using only three points including one from the previously measured$^{23}$ rate of methoxide ion substitution in 5Za, an approximate Hammett $\rho$-value (Figure 4) for substitution in Z-hydroximoyl cyanides (5Z) can be calculated ($\rho = +2.51$). This $\rho$-value is consistent with an addition-elimination mechanism. Interestingly, a small positive entropy of activation was calculated for the reaction of 5Zd to 4Zd (Table 9). A change of the sign in the entropy of activation for substitution of 5Zd to 4Zd as compared to the isomerization of 5Ed may indicate that the rate-limiting step has changed to the elimination step. If the tetrahedral intermediate 7A slowly decomposes to one molecule of 4Zd and one methoxide ion, a positive entropy of activation would be expected.
Since cyanide ion is a poorer leaving group than methoxide ion, the isomerization rate constant \( k = 2.37 \times 10^{-3}\) M\(^{-1}\) s\(^{-1}\) for 5Ed to 5Zd at 44.6°C is considerably higher than the rate constant for nucleophilic substitution \( k = 1.15 \times 10^{-4}\) M\(^{-1}\) s\(^{-1}\) for 5Zd to 4Zd. In order to compare the difference in the rate constants between the reactions of 5Ed to 5Zd, 5Zd to 5Ed and 5Zd to 4Zd, the plots of \( \ln k/T \) vs \( 1/T \) for these three reactions were extrapolated to 25°C, and their rate constants were calculated and are shown in Table 10. The rate ratio of 12.7 between the isomerization reaction (5Ed → 5Zd) and its reverse reaction (5Zd → 5Ed) at 44.6°C is close to the value obtained at 25°C (11.9). The observed equilibrium constant for the isomerization of 5Zd to 5Ed is ca. 0.1, and the change of free energy between 5Ed and 5Zd is ca. 1.36 kcal/mol, which may contribute to the difference in energy between the tetrahedral intermediates 7A and 7B (Scheme IV) and cause the difference in rates between the reactions 5Ed → 5Zd and 5Zd → 5Ed. However, the rate ratio of \( k_{5Ed\rightarrow5Zd} / k_{5Zd\rightarrow4Zd} \) of 41.9 at 25°C is much larger than that of 20.6 at 44.6°C, which indicates the relative difficulty of losing cyanide ion from the tetrahedral intermediate 7A to give the substitution product. Since these three reactions share the same intermediates, it seems that rate-determining elimination of the poor leaving group, cyanide ion, allows the tetrahedral intermediate to undergo stereomutation. According
to the calculations by Johnson, Jano and McAllister\textsuperscript{30}, the intermediate 7C is
unstable in comparison to 7A and 7B, so it cannot form the product 4E.

Table 10. Calculated 2nd-order rate constants for
isomerization and substitution reactions at 25\textdegree{}C and at
44.6\textdegree{}C

<table>
<thead>
<tr>
<th>Reaction</th>
<th>( k_2, \text{M}^{-1} \text{s}^{-1} ) (25\textdegree{}C)</th>
<th>( k_2, \text{M}^{-1} \text{s}^{-1} ) (44.6\textdegree{}C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5Ed→5Zd</td>
<td>( 3.49 \times 10^{-4} )</td>
<td>( 2.37 \times 10^{-3} )</td>
</tr>
<tr>
<td>5Zd→5Ed</td>
<td>( 2.93 \times 10^{-5} )</td>
<td>( 1.87 \times 10^{-4} )</td>
</tr>
<tr>
<td>5Zd→4Zd</td>
<td>( 8.32 \times 10^{-6} )</td>
<td>( 1.15 \times 10^{-4} )</td>
</tr>
</tbody>
</table>

a. Calculated by extrapolating the plot of \( \ln k/T \) vs \( 1/T \).

<table>
<thead>
<tr>
<th>Temp.(\textdegree{}C)</th>
<th>( k_{(5Ed→5Zd)}/k_{(5Zd→5Ed)} )</th>
<th>( k_{(5Ed→5Zd)}/k_{(5Zd→4Zd)} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>11.9</td>
<td>41.9</td>
</tr>
<tr>
<td>44.6</td>
<td>12.7</td>
<td>20.6</td>
</tr>
</tbody>
</table>
Figure 4. Hammett plot for hydrolysis and substitution reactions of 5Z with methoxide ion at 44.6°C

\[ y = 1.960x + 0.048 \]

\[ y = 2.509x + 0.069 \]

<table>
<thead>
<tr>
<th>Reaction with MeO(^-)</th>
<th>2nd-order rate constants (M(^{-1})S(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>5Za (\rightarrow) 4Za</td>
<td>(4.34 \times 10^{-4})</td>
</tr>
<tr>
<td>(\rightarrow) 8a</td>
<td>(6.65 \times 10^{-4})</td>
</tr>
<tr>
<td>5Zb (\rightarrow) 4Zb</td>
<td>(2.09 \times 10^{-3})</td>
</tr>
<tr>
<td>(\rightarrow) 8b</td>
<td>(2.23 \times 10^{-3})</td>
</tr>
<tr>
<td>5Zd (\rightarrow) 4Zd</td>
<td>(1.15 \times 10^{-4})</td>
</tr>
<tr>
<td>(\rightarrow) 8d</td>
<td>(2.31 \times 10^{-4})</td>
</tr>
</tbody>
</table>

* Data from ref. 23.
It appears that in the isomerization of 5E to 5Z the first formed conformation of the tetrahedral intermediate is 7B which undergoes stereomutation to give conformation 7A. Elimination of methoxide ion from 7A gives the thermodynamically more stable Z-hydroximoyl cyanide (5Z). The reaction of 5Z with methoxide ion first forms the tetrahedral intermediate 7A. The tetrahedral intermediate 7A can reversibly rotate to 7B which eliminates methoxide ion to form 5E or 7A can lose cyanide ion to form the substitution product 4Z.

In the case of isomerization of the para-nitro compound (5Ee) another competing reaction was observed. This kind of reaction also took place in the reaction of 5Ze with methoxide ion. Two mechanisms were considered for these substitution reactions: 1) nucleophilic aromatic substitution (SNAr) by methoxide ion for the nitro group shown in Scheme XI; 2) radical nucleophilic aromatic substitution mechanism shown in Scheme XII. It has been found that methoxide substitution in the Z isomer (5Ze) gives only (Z)-O-methyl-p-methoxybenzohydroximoyl cyanide (5Zd). The nitro group has been found to have a high nucleofugality in substitution reactions at sp² hybridized carbon. Its relative reactivity is 5750 as compared with 6900 for fluoride ion, and 11.6 for chloride ion. So, its departure from an aromatic system containing other electron-withdrawing groups can occur. Assuming mechanism 1 is correct, two interesting conclusions can be drawn concerning these reactions: 1) The fact that Z/E isomerization did not take place during the substitution indicates that
delocalization of the negative charge does not take place to a significant extent into the hydroximoyl cyanide functional group. If the negative charge was extensively delocalized into this group, the carbon-nitrogen bond order should be diminished resulting in Z/E isomerization. 2) The rate constant for methoxide ion substitution in 5Ee is about 7 times greater than the rate constant for substitution in 5Ze. This difference can be explained by the greater polarity of the E configuration of the hydroximoyl cyanide functional group. This has been determined previously by Johnson, et al., from measurements of the dipole moments of the Z and E isomers of O-methylbenzohydroximoyl cyanide.

Mechanism 2 cannot be ruled out. Methoxy radical (MeO·) can be generated via initial nucleophilic attack by the electron-rich nucleophile methoxide ion which can transfer an electron to the substrate since it has strong electrophilic reactivity. Also, radical anion formation can be promoted by an activated SNAr nucleophilic aromatic substitution pathway.

An approximate Hammett ρ-value for nucleophilic attack at the cyano group of Z-hydroximoyl cyanides is + 1.96 (Figure 4). A reasonable mechanism is shown in Scheme XIII. It is assumed that an imidate is formed from nucleophilic attack on the cyano group. Hydrolysis of this imidate to amide 6Zd would be expected during work up of the reaction or in HPLC analysis of the reaction mixture. The lower Hammett ρ-value (+ 1.96) for attack at the nitrile
carbon atom as compared to attack at the carbon-nitrogen double bond ($\rho = + 2.51$) is to be expected since the nitrile carbon atom is further from the aromatic ring than the carbon atom of the carbon-nitrogen double bond.

SCHEME XI

\[
\begin{align*}
\text{MeOH:DMSO} &= 10:90 \\
\end{align*}
\]
SCHEME XIII

\[
\begin{align*}
\text{5Z} & \xrightarrow{\text{reaction}} \text{14} & \xrightarrow{\text{H}^+} \text{15} \\
\text{15} & \xrightarrow{\text{HO}^-} \text{16} & \xrightarrow{\text{reaction}} \text{6}
\end{align*}
\]
CHAPTER III
EXPERIMENTAL

A. General Procedures

All chemicals used in this research were reagent grade except as noted. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined with a MAGNA-IR 560 Spectrometer. NMR spectra were obtained on a Varian 300MHz NMR spectrometer. Low resolution mass spectra were determined on a Varian Saturn 3 ion-trap GC/MS spectrometer. Elemental analyses of the new compounds prepared in this work were performed by Atlanta Microlab, Inc., Atlanta, GA. The HPLC equipment consisted of a Spectra Physics IsoChrom LC pump, a Rheodyne injector, a Spectra Physics 8450 variable wavelength UV/Vis detector, and a B & J OD5 Octadecyl Column (5 µ, 25 x 0.46 cm).

1. The Column Chromatographic Method

The silica gel, MN-Kieselgel 60 0.1-0.2mm/70-130 mesh ASTM, was dried at 100°C for at least an hour before packing the column. A ratio of 100:1 of silica gel to sample was used. The eluent for separation of the isomers was a mixture of hexane and chloroform in a suitable ratio (v/v) as indicated by TLC analysis of the mixtures. The silica gel was first mixed with hexane and then
poured into the column. The sample was dissolved in a small amount of eluent and was placed on the top of the column. The eluent was allowed to run through the column until the product was eluted from the column. The solvent was removed by evaporation using a rotary evaporator at aspirator pressure. The products were further purified by rechromatography or by recrystallization.

2. The Kinetic Method

The hydroximoyl cyanides were weighed into a 50 ml volumetric flask, distilled dimethyl sulfoxide (38 ml) was added, and the flask was thermostated in a constant temperature bath (± 0.01 °C). The temperature of the constant temperature bath was monitored with a Hewlett Packard Quartz Thermometer. The standardized sodium methoxide solution was thermostated for 15 minutes in a 25 ml volumetric flask. The sodium methoxide solution (5 ml) was added with a 5 ml pipette to this 50 ml volumetric flask. The reaction mixture was quickly diluted to the mark with the previously thermostated dimethyl sulfoxide and then shaken to ensure complete mixing of the solutions. When the first aliquot were taken by a pipette from the reaction solution, the timer was started. Aliquots were quickly quenched by a same volume of a similar concentration of hydrochloric acid solution to ensure that the pH value of the mixture was close to 7. The time of quenching was recorded for each aliquot. A 20 µl sample of each aliquot was injected into the HPLC. The HPLC mobile phase was of
distilled in glass water and acetonitrile (B & J). The ratio of water/acetonitrile (v/v) in the mobile phase was adjusted by injecting pure samples of starting material and products.

Normalization factors for peak areas were determined by analysis of samples containing known amounts of reactant and products. The normalized peak area ratios for reactants and products were converted into percentages. The rate constants for the E to Z isomerization of 5Ea, 5Eb, 5Ec and 5Ed were obtained by plotting In Eo/E (where Eo is equal to the initial concentration of the E isomer and E is equal to the corrected concentration of the E isomer at time t) vs t. The rate constants for the competing pseudo-first-order reactions and the competing second-order reactions were obtained by methods described in Chapter II. Rate constants and correction coefficients were calculated using the computer program Cricket Graph.

3. Preparation of Solvents and Solutions Used for Kinetics

Dimethyl sulfoxide (HPLC grade, B & J) was stored over sodium hydroxide pellets for more than 24 hours and then distilled from the sodium hydroxide pellets under vacuum. Distilled solvent with a constant boiling point was collected and then stored in a desiccator.

Methanol (Karl Fischer Grade) was distilled from the magnesium by distillation with an anhydrous calcium sulfate drying tube. Distilled solvent with a constant boiling point was collected and then stored in a desiccator.
Standardization of hydrochloric acid solution: The hydrochloric acid solution was made by placing 8.33 ml of 12 M hydrochloric acid solution in a 1000 ml volumetric flask and diluting to mark with distilled water. This solution was standardized using primary standard analytical reagent-grade anhydrous sodium carbonate (99.95%) which was dried at 100°C for 10 hours and kept in a desiccator before use.

Preparation of sodium methoxide solution: The sodium methoxide solutions were prepared by adding metallic sodium to anhydrous methanol. The sodium methoxide solutions were stored in a closed flask under dry nitrogen. The solution of sodium methoxide was titrated with standardized hydrochloric acid solution using methyl red solution as an indicator.

B. Synthesis of Substituted Z-Oximinophenylacetonitrile \(31, 38, 34\)

\((Z)-p\)-Methylbenzohydroximoyl cyanide(9c)

\(p\)-Methylbenzoyl cyanide (25 g, 0.19 mol) and \(n\)-butyl nitrite (22.3 ml, 0.19 mol) were dissolved in 100 ml ethanol. This solution was cooled in an ice-cold bath and a solution of sodium ethoxide (from 4.4 g, 0.19 mol of sodium and 50 ml of ethanol) was added dropwise. The resulting solution was stirred about 3 hours at room temperature. Then ethanol was evaporated until 50 ml solution was left. Ether (50 ml) was added to the residue, and the solid sodium salt of the product was filtered and dissolved in water (100 ml). The aqueous solution was adjusted to pH 5 with 3 M hydrochloric acid solution. The solid that formed
was recrystallized from a hexane-chloroform solution, giving 9c as a white solid (13.21 g, 0.083 mol, 43%): mp, 117-118°C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.401 (s, 3H, CH\(_3\)), 7.266, 7.694 (AA'BB', J = 8.4 Hz, 4H, aromatic H), 6.878 (s, 1H, OH); \(^{13}\)C NMR (300 MHz, CDCl\(_3\)) \(\delta\) 21.467, 109.078, 126.048, 126.084, 129.599, 133.802, 141.813; IR (KBr), 1607, 2241, 3335 cm\(^{-1}\); Anal. Calcd. for C\(_9\)H\(_8\)N\(_2\)O: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.29; H, 5.05; N, 17.39.

(Z)-\(p\)-Methoxybenzohydroximoyl cyanide (9d)

\(p\)-Methoxyphenyl acetonitrile (48.5 g, 0.33 mol) and \(n\)-butyl nitrite (38.5 ml, 0.33 mol) were dissolved in 100 ml ethanol. This solution was cooled in an ice-cold bath and a solution of sodium ethoxide (from 7.7 g, 0.33 mol of sodium and 50 ml of ethanol) was added dropwise. The resulting solution was stirred about 3 hours at room temperature. The ethanol was evaporated until 50 ml of solution was left. Ether (50 ml) was added to the residue, and the solid sodium salt of the product was filtered and dissolved in water (100 ml). The aqueous solution was adjusted to pH 5 with 3 M hydrochloric acid solution. The solid that formed was recrystallized from a hexane-chloroform solution, giving 9d as a white solid (18.41 g, 0.105 mol, 31.6%): mp, 77-79°C; This sample apparently was a half-hydrate; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.856 (s, 3H, OCH\(_3\)), 6.964, 7.734 (AA'BB', J = 9.0 Hz, 4H, aromatic H), 9.537 (s, 1H, OH); \(^{13}\)C NMR (300 MHz, CDCl\(_3\)) \(\delta\) 55.443, 109.315, 114.379, 121.544, 127.705, 133.135, 161.796;
(Z)-O-Methyl-p-chlorobenzohydroximoyl cyanide (5Zb)

(Z)-p-Chlorobenzohydroximoyl cyanide (9.03 g, 0.05 mol) was dissolved in a solution of sodium methoxide in methanol [prepared by adding 2.3 g (0.1 mol) of sodium to 100 ml of methanol]. Methyl iodide (8.34 ml, 0.13 mol) was added and the solution was stirred at room temperature for 72 h. The methanol was evaporated at aspirator pressure. Water (100 ml) was added to the residue and the insoluble solid was filtered. The solid was recrystallized from a hexane-chloroform solution to give 5Zb as a white solid (5.2 g, 0.027 mol, 53%): mp, 70-71 °C; 1H NMR (300 MHz, CDCl₃) δ 4.208 (s, 3H, OCH₃), 7.434, 7.745 (AA'BB', J = 8.7 Hz, 4H, aromatic H); 13C NMR (300 MHz, CDCl₃) δ 64.330, 109.071, 127.174, 127.512, 129.154, 130.409, 137.201; IR (KBr), 1593, 2223, 2939 cm⁻¹; Anal. calcd. for C₉H₇N₂OCl: C, 55.54; H, 3.63; N, 14.39; Cl, 18.22. Found: C, 55.47; H, 3.70; N, 14.35; Cl, 18.31.

(E)-O-Methyl-p-chlorobenzohydroximoyl cyanide (5Eb)

A hexane solution of (Z)-O-methyl-p-chlorobenzohydroximoyl cyanide 5Zb was irradiated for 3 hours in a Rayonet reactor fitted with 16 low pressure mercury lamps (254 nm). After the irradiation was complete, the hexane solution was shaken with solid, anhydrous sodium carbonate and the hexane
was evaporated at aspirator pressure. The residue was a mixture of 5Zb and 5Eb (5Eb/5Zb = 36:64). The mixture was separated by column chromatography (silica gel-60) using chloroform-hexane (70:30) to give the E-isomer (5Eb) as a white solid: mp, 39-40°C; 1H NMR (300 MHz, CDCl₃) δ 4.184 (s, 3H, OCH₃), 7.455, 7.933 (AA'BB', J = 9.0Hz, 4H, aromatic H); 13C NMR (300 MHz, CDCl₃) δ 64.939, 114.235, 125.883, 128.853, 130.761, 133.135, 137.546; IR (KBr), 1588, 2236, 2939 cm⁻¹; Anal. calcd. for C₉H₇N₂OCI: C, 55.54; H, 3.63; N, 14.39; Cl, 18.22. Found: C, 55.58; H, 3.68; N, 14.33; Cl, 18.32.

(Z)-O-Methyl-p-methylbenzohydroximoyl cyanide (5Zc)

(Z)-p-Methoxybenzohydroximoyl cyanide (8.01 g, 0.05 mol) was dissolved in a solution of sodium methoxide in methanol [prepared by adding 2.3 g (0.1 mol) of sodium to 150 ml of methanol]. Methyl iodide (8.4 ml, 0.13 mol) was added and the solution was stirred at room temperature for 72 hours. The methanol was evaporated at aspirator pressure. Water (100 ml) was added to the residue and the solution was extracted with diethyl ether (3 × 50 ml). The ether extracts were dried over anhydrous magnesium sulfate and the ether was evaporated to give a crude solid. The solid was purified by column chromatography to give 5Zc as a white solid (6.0 g, 0.035 mol, 68%): mp, 47-48°C. 1H NMR (300 MHz, CDCl₃) δ 2.390 (s, 3H, CH₃), 4.179 (s, 3H, OCH₃), 7.247, 7.684 (AA'BB', J = 8.4 Hz, 4H, aromatic H); 13C NMR (300 MHz, CDCl₃) δ
(E)-O-Methyl-p-methylbenzohydroximoyl cyanide (5Ec)

A hexane solution of (Z)-O-methyl-p-methylbenzohydroximoyl cyanide 5Zc was irradiated for 3 hours in a Rayonet reactor fitted with 16 low pressure mercury lamps (254 nm). After the irradiation was complete, the hexane solution was shaken with solid, anhydrous sodium carbonate and the hexane was evaporated at aspirator pressure. The residue was a mixture of 5Zc and 5Ec (5Zc/5Ec = 64/36). The mixture was separated by column chromatography using chloroform-hexane (70:30) to give a yellowish oil. That oil was distilled under vacuum (0.1 Torr) in a short-path distillation apparatus (Kontes K548250) to give 5Ec as a colorless oil: 1H NMR (300 MHz, CDCl₃) δ 2.397 (s, 3H, CH₃), 4.153 (s, 3H, OCH₃), 7.271, 7.879 (AA'BB', J = 8.7 Hz, 4H, aromatic H); 13C NMR (300 MHz, CDCl₃) δ 21.546, 64.609, 114.651, 124.894, 129.190, 129.441, 134.232, 142.093; IR (KBr), 1611, 2230, 2945 cm⁻¹; Anal. calcd. for C₁₀H₁₀N₂O: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.98; H, 5.81; N, 16.14.

(Z)-O-Methyl-p-methoxybenzohydroximoyl cyanide (5Zd)

(Z)-p-Methoxybenzohydroximoyl cyanide (10.3 g, 0.058 mol) was dissolved
in a solution of sodium methoxide in methanol [prepared by adding 2.69 g (0.117 mol) of sodium to 150 ml of methanol]. Methyl iodide (9.62 ml, 0.155 mol) was added and the solution was stirred at room temperature for 72 hours. The methanol was evaporated at aspirator pressure. Water (150 ml) was added to the residue and the solution was extracted with diethyl ether (3 x 50 ml). The ether extracts were dried over anhydrous magnesium sulfate and the ether was evaporated to give the crude product. The crude product was purified by column chromatography to give 5Zd as a white solid (9.02 g, 0.0475 mol, 82%): mp, 75-76°C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.848 (s, 3H, OCH\(_3\)), 4.160 (s, 3H, OCH\(_3\)), 6.951, 7.733 (AA'BB', \(J = 8.7\) Hz, 4H, aromatic H); \(^13\)C NMR (300 MHz, CDCl\(_3\)) \(\delta\) 55.378, 63.871, 109.516, 114.293, 121.616, 127.590, 131.004, 161.731; IR (KBr), 1514, 1607, 2223, 2945 cm\(^{-1}\); Anal. calcd. for C\(_{10}\)H\(_{10}\)N\(_2\)O\(_2\): C, 63.15; H, 5.30; N, 14.73. Found: C, 63.14; H, 5.35; N, 14.73.

(E)-O-Methyl-p-methoxybenzohydroximoyl cyanide (5Ed)

A hexane solution of (Z)-O-methyl-p-methoxybenzohydroximoyl cyanide 5Zd was irradiated for 3 hours in a Rayonet reactor fitted with 16 low pressure mercury lamps (254 nm). After the irradiation was complete, the hexane solution was shaken with solid anhydrous sodium carbonate and the hexane was evaporated at aspirator pressure. The residue was a mixture of 5Zd and 5Ed (5Zd/5Ed = 67/33) and was separated by column chromatography to give 5Ed.
as a white solid: mp, 63-64°C; ¹H NMR (300 MHz, CDCl₃) δ 3.862 (s, 3H, OCH₃), 4.151 (s, 3H, OCH₃), 6.964, 7.993 (AA'BB', J = 8.7 Hz, 4H, aromatic H); ¹³C NMR (300 MHz, CDCl₃) δ 55.371, 64.502, 113.819, 114.702, 120.439, 131.564, 133.752, 161.538; IR (KBr), 1605, 2229, 2945 cm⁻¹; Anal. calcd. for C₁₀H₁₀N₂O₂: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.25; H, 5.37; N, 14.68.

**Z-O-Methyloxime of 1-Keto-ᵽ-chlorophenyl acetamide (6Zb)**

(Z)-O-Methyl-ᵽ-chlorobenzohydroximoyl cyanide 5Zb (1.0 g, 0.0051 mol) was dissolved in a solution of 2 N sodium hydroxide (10 ml) in ethanol (10 ml). Hydrogen peroxide 30% (2 ml) was added slowly. The mixture was gently heated and well shaken for 10 minutes. A vigorous evolution of oxygen takes place. The amide was extracted with ether (3 x 50 ml). The ether solution was dried with anhydrous magnesium sulfate and evaporated to give the crude product. Recrystallization of the crude solid with chloroform-hexane gave 6Zb as a white solid (0.75 g, 0.0035 mol, 69%): mp, 139-141°C; ¹H NMR (300MHz, CDCl₃) δ 4.039 (s, 3H, OCH₃), 6.039, 6.209 (s, NH₂), 7.342, 7.597 (AA'BB', J = 8.4 Hz, 4H, aromatic H); ¹³C NMR (300MHz, CDCl₃) δ 63.074, 127.999, 128.659, 129.383, 136.018, 150.822, 164.191; IR (KBr) 1669, 2932, 3177, 3370 cm⁻¹.

**Z-O-Methyloxime of 1-Keto-ᵽ-methylphenyl acetamide (6Zc)**

(Z)-O-Methyl-ᵽ-methylbenzohydroximoyl cyanide 5Zc (1.3 g, 0.0075 mol) was dissolved in a solution of 2 N sodium hydroxide (10 ml) in ethanol (10 ml).
Hydrogen peroxide 30% (3 ml) was added slowly. The mixture was gently heated and well shaken for 10 minutes. A vigorous evolution of oxygen takes place. The amide was extracted with ether (3 x 50 ml). The ether solution was dried with anhydrous magnesium sulfate and evaporated to give the crude product. Recrystallization of the crude solid with chloroform-hexane gave 6Zc (0.85 g, 0.0044 mol, 59%) as a white solid: mp, 152-154°C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 2.359 (s, 3H, CH\(_3\)), 4.014 (s, 3H, OCH\(_3\)), 6.069, 6.471 (s, NH\(_2\)), 7.176, 7.549 (AA'BB', J = 8.4 Hz, 4H, aromatic H); \(^13\)C NMR (300 MHz, CDCl\(_3\)): \( \delta \) 21.374, 62.773, 126.507, 127.920, 129.161, 140.235, 152.084, 164.923; IR (KBr), 1613, 1667, 2936, 3162 cm\(^{-1}\).

**Z-O-Methyloxime of 1-Keto-p-methoxyphenyl acetamide (6Zd)**

\((Z)-O\)-Methyl-p-methoxybenzohydroximoyl cyanide 5Zd (1 g, 0.0053 mol) was dissolved in a solution of 2 N sodium hydroxide (10 ml) in ethanol (10 ml). Hydrogen peroxide 30% (2 ml) was added slowly. The mixture was gently heated and well shaken for 10 minutes. A vigorous evolution of oxygen takes place. The amide was extracted with ether (3 x 50 ml). The ether solution was dried with anhydrous magnesium sulfate and evaporated to give the crude product. Recrystallization of the crude solid with methanol-chloroform gave 6Zd (0.7 g, 0.00336 mol, 64%) as a white solid: mp, 164-165°C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 3.825 (s, 3H, OCH\(_3\)), 4.015 (s, 3H, OCH\(_3\)), 6.132, 6.158 (s, NH\(_2\)), 6.908,
7.629 (AA'BB', J = 9.3 Hz, 4H, aromatic H); $^{13}$C NMR (300 MHz, CDCl$_3$) δ 55.278, 62.723, 113.941, 123.251, 128.143, 151.711, 160.978, 164.779; IR (KBr), 1589, 1693, 3303, 3423 cm$^{-1}$; Anal. Calcd. for C$_{10}$H$_{12}$N$_2$O$_3$: C, 57.63; H, 5.81; N, 13.45. Found: C, 57.68; H, 5.81; N, 13.39.

**Z-O-Methyl oxime of 1-Keto-p-nitrophenyl acetamide (6Ze)**

(Z)-O-Methyl-p-nitrobenzohydroximoyl cyanide 5Ze (1.0 g, 0.0049 mol) was dissolved in a solution of 2 N sodium hydroxide (10 ml) in ethanol (10 ml). Hydrogen peroxide 30% (2 ml) was added slowly. The mixture was gently heated and well shaken for 10 minutes. A vigorous evolution of oxygen takes place. The amide was extracted with ether (3 × 50 ml). The ether solution was dried with anhydrous magnesium sulfate and evaporated to give the crude product. Recrystallization of the crude solid with chloroform-hexane gave 6Ze (0.55 g, 0.0025 mol, 51%) as a white solid: mp, 147-148°C; $^1$H NMR (300 MHz, CDCl$_3$) δ 4.043 (s, 3H, OCH$_3$), 5.716, 6.827 (s, NH$_2$), 7.617, 8.269 (AA'BB', J = 8.7 Hz, 4H, aromatic H); $^{13}$C NMR (300 MHz, CDCl$_3$) δ 63.842, 122.749, 130.653, 134.555, 147.573, 147.860, 163.567; IR (KBr), 1517, 1702, 3005, 3215 cm$^{-1}$. 
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