MECHANISMS OF ACID CATALYZED Z/E ISOMERIZATION OF HYDROXIMATES

A THESIS

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BY

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To the Dean of the Graduate School:

I am submitting herewith a thesis written by Krista M. Small entitled "Mechanisms of Acid-Catalyzed Z/E Isomerizations of Hydroximates." 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 Masters of Science with a major in Chemistry.

James E. Johnson

James E. Johnson PhD., Major Professor

We have read this thesis and recommend its acceptance:

Department Chair

Accepted:

Jennifer Marlow

Dean of the Graduate School

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ABSTRACT

KRISTA M. SMALL

MECHANISMS OF ACID-CATALYZED Z/E ISOMERIZATION OF HYDROXIMATES

AUGUST 2010

The acid-catalyzed isomerization of methyl O-methylcinnamohydroximate (1Zb and 1Eb) was investigated with four different acids in acetonitrile at 25 °C. There are two reasonable mechanisms in which isomerization can take place. The first being nucleophilic catalysis, where the acid counter ion undergoes nucleophilic attack on the protonated carbon-nitrogen bond. Rotation about the carbon-nitrogen single bond of the tetrahedral intermediate leads to Z/E isomerization. The second method is iminium ion rotation where the nitrogen atom of the carbon-nitrogen double bond is protonated, followed by rotation around the weakened carbon-nitrogen double bond. It is believed that the rates of isomerization will be higher than rates studied previously. However, our results were inconclusive.

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CHAPTER I

INTRODUCTION

Compounds containing the carbon-nitrogen double bond (imines) have become more important in organic synthesis over the past decades. This is largely due to the increased biological importance of the imine functional group. For example, the visual pigment rhodopsin contains an imine functional group. The carbon-nitrogen double bond has been incorporated into therapeutic agents such as cephalosporins,[1-3] which are among the most commonly prescribed antibiotics. Oximidines, which may act as selective antitumor drugs, also contain an O-alkyloxime moiety. Gemifloxacin, better known as Factive, is used to treat bacterial infections resistant to antibiotics contains an oxime functional group. It is likely that in the future more pharmaceutical agents containing the imine functional group will be discovered.

In recent years there have been many studies on the mechanisms and kinetics of compounds containing a carbon-nitrogen double bond.[4-15] It has been reported that most imines are capable of undergoing uncatalyzed Z/E isomerizations[16-18] as well as acid catalyzed Z/E isomerizations.[1-3, 6, 11-12, 19-26] Although rare, it has also been found that some imines can undergo base catalyzed isomerizations.[27-28] Uncatalyzed isomerizations of imines have been studied extensively, [16-18] and it has been found that in most cases they follow an inversion mechanism. Even though acid-catalyzed Z/E

isomerization of compounds containing a carbon-nitrogen double bond is a well known process and the mechanism of this isomerization has been investigated extensively, a true understanding is lacking.

There are two reasonable mechanisms for the acid catalyzed Z/E isomerizations of simple imines. The first mechanism being Iminium Ion Rotation (Mechanism I), which involves rotation around the carbon-nitrogen double bond of the N-protonated imine. Since protonation can reduce the carbon-nitrogen bond order, it is possible that the rotation takes place around the carbon-nitrogen bond axis of the iminium ion. After the proton leaves, the iminium ion changes into either the Z or E isomer.

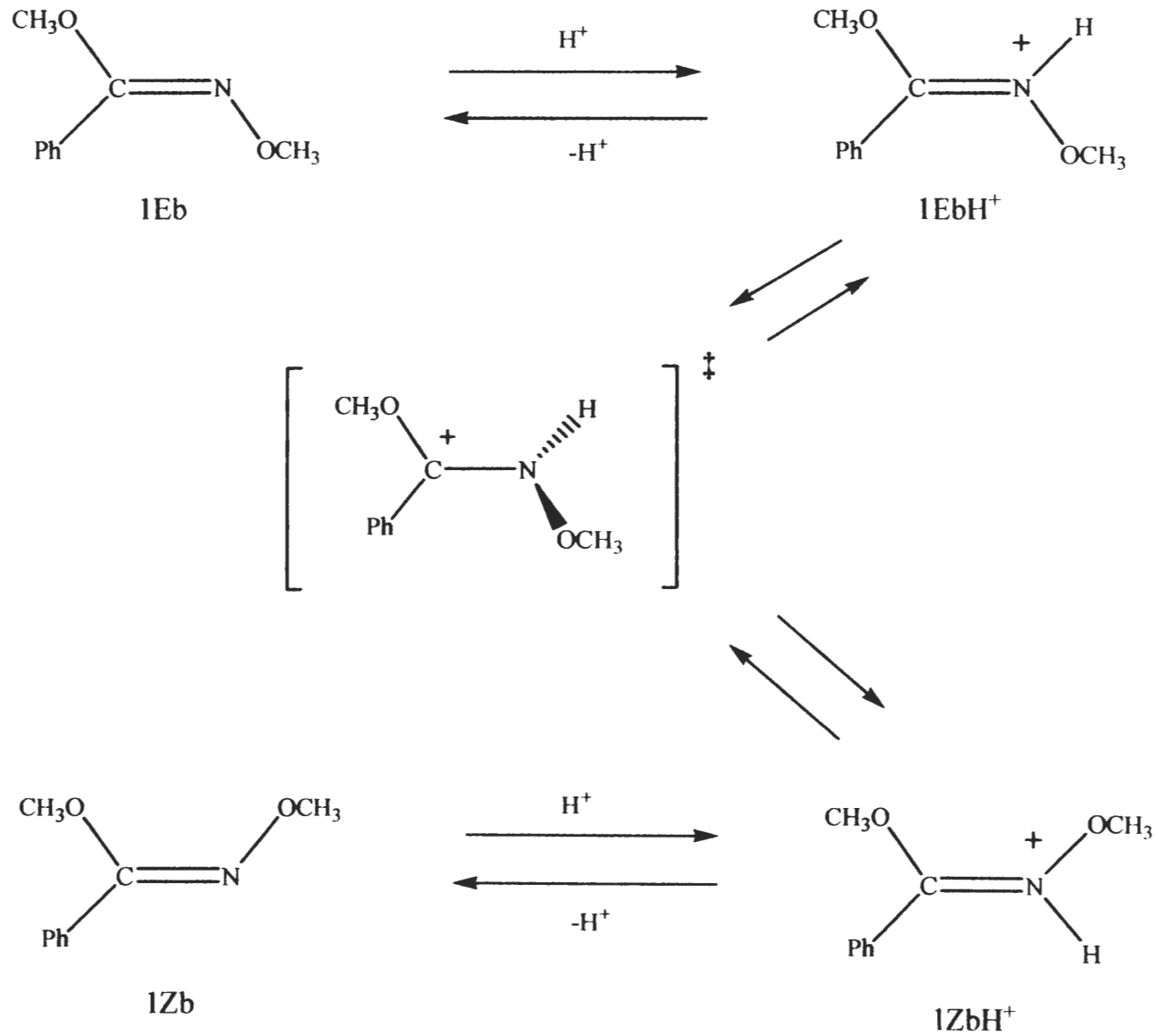


FIGURE 1. Mechanism 1: Iminium Ion Rotation

In Nucleophilic Catalysis (Mechanism II), the iminium ion undergoes nucleophilic attack by the acid counter ion at the carbon atom of the carbon-nitrogen double bond to give a tetrahedral intermediate. The tetrahedral intermediate produced from such an attack undergoes stereomutation by rotation around the carbon-nitrogen single bond, proton exchange on the nitrogen atom, and nitrogen inversion. This would result in an iminium ion of the opposite configuration. Loss of a proton from the iminium ion gives the imine.

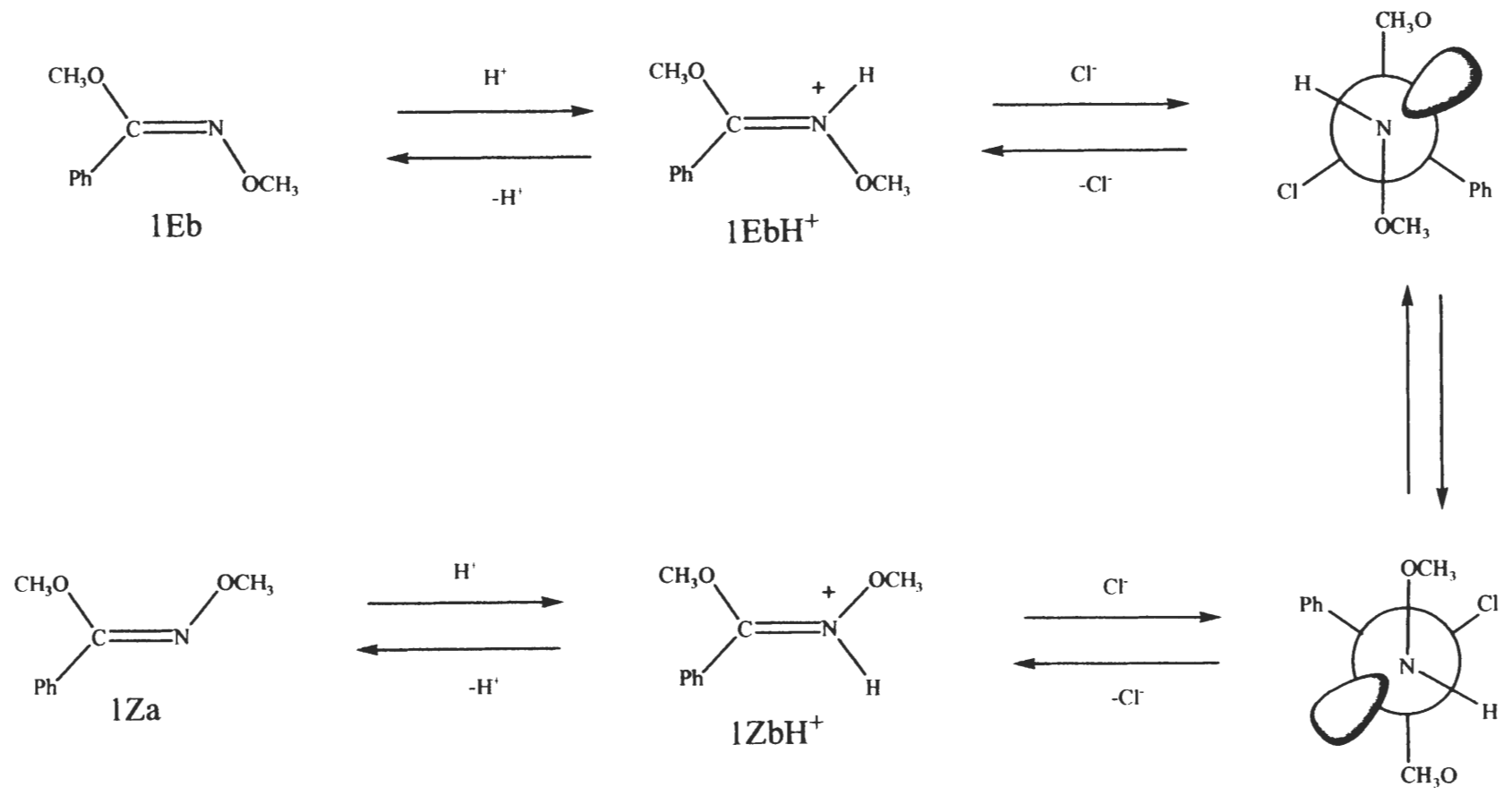


FIGURE 2. Mechanism 2: Nucleophilic Catalysis

Idoux and Sikorski, studied the sulfuric acid-catalyzed Z/E isomerization of a series of α-substituted acetophenone 2,4 –dinitrophenylhydrazones (DNP's). They concluded that the isomerization is influenced not only by steric effects but also by polar effects. The steric effect was the most important. They suggested that the isomerization was following a nucleophilic catalysis mechanism.[19]

Jennings and his coworkers studied the rate of E/Z isomerizations of N-(α-phenyl-4-nitrobenzylidene) methylamine in diphenyl ether at 35° C. They found that the rate of E/Z isomerization was very fast at 35° C and that the rate of isomerization was increased with the addition of trace amounts of benzoic acid. Their conclusions started that this mechanism proceeds by nucleophilic catalysis.[20]

Holloway and Vuik measured the rates of isomerization of (Z)-acetaldoxime in deuterium oxide (D_2O), using various concentrations of sulfuric acid in D_2O, sodium hydroxide in D_2O, and pure D_2O. [21] It was found that the rate of isomerization was dramatically affected by both hydrogen and hydroxide ions. Oximes reached equilibrium by first-order kinetics and the equilibrium constants were independent of temperature as well as the concentration of the acid or base. In carbon tetrachloride solution, however, the reaction rate was independent of the acetaldoxime, thus making it more complicated to determine the equilibrium.

Cunningham and Hegarty measured the rate of Z/E isomerizations of amidines in buffered aqueous solutions at 25° C.[23] Potassium chloride was added to the solution to maintain an ionic strength of 1.0. It was found that the acetamidines show a range of isomerization mechanisms including: acid-catalyzed, base-catalyzed, and uncatalyzed. The acid-catalyzed isomerizations of Z to E occurred so fast that the (Z)-amidines can only be isolated at a high pH. The acid-catalyzed isomerization pathway is much faster than that of the one observed for amidoximes due to their lower basicity. Uncatalyzed isomerizations occur over a limited high pH range and probably involves rate-

determining nitrogen inversion. They proposed that the acid-catalyzed process was taking place by iminium ion rotation.

In the past Johnson and his coworkers have investigated the acid catalyzed isomerizations of O-methylhydroximoyl chlorides and methyl O-methylbenzohydroximates. [12, 24-25] These compounds are unique, in that unlike other imines, they are particularly resistant to thermal isomerization.

In previous work,[24] Johnson, et.al. demonstrated that the E to Z isomerization of benzohydroximoyl chloride in HCl dioxane solution takes place by nucleophilic catalysis. This was demonstrated by observing that the rate constant for the incorporation of $^{36}Cl^-$ was one half the magnitude of the rate constant for the isomerization of benzohydroximoyl chloride.[25]

In 2001, Johnson and his coworkers investigated the kinetics and mechanisms[25] of acid-catalyzed isomerizations of O-methylbenzohydroximoyl chlorides (1Za and 1Ea), methyl O-methylbenzohydroximates (1Zb and 1Eb), ethyl O-methylbenzohydroximates (1Zc and 1Ec), O-methylcinnamohydroximoyl chlorides (2Za and 2Ea), and methyl O-methylcinnamohydroximates (2Zb and 2Eb).

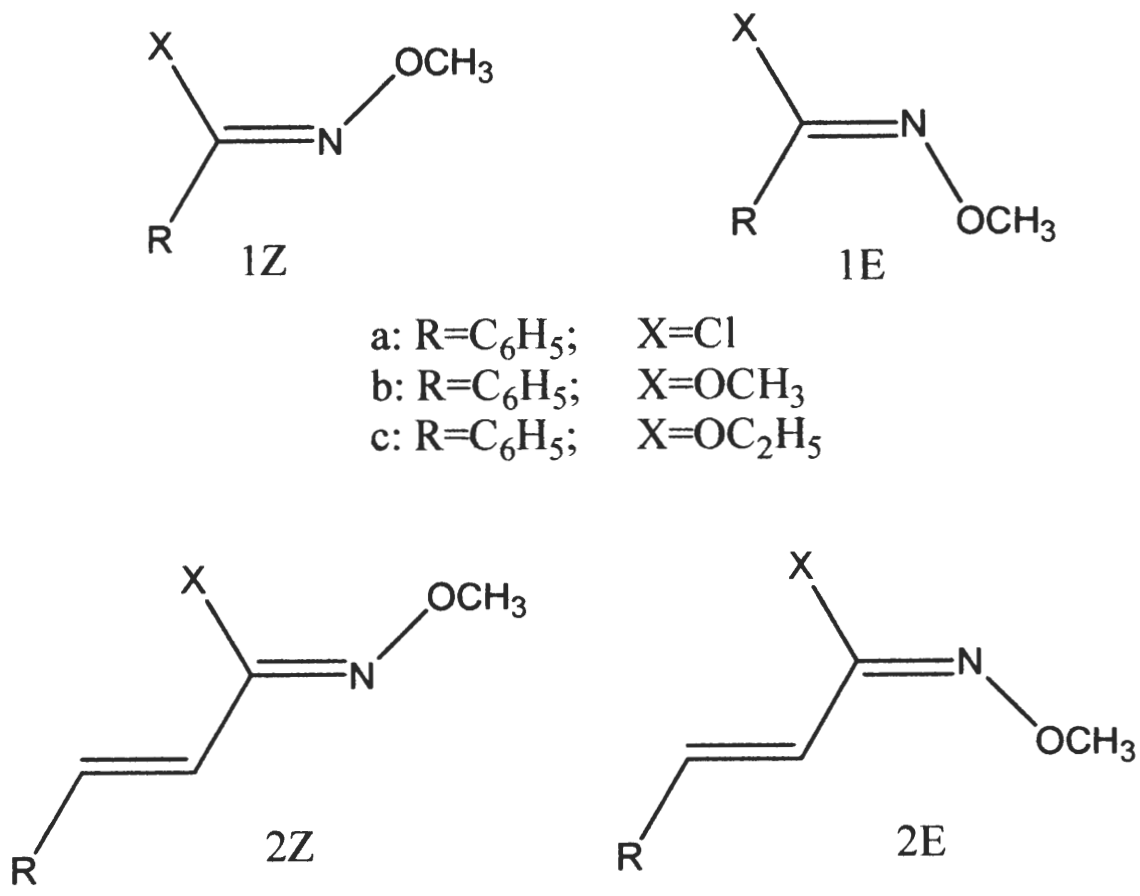


FIGURE 3. Kinetic Isomers

The kinetic constants of Z/E isomerizations of the imines in glacial acetic acid (1Za and 1Ea) and in dioxane solutions containing hydrochloric acid, trifluoromethane sulfonic acid or tetrafluoroboric acid (1Ea, 1Zb, 2Ea and 2Zb) were measured. Their results showed that isomerization takes place by either iminium ion rotation (Mechanism I) or nucleophilic catalysis (Mechanism II). The hydroximoyl chlorides (1Ea and 2Ea) only isomerized by nucleophilic catalysis. The hydroximate 1Zb is capable of isomerizing by both mechanisms. The hydroximate 2Zb may only be isomerizing by iminium ion rotation. Theoretical calculations showed that the increased conjugation in the protonated imine increased the rate of iminium ion rotation, which is consistent with their conclusions.[25]

Recently Dia[30] investigated the acid-catalyzed isomerization of methyl O-methylbenzohydroximate with eight different acids in acetonitrile at 25° C. This study showed that under the same conditions, the rate constant of the hydrochloric acid reaction with methyl (E)-O-methylbenzohydroximate is 200 times faster than in trichloroacetic acid. Since these two acids have similar pKa's it was concluded that the isomerization in hydrochloric acid was proceeding by nucleophilic catalysis. A plot of log k (isomerization) vs. pKa gave a curved line (see figure below) The rate of isomerization with acids containing weakly nucleophilic counter ions increased as the pKa of the acid decreased. The rate leveled off with the triflic acid and fluorosulfonic acid. It is clear from this data that the hydroximate is completely protonated in triflic acid and flurosulfonic acid. The rate constant for isomerization in these two acids most corresponds to the rate constant for iminium ion rotation.

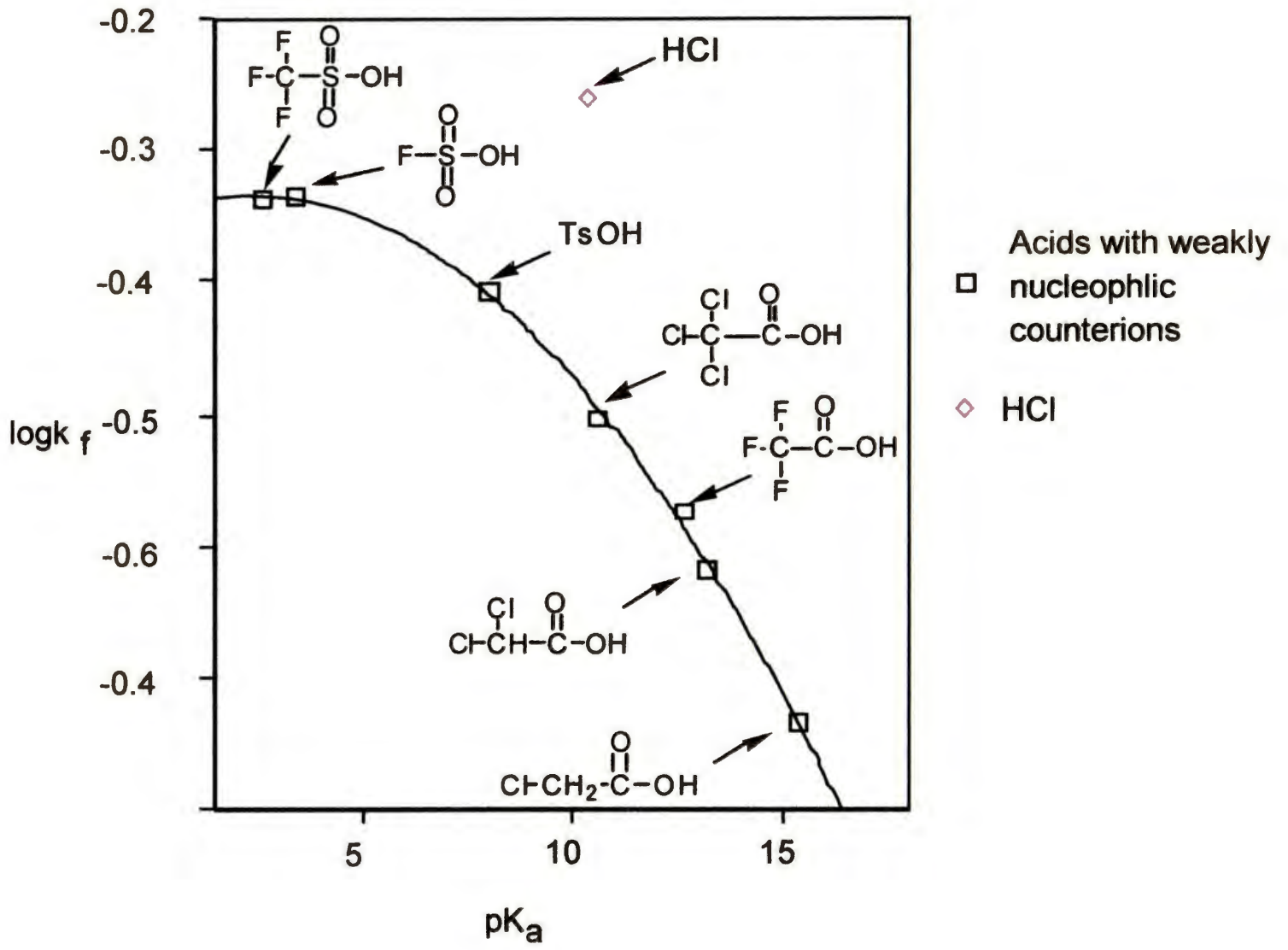
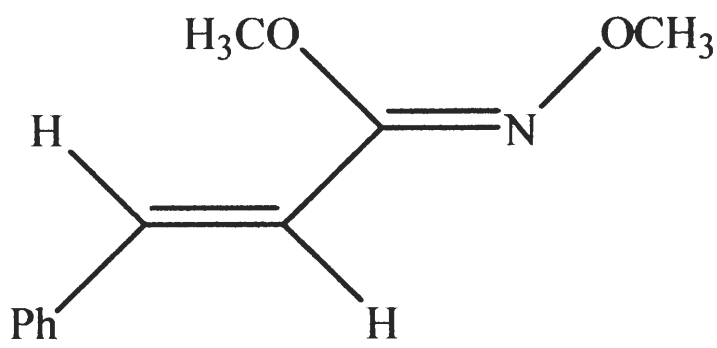


FIGURE 4. Plot of the pKa of the acid vs. log k of the forward reaction (E to Z)

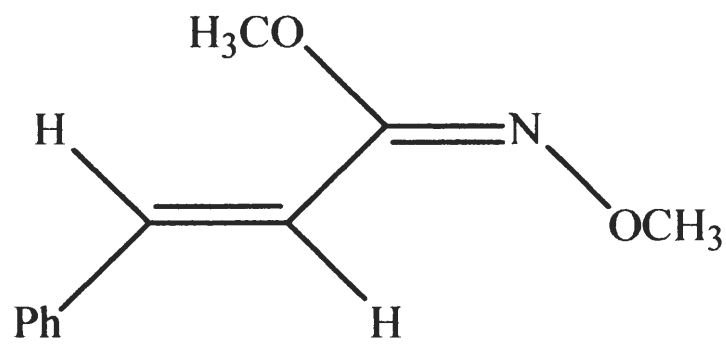
CHAPTER II

RESULTS AND DISCUSSION

The Z and E isomers of methyl O-methyl cinnamohydroximate were synthesized according to the procedure described in chapter IV.



Z



E

FIGURE 5. Z and E Methyl O-methylcinnamohydroximate

Synthesizing and separating the Z and E isomers of methyl O-methylcinnamohydroximate proved to be complicated. When starting the synthesis, a solution of methyoxylamine hydrochloride and triethylamine were added to the cinnamoyl chloride which gave the cinnamohydroximate. The reaction produced an orange gelatinous material that proved to be difficult to separate by column chromatography. The separation only yielded minuscule amounts of a white powdery solid. An alternate procedure was then attempted. Methoxylamine hydrochloride and pyridine were combined with the cinnamoyl chloride resulting in a much better product that was able to be purified by recrystallization using chloroform and hexane. The cinnamohydroxamate was then reacted with phosphorus pentachloride to create (Z) O-methylcinnamohydroximoyl chloride as an orange semi-solid that was purified by microdistillation. The cinnamohydroximoyl chloride was then reacted with sodium methoxide in dimethylsulfoxide to give the methyl (Z)-O-

methylcinnamohydroximate. The methyl (Z)-O-methylcinnamohydroximate was then reacted with glacial acetic acid for several hours and quenched with sodium hydroxide (6 M) to produce a mixture of the Z and E isomers of methyl O-methylcinnamohydroximate. The Z and E isomer were then separated using flash column chromatography using a mixture of chloroform and hexane (80:20) as the mobile phase. The progress of the column was followed by thin layer chromatography.

Following purification of the Z and E isomers of methyl O-methylcinnamohydroximate, a kinetic method was developed to use four acids to study the acid-catalyzed reaction rates for the isomerization of the Z and E methyl O-methylcinnamohydroximate.

The acid catalyzed reaction rates for the isomerization of (Z)-methyl O-methylcinnamohydroximate were studied at 24.9 ± 0.01 °C in acetonitrile solution. Aliquots (1 mL) of the reaction were taken at time specific intervals, and quickly quenched by adding ice cold sodium hydroxide solution (0.6 M) which brought the pH > 8. The solutions were then analyzed by high performance liquid chromatography (HPLC) after the pH was brought back to a pH range of 4-7 using potassium dihydrogen phosphate. All solutions were kept on ice before analysis.

The acids used to measure the kinetic constants were trifluoromethane sulfonic acid (CF_3SO_3H), trichloroacetic acid (CCl_3COOH), dichloroacetic acid ($Cl_2CHCOOH$) and monochloroacetic acid ($ClCH_2COOH$).

Analyzing the results proved unsuccessful. One possible reason for this discrepancy in the kinetic data is the fact that there was condensation build up in the flasks and on the equipment that was being used. The condensation could have resulted from an air leak inside the dry box.

Results show that isomerization did take place and was occurring at a rate much higher than expected. However, after several weeks the acids no longer isomerized to the Z or E isomers, even under the original conditions.

Table 1 contains the data from the kinetic reaction of (E) methyl O-methylcinnamohydroximate to (Z) methyl O-methylcinnamohydroximate in acetonitrile containing trichloroacetic acid at 25 °C. Figure 6 shows the plot for the first order isomerization of (E)-methyl O-methylcinnamohydroximate in acetonitrile containing trichloroacetic acid. As it is clearly visible, there was no isomerization that took place, therefore no calculations could be obtained from this data.

Table 2 contains the data from the kinetic reaction of (Z)-methyl O-methylcinnamohydroximate to (E)-methyl O-methylcinnamohydroximate in acetonitrile containing trichloroacetic acid at 25 °C. Figure 7 shows the plot for the first order isomerization of (Z)-methyl O-methylcinnamohydroximate in acetonitrile containing trichloroacetic acid. The rate of reaction occurred to quickly (< 1 minute) for us to determine the rate of reaction and no accurate data could be obtained.

Table 3 contains the data from the kinetic reaction of (Z)-methyl O-methylcinnamohydroximate to (E)-methyl O-methylcinnamohydroximate in acetonitrile containing trichloroacetic acid at 25 °C. This reaction was run with a 1:5 ratio for the hydroximate to the acid. Figure 8 shows the plot for the first order isomerization of (Z)-methyl O-methylcinnamohydroximate in acetonitrile containing trichloroacetic acid. The rate of reaction occurred to quickly (< 1 minute) for us to determine the rate of reaction and no accurate data could be obtained.

Table 4 contains the data from the kinetic reaction of (Z)-methyl O-methylcinnamohydroximate to (E)-methyl O-methylcinnamohydroximate in acetonitrile containing trichloroacetic acid at 25 °C. This reaction was run with a 1:2 ratio for the hydroximate to the acid. Figure 9 shows the plot for the first order isomerization of (Z)-methyl O-methylcinnamohydroximate in acetonitrile containing trichloroacetic acid. As can be seen, there was no isomerization and the rate of the reaction could not be calculated.

Table 5 contains the data from the kinetic reaction of (Z)-methyl O-methylcinnamohydroximate to (E)-methyl O-methylcinnamohydroximate in acetonitrile containing trichloroacetic acid at 25 °C. The concentration of the trichloroacetic acid was brought back to its original concentration of 0.0173 M. Figure 10 shows the plot for the first order isomerization of (Z)-methyl O-methylcinnamohydroximate in acetonitrile containing trichloroacetic acid. As can be seen, there was no isomerization and the rate of the reaction could not be calculated.

Table 6 contains the data from the kinetic reaction of (Z)-methyl O-methylcinnamohydroximate to (E)-methyl O-methylcinnamohydroximate in acetonitrile containing dichloroacetic acid at 25 °C. Figure11 shows the plot for the first order isomerization of (Z)-methyl O-methylcinnamohydroximate in acetonitrile containing dichloroacetic acid. The rate of reaction occurred to quickly (< 1 minute) for us to determine the rate of reaction and no accurate data could be obtained.

Table 7 contains the data from the kinetic reaction of (Z)-methyl O-methylcinnamohydroximate to (E)-methyl O-methylcinnamohydroximate in acetonitrile containing dichloroacetic acid at 25 °C. This reaction was run with a 1:5 ratio for the

hydroximate to the acid. Figure 12 shows the plot for the first order isomerization of (Z)-methyl O-methylcinnamohydroximate in acetonitrile containing dichloroacetic acid. As can be seen, there was no isomerization and the rate of the reaction could not be calculated.

Table 8 contains the data from the kinetic reaction of (Z)-methyl O-methylcinnamohydroximate to (E)-methyl O-methylcinnamohydroximate in acetonitrile containing dichloroacetic acid at 25 °C. The concentration of the dichloroacetic acid was brought back to its original concentration of 0.0173 M. Figure 13 shows the plot for the first order isomerization of (Z)-methyl O-methylcinnamohydroximate in acetonitrile containing dichloroacetic acid. As can be seen, there was no isomerization and the rate of the reaction could not be calculated.

Table 9 contains the data from the kinetic reaction of (Z)-methyl O-methylcinnamohydroximate to (E)-methyl O-methylcinnamohydroximate in acetonitrile containing monochloroacetic acid at 25 °C. The concentration of the monochloroacetic acid at its original concentration. Figure 14 shows the plot for the first order isomerization of (Z)-methyl O-methylcinnamohydroximate in acetonitrile containing monochloroacetic acid. As can be seen, there was no isomerization and the rate of the reaction could not be calculated.

No clear data could be obtained from the isomerization using trifluoromethansulfonic acid.

TABLE 1. Data from Experiment 1 for the Isomerization of (E)-methyl O-methylcinnamohydroximate in Acetonitrile Containing Trichloroacetic Acid at 25 °C

$[CCl_3COOH] = 0.0173$ M, [isomer] = 5.719×10^{-04} M

Time (sec)	% E	$\ln(C_o/C)$
1200	5.2	2.95
1800	5.3	2.94
2400	4.7	3.06
3000	3.4	3.39
3600	2.2	3.83
4200	3.4	3.37
4800	2.7	3.63
6600	3.6	3.31
7800	35	3.35
8400	3.4	3.38
9000	3.3	3.40
9600	4.3	3.15
10200	3.9	3.25
11400	3.7	3.31
13200	5.7	2.87

$[CCl_3COOH] = 0.0173$ M, [isomer] = 5.719×10^{-04} M

$y = -5.0x10^{-06}x + 3.3139$

$r^2 = 0.0061$

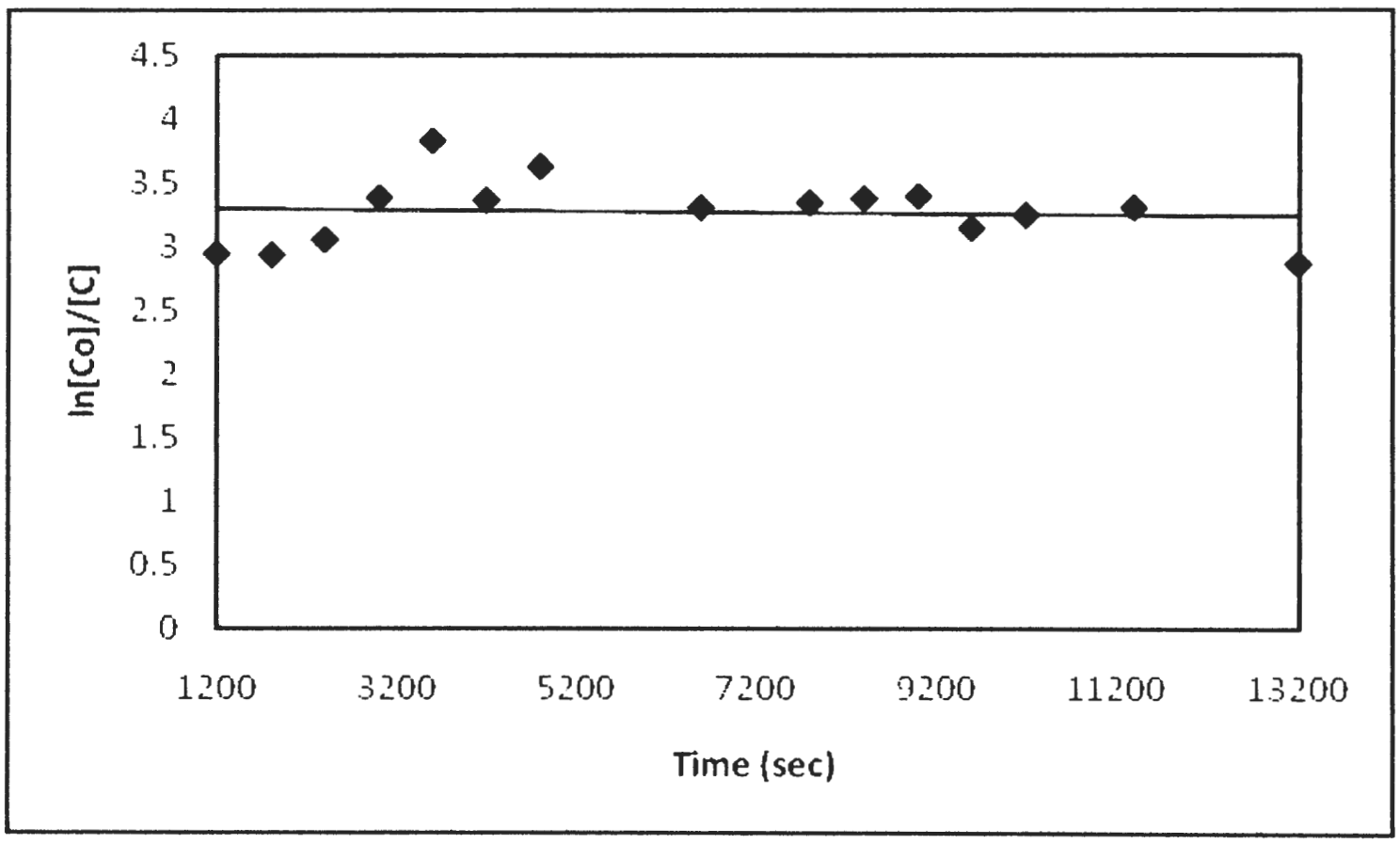


FIGURE 6. First order plot for the isomerization of (E)-methyl O-methylcinnamohydroximate in acetonitrile containing trichloroacetic acid.

TABLE 2. Data from Experiment 1 for the Isomerization of (Z)-methyl O-methylcinnamohydroximate in Acetonitrile Containing Trichloroacetic Acid at 25 °C

$[CCl_3COOH] = 0.0173$ M, [isomer] = 5.688×10^{-05} M

Time (sec)	% Z	$\ln(C_o/C)$
54	72.1	0.327
5066	74.5	0.294
16192	75.1	0.287

$[CCl_3COOH] = 0.0173$ M, [isomer] = 5.688×10^{-05} M

$y = -2.0x10^{-04}x + 0.3181$

$r^2 = 0.7048$

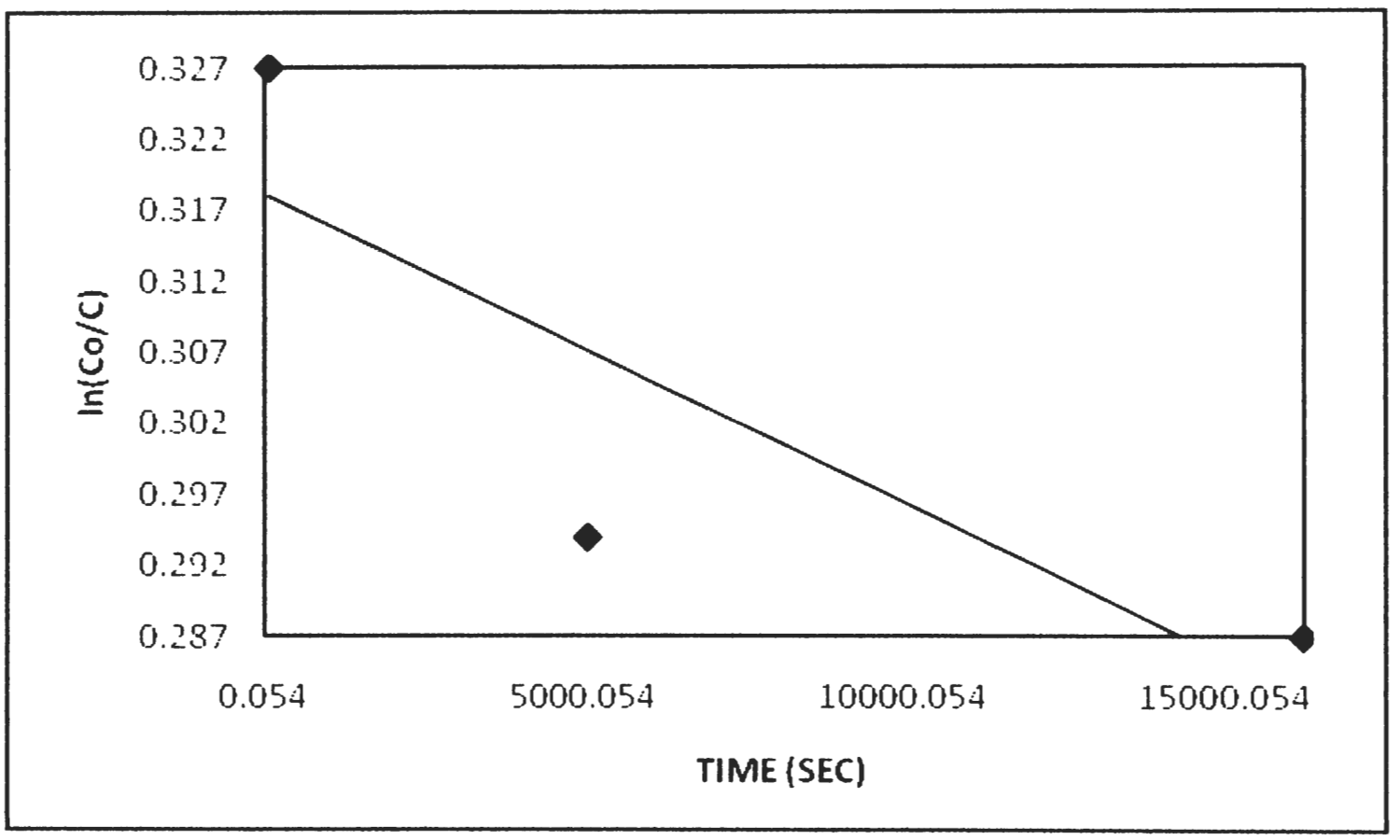


FIGURE 7. First order plot for the isomerization of (Z)-methyl O-methylcinnamohydroximate in acetonitrile containing trichloroacetic acid

TABLE 3. Data from Experiment 2 for the Isomerization of (Z)-methyl O-methylcinnamohydroximate in Acetonitrile Containing Trichloroacetic Acid At 25 °C

$[CCl_3COOH] = 2.87x10^{-03}$ M, [isomer] = 5.688×10^{-05} M

Time (sec)	% Z	$\ln(C_o/C)$
26	78.6	0.241
5202	79.1	0.234
16335	83.2	0.184

$[CCl_3COOH] = 2.87x10^{-03}$ M, [isomer] = 5.688×10^{-05} M

$y = -4.0x10^{-06}x + 0.2459$

$r^2 = 0.9594$

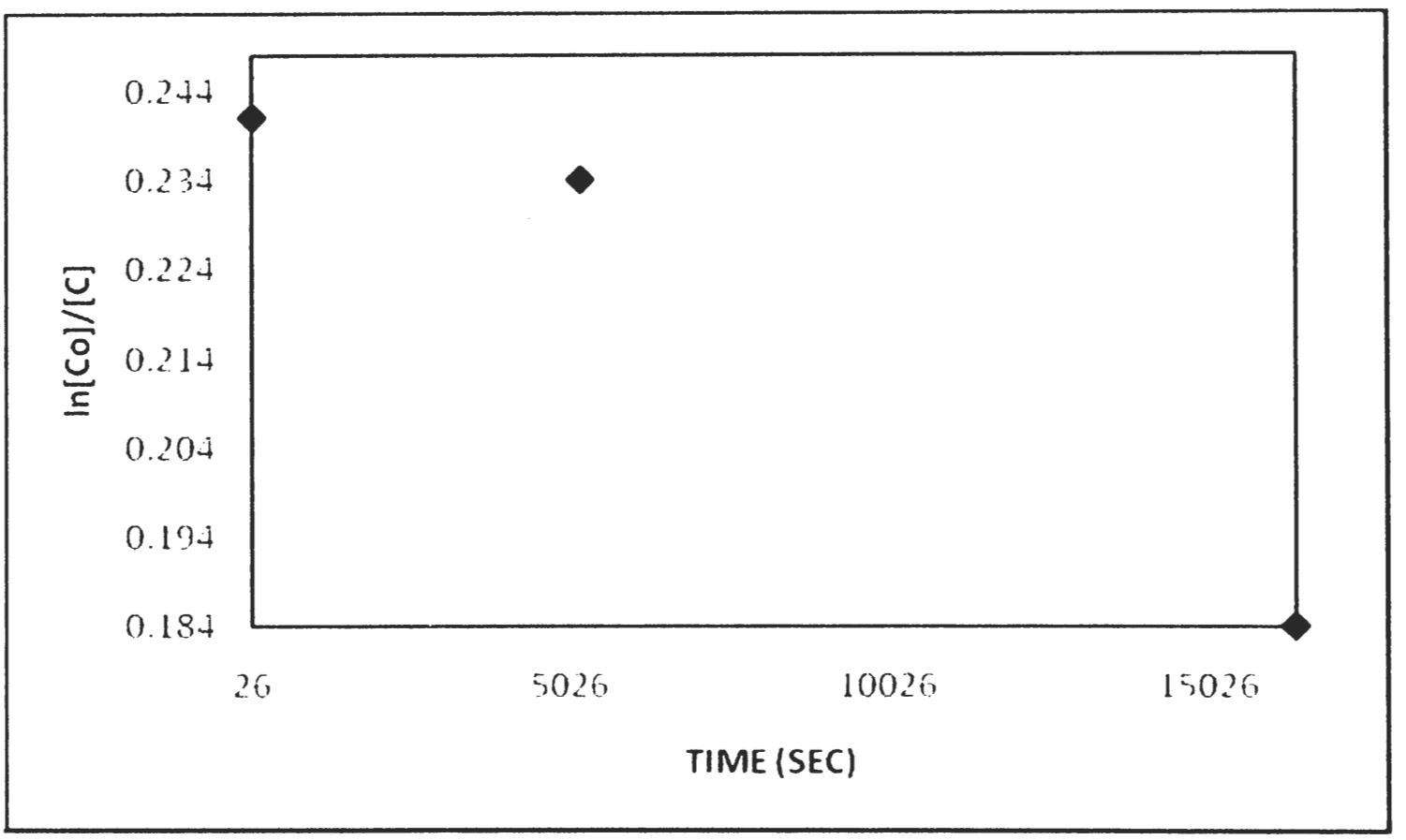


FIGURE 8. First order plot for the isomerization of (Z)-methyl O-methylcinnamohydroximate in acetonitrile containing trichloroacetic acid

TABLE 4. Data from Experiment 3 for the Isomerization of (Z)-methyl O-methylcinnamohydroximate in Acetonitrile Containing Trichloroacetic Acid at 25 °C

$[CCl_3COOH] = 1.1712x10^{-04}$ M, [isomer] = 5.688×10^{-05} M

Time (sec)	% Z	$\ln(C_o/C)$
21	100	0
6554	100	0
84128	100	0
251831	100	0

$[CCl_3COOH] = 1.1712x10^{-04}$ M, [isomer] = 5.688×10^{-05} M

$y = 0$

$r^2 = N/A$

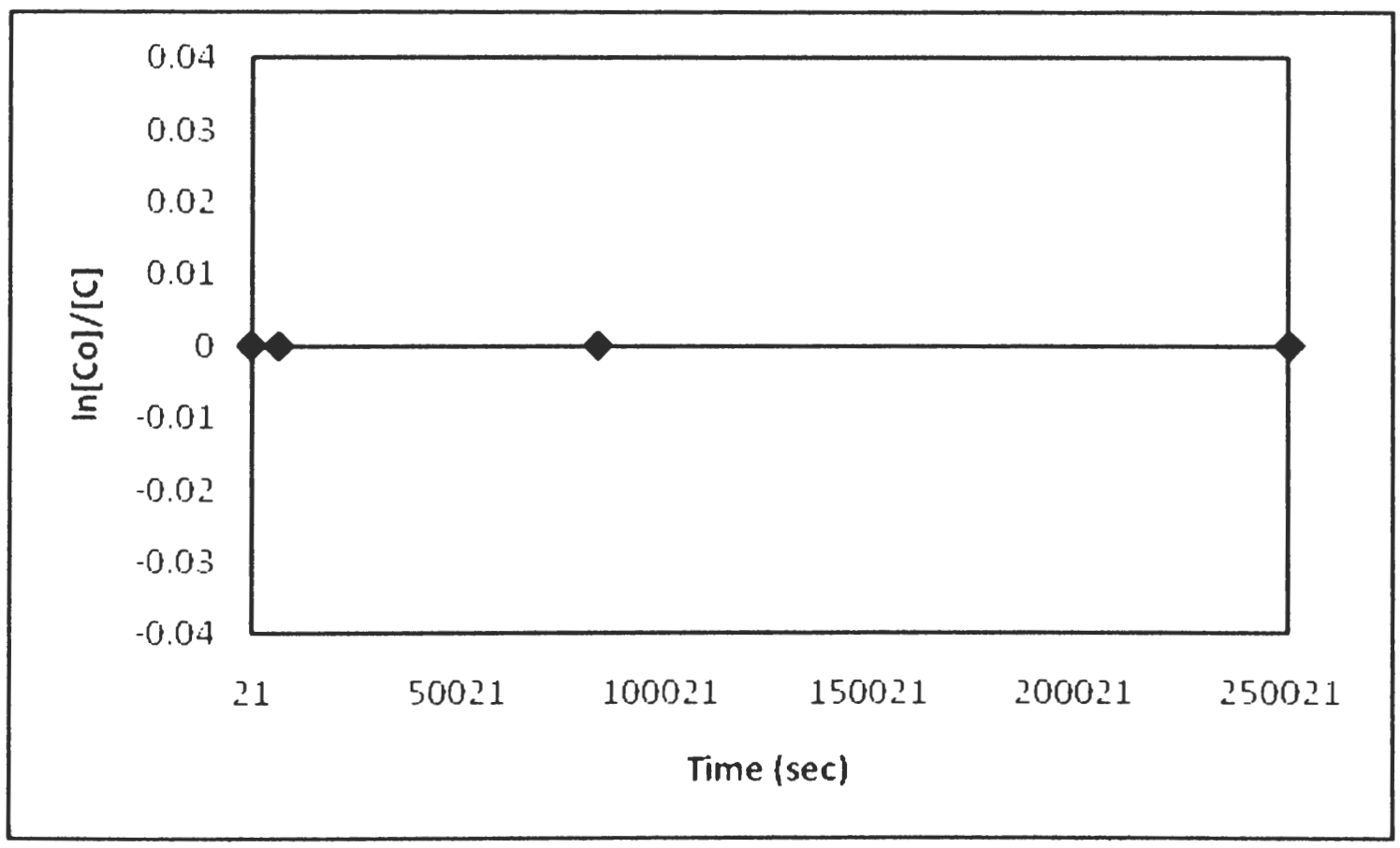


FIGURE 9. First order plot for the isomerization of (Z)-methyl O-methylcinnamohydroximate in acetonitrile containing trichloroacetic acid

TABLE 5. Data from Experiment 4 for the Isomerization of (Z)-methyl O-methylcinnamohydroximate in Acetonitrile Containing Trichloroacetic Acid at 25 °C

$[CCl_3COOH] = 0.0173$ M, [isomer] = 5.688×10^{-05} M

Time (sec)	% Z	$\ln(C_o/C)$
21	100	0
8663	100	0
71579	100	0

$[CCl_3COOH] = 0.0173$ M, [isomer] = 5.688×10^{-05} M

$y = 0$

$r^2 = N/A$

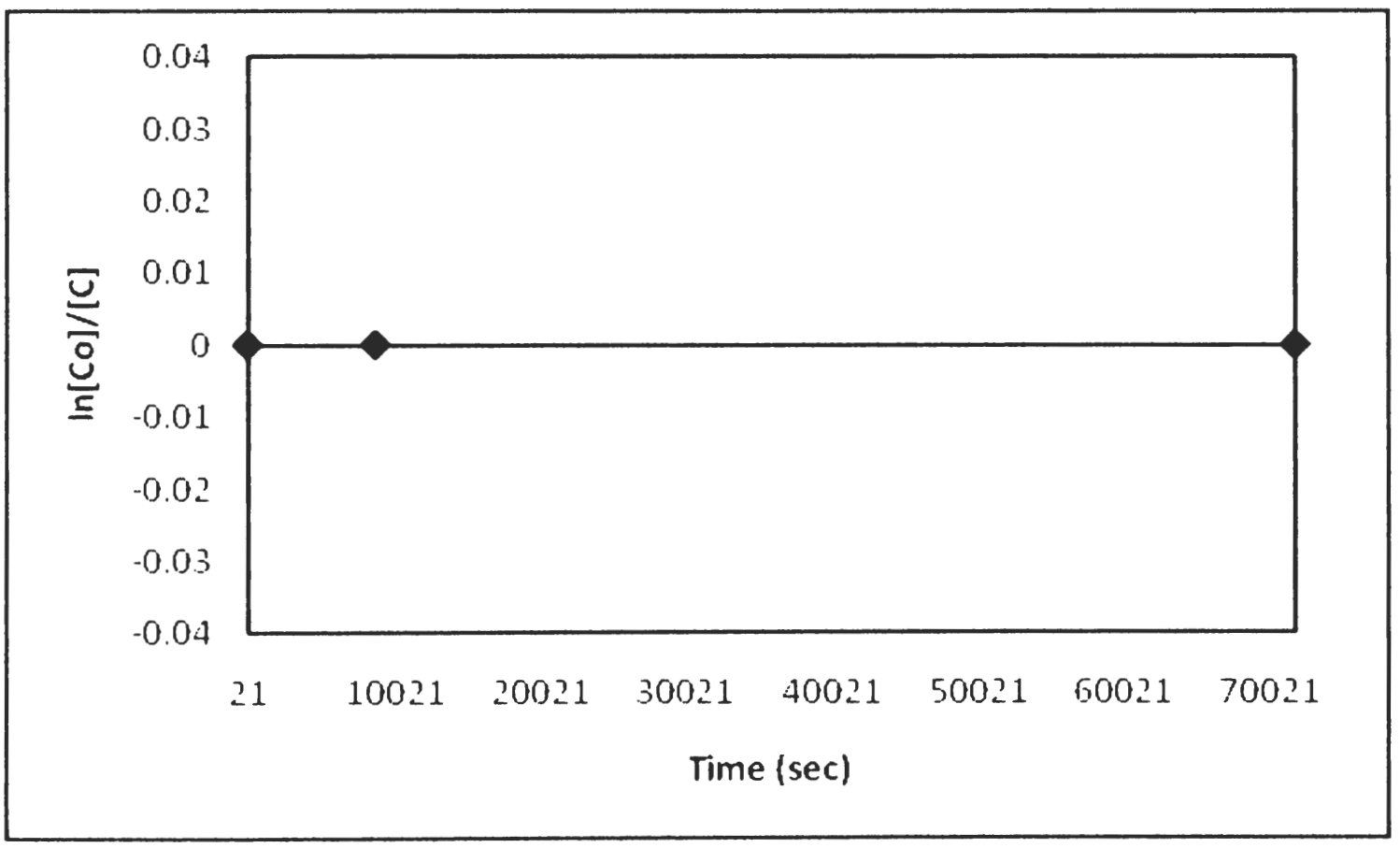


FIGURE 10. First order plot for the isomerization of (Z)-methyl O-methylcinnamohydroximate in acetonitrile containing trichloroacetic acid

TABLE 6. Data from Experiment 1 for the Isomerization of (Z)-methyl O-methylcinnamohydroximate in Acetonitrile Containing Dichloroacetic Acid at 25 °C

$[Cl_2CHCOOH] = 0.0713$ M, [isomer] = 5.688×10^{-05} M

Time (sec)	% Z	$\ln(C_o/C)$
44	73.8	0.303
9884	77.5	0.255
32084	79.1	0.234

$[Cl_2CHCOOH] = 0.0173$ M, [isomer] = 5.688×10^{-05} M

$y = -2.0x10^{-06}x + 0.2913$

$r^2 = 0.8175$

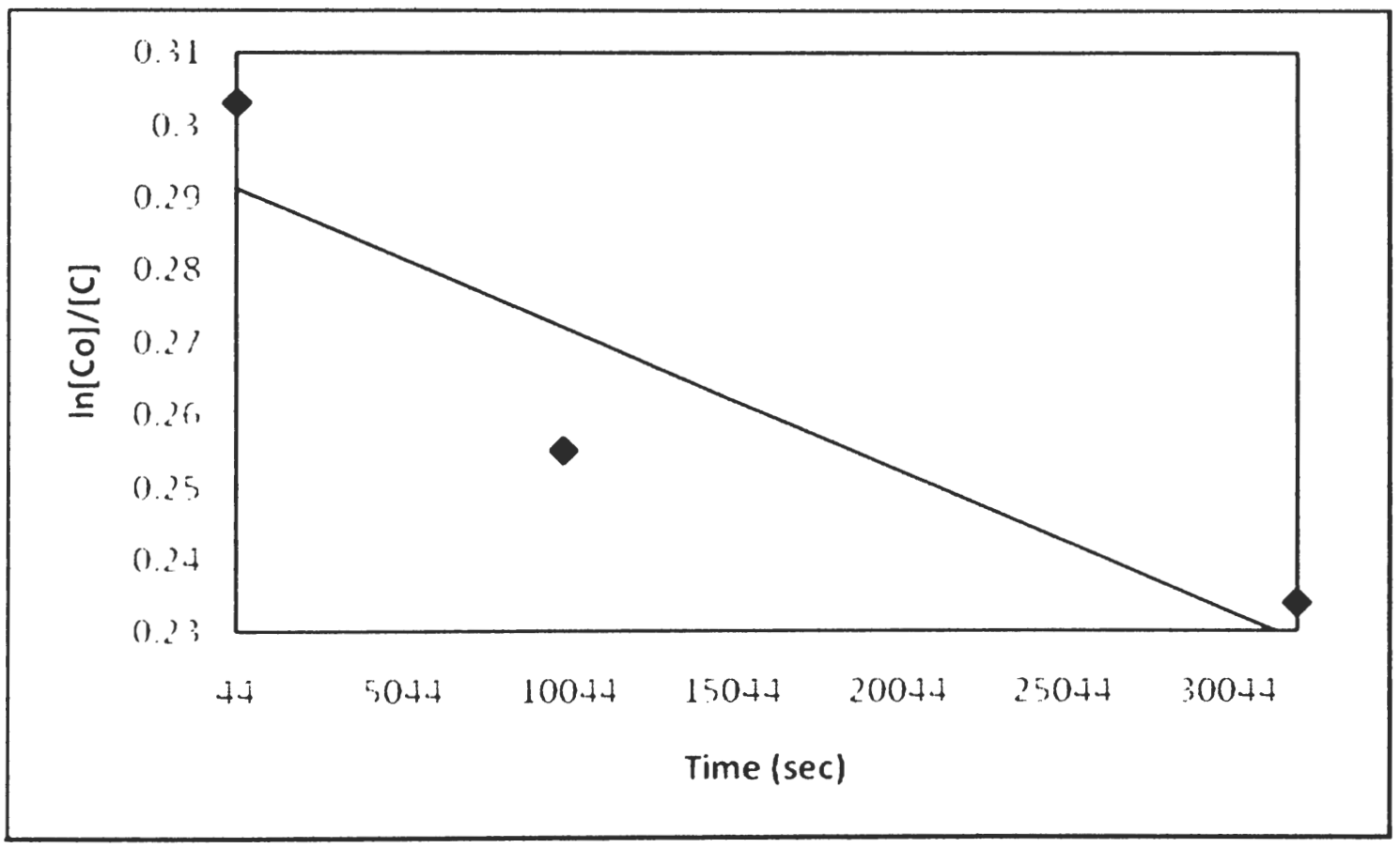


FIGURE 11. First order plot for the isomerization of (Z)-methyl O-methylcinnamohydroximate in acetonitrile containing dichloroacetic acid

TABLE 7. Data from Experiment 2 for the Isomerization of (Z)-methyl O-methylcinnamohydroximate in Acetonitrile Containing Dichloroacetic Acid at 25 °C

$[Cl_2CHCOOH] = 2.87x10^{-03}$ M, [isomer] = 5.688×10^{-05} M

Time (sec)	% Z	$\ln(C_0/C)$
33	100	0
8741	100	0
71643	100	0

$[Cl_2CHCOOH] = 2.87x10^{-03}$ M, [isomer] = 5.688×10^{-05} M

$y = 0$

$r^2 = N/A$

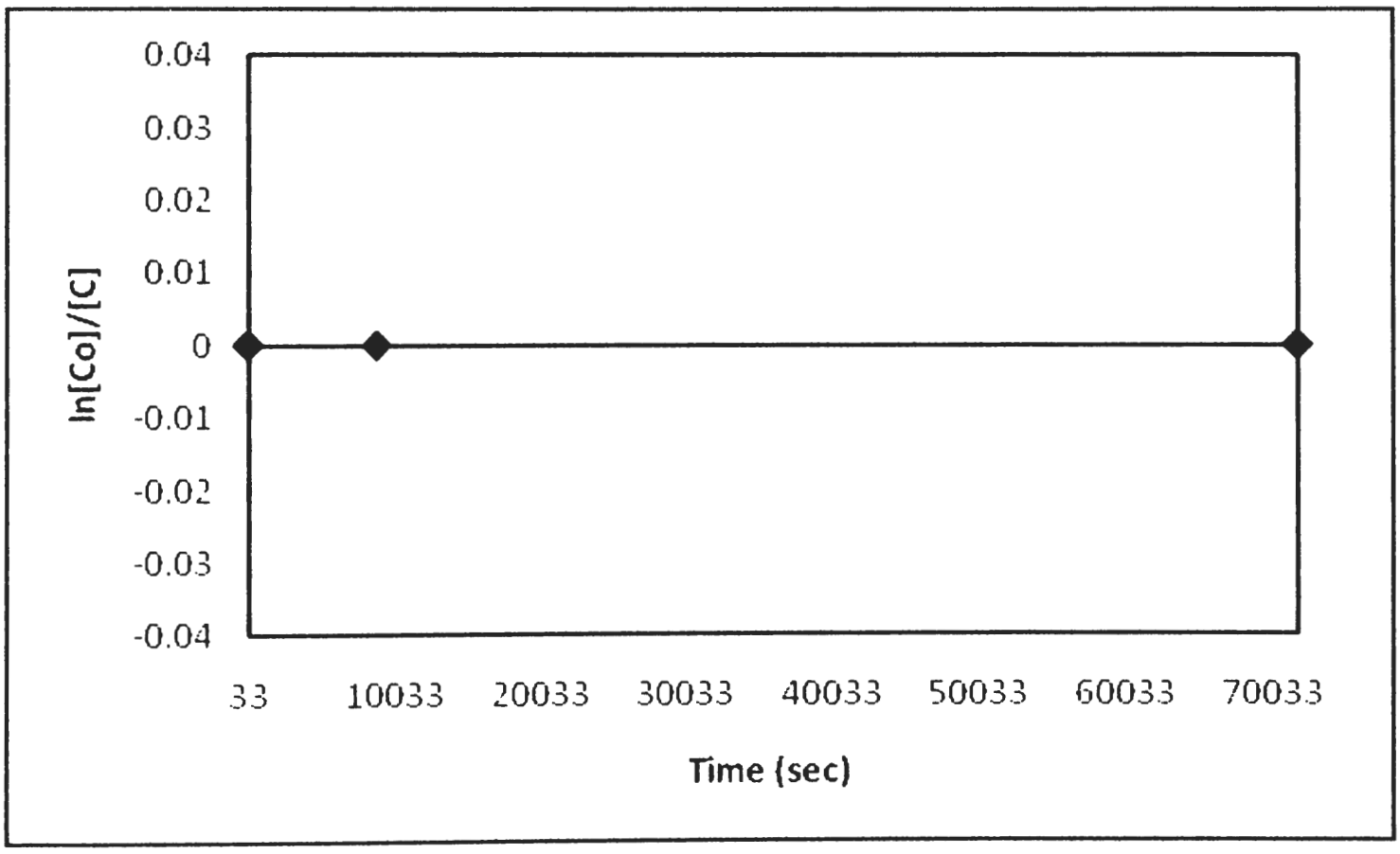


FIGURE 12. First order plot for the isomerization of (Z)-methyl O-methylcinnamohydroximate in acetonitrile containing dichloroacetic acid

TABLE 8. Data from Experiment 3 for the Isomerization of (Z)-methyl O-methylcinnamohydroximate in Acetonitrile Containing Dichloroacetic Acid at 25 °C

$[Cl_2CHCOOH] = 0.0713$ M, [isomer] = 5.688×10^{-05} M

Time (sec)	% Z	$\ln(C_o/C)$
41	100	0
78905	100	0
190818	100	0

$[Cl_2CHCOOH] = 0.0173$ M, [isomer] = 5.688×10^{-05} M

$y = 0$

$r^2 = N/A$

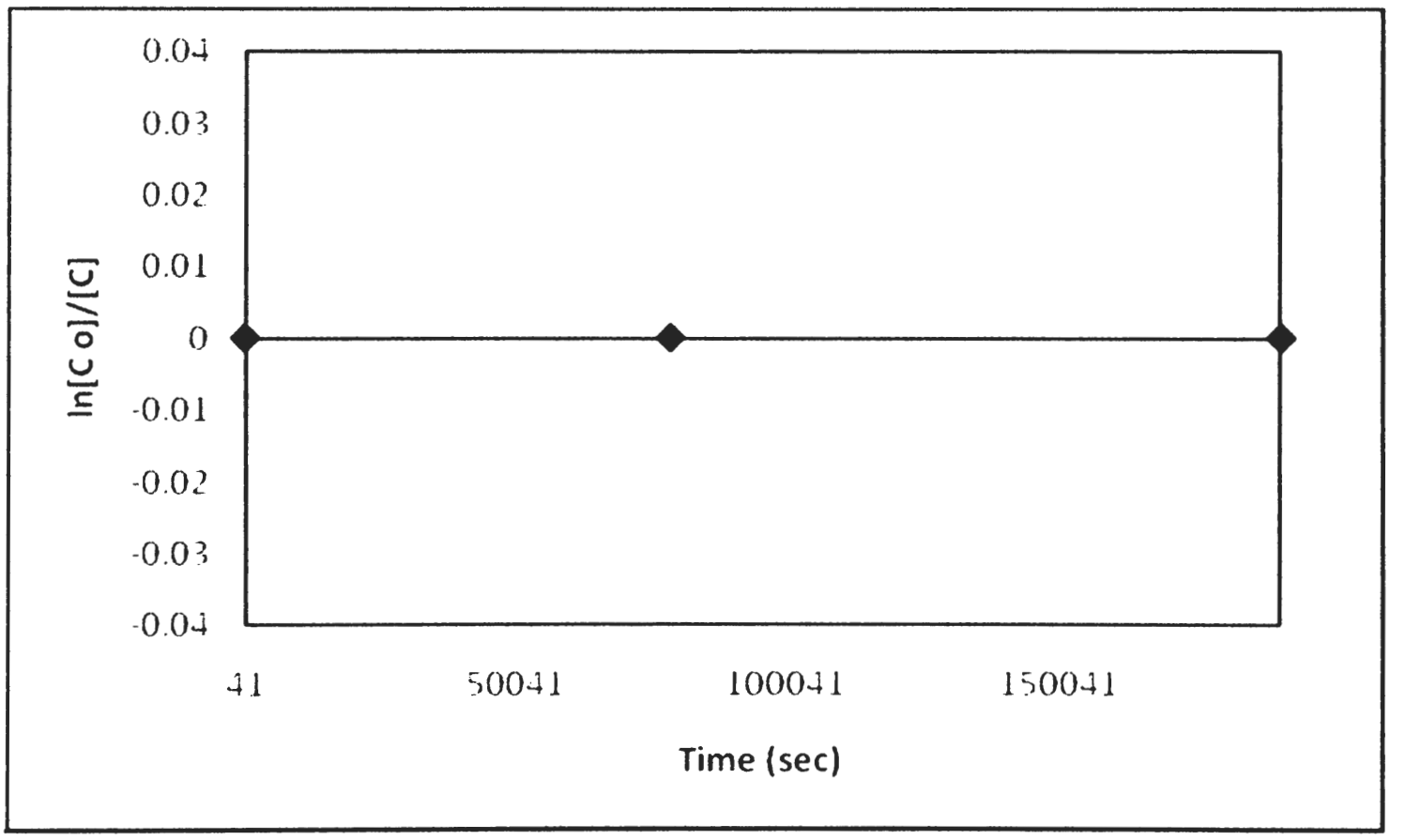


FIGURE 13. First order plot for the isomerization of (Z)-methyl O-methylcinnamohydroximate in acetonitrile containing dichloroacetic acid

TABLE 9. Data from Experiment 1 for the Isomerization of (Z)-methyl O-methylcinnamohydroximate in Acetonitrile Containing Monochloroacetic Acid at 25 °C

$[ClCH_2COOH] = 0.0713$ M, [isomer] = 5.688×10^{-05} M

Time (sec)	% Z	$\ln(C_o/C)$
21	100	0
6554	100	0
84128	100	0
251831	100	0

$[ClCH_2COOH] = 0.0173$ M, [isomer] = 5.688×10^{-05} M

$y = 0$

$r^2 = N/A$

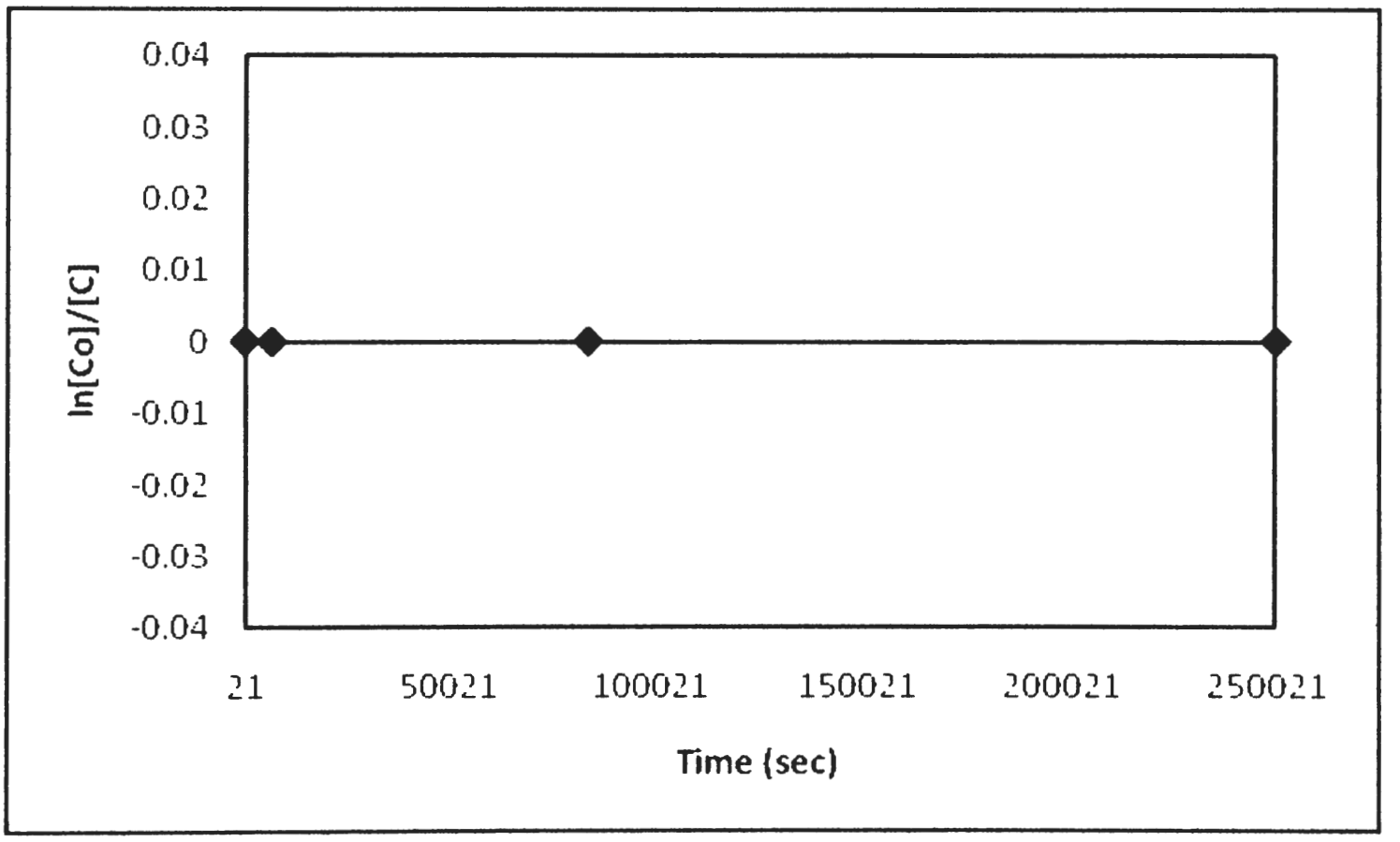


FIGURE 14. First order plot for the isomerization of (Z)-methyl O-methylcinnamohydroximate in acetonitrile containing monochloroacetic acid

CHAPTER III

EXPERIMENTAL SECTION

General Procedures

All chemicals used in this research are reagent grade unless otherwise noted. Methyl O-methylcimmanohydroximate was synthesized according to the procedure outlined in chapter IV. Melting points were determined on a Mel-Temp capillary melting point apparatus and are uncorrected. Mass spectra were determined on a Varian Saturn 2200 GC/MS spectrometer fitted with a J and W DM5MS (I.D. of 0.25 mm and a length of 30 m, coated with 0.25 μm film of 5% phenylmethylpolysiloxane).

The HPLC was a Gilson, with a Grace Alltima C8 5u HPLC column. The mobile phase used to monitor the kinetics of the Z and E methyl O-methylcinnamohydroximate was 60:40 of acetonitrile:water (volume/volume). Retention times and normalization factors for peak areas were determined by analysis of a sample containing known amounts of reactants and products.

Kinetic Method

Volumetric flasks and 50 mL Erlenmeyer flasks were dried in an oven for at least one hour at 100° C. After they were dried they were placed in a dessicator, and allowed to cool.

A stock solution of (Z)-methyl O- methylcinnamohydroximate was prepared as follows:

(Z)-Methyl O-methylcinnamohydroximate was weighed into a 50 mL volumetric flask on an analytical balance. Fresh acetonitrile was quickly pipetted into the flask to the mark and the flask was capped and shaken.

A 25 mL volumetric flask and two Erlenmeyer flasks with stoppers were placed in a dry box. The chamber was purged with nitrogen during the preparation of the samples. An acid was weighed into a volumetric flask on an analytical balance. Acetonitrile was added into the flask to the mark. The volumetric flask was capped and shaken. About 8 mL of this acid solution was poured into an Erlenmeyer flask, and 8 mL of acetonitrile was added. The flasks were corked and removed from the dry box.

The stock solution (2 mL) was pipetted into another 25 mL volumetric flask, which had been purged with nitrogen. Acetonitrile (18 mL) was added to the flask.

The 25 mL volumetric flask containing the Z hydroximate and the acid solution were placed in a water bath at 24.9 ± 0.01° C for at least 30 minutes. Once the solutions were thermally equilibrated, 5 mL of the acid solution was pipetted into the 25 mL flask containing the Z hydroximate and the time was started.

The timer was started and aliquots (about 1 mL) were removed at regular intervals. The aliquots were quenched with ice-cold 0.6 M sodium hydroxide (about 3-4 drops) and brought to pH>8.

Samples (20 µl) were injected into a Grace Alltima C8 5u HPLC column attached to a Gilson UV-VIS detector set at 254 nm. A degassed solution of acetonitrile and water (60:40) was used as the mobile phanse. Before the samples were injected into the column, the pH was brought to 4-7 by adding 0.6 M potassium dihydrogen phosphate (about 3-4 drops) The solutions were kept in an ice bath during the analysis.

A correction factor for peak area ratio to concentration ratio was measured using the following procedure. Rate constants were calculated using a linear regression program (excel).

Measurement of the Correction Factor

Volumetric flasks were dried in an oven at 100° C. When they were dried they were placed in a dessicator and allowed to cool to room temperature.

(Z)-Methyl O-methylcinnamohydroximate was weighted into a 50 mL volumetric flask. Approximately the same amount of (E)-methyl O-methylcinnamohydroximate was weighted into another 50 mL volumetric flask. A solution of acetonitrile and water (60:40) was added to the mark in both flasks. The Z and E hydroximate solutions were used to prepare 90:10, 80:20, 70:30, 60:40, 50:50, 40:60, 30:70, 20:80, and 10:90 (volume/volume) solutions.

These solutions were analyzed by HPLC using a flow rate of 0.880 mL/min. Aliquots (20 µl) of the above solutions were injected into the Grace Alltima C8 5u column using degassed acetonitrile and water (60:40) solution as the mobile phase. After

all of the above solutions were analyzed, the ratios of peak areas verses the ratios of molarities were plotted. The equation for the line was used to calculate the correction factor.

Preparation of Acid Solutions Used for Kinetics

Trifluoromethanesulfonic acid, trichloroacetic acid, dichloroacetic acid and monochloroacetic acid.

All of these acids were weighted into a 25 mL volumetric flask in a dry box under a nitrogen atmosphere. All of these solutions were used within two days of preparation.

CHAPTER IV

SYNTHESIS OF ISOMERS

The Z and E isomers of methyl O-methylcinnamohydroximate were synthesized according to the following procedures.

Experimental Section

Methylcinnamohydroxamate. Cinnamoyl chloride (24.9 g, 0.149 mol) in 600 mL of methylene chloride was added to a 1000 mL round bottomed flask fitted with a J-KEM 9900 temperature probe, a dropping funnel, and a gas trap. Methoxylamine hydrochloride (13.8 g, 0165 mol) was added to the stirred solution under a nitrogen atmosphere at room temperature. After the solution was stirred at room temperature for 15 minutes it was cooled to 0° C, pyridine (27.76 g, 0.351 mol) was added dropwise though the dropping funnel. Once all the pyridine was added the mixture was brought back to room temperature and stirred for 2 hours. The solution was then poured into a 2000 mL separatory funnel and extracted with water (3 X 400 mL). The organic layers were then dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporation under vacuum pressure to give a chunky white solid (24.71 g, 0.139 mol, 96.3%). Recrystallization from 50:50 chloroform/hexane mixture gave white crystals: mp 88.1 - 90° C. The reported mp was 93-95° C.

(Z)-O-Methylcinnamohydroximoyl chloride. Methylcinnamohydroxamate (18.01 g, 0.10164 mol) in carbon tetrachloride (25 mL) was placed in a 250 mL round bottomed flask fitted with a condenser, J-KEM temperature probe, and a solid addition funnel. Phosphorous pentachloride (21.17 g, 0.10164 mol) was added slowly though the addition funnel to the stirred solution. With continued addition of phosphorous pentachloride, the solution turned a vivid yellow color with an outflow of gas. The temperature of the solution was maintained between 37-43° C. After the addition of phosphorous pentachloride, the solution was heated to 68° C and maintained at that temperature for 6 hours. The resulting liquid was allowed to cool to room temperature and was then slowly poured into ice-cold water. The mixture was extracted with ether (4 X 100 mL). The ether extracts were then extracted with saturated sodium bicarbonate solution and dried with anhydrous magnesium sulfate. The solvent was removed by rotary evaporation under vacuum pressure to yield a golden oil with a semi-solid at the bottom (12 g, 0.613 mol, 60.3%)

(Z)-Methyl O-Methylcinnamohydroximate. Sodium metal (1.97 g, 0.02854 mol) was dissolved in methanol (25 mL) in a 250 round bottomed flask fitted with a condenser, a dropping funnel, and a J-KEM temperature probe. A solution of (Z)-O-methylcinnamohydroximoyl chloride (5.58 g, 0.0285 mol) in dimethyl sulfoxide (100 mL) was added though the dropping funnel with stirring. The mixture was stirred and heated to 50° C for 3 hours and rapidly cooled to room temperature in an ice-bath. The mixture was then poured into ice-cold water (300 mL). The mixture was extracted with

ether (4 X 100 mL). The ether extracts were dried over anhydrous magnesium sulfate. The ether was removed by rotary evaporation under vacuum pressure to give a yellow oil.

(E)-Methyl O-Methylcinnamohydroximate. A solution of (Z)-methyl O-methylcinnamohydroximate (2.80 g) and glacial acetic acid (100 mL) was heated to 80° C for 4 hours. The reaction mixture was quenched with 6 M NaOH (400 mL) at the end of the reaction period. The resulting solution was extracted with ether (3 X 200 mL). The ether extracts were dried over anhydrous magnesium sulfate, and the ether was evaporated under vacuum pressure. The resulting oil was analyzed by GC/MS to determine the ratio of the Z-hydroximate to the E-hydroximate.

Separation of Z and E isomers. The Z and E isomers were separated using flash column chromatography. A mixture of 80:20 chloroform: hexane was used as the mobile phase. The separation was followed by thin layer chromatography.

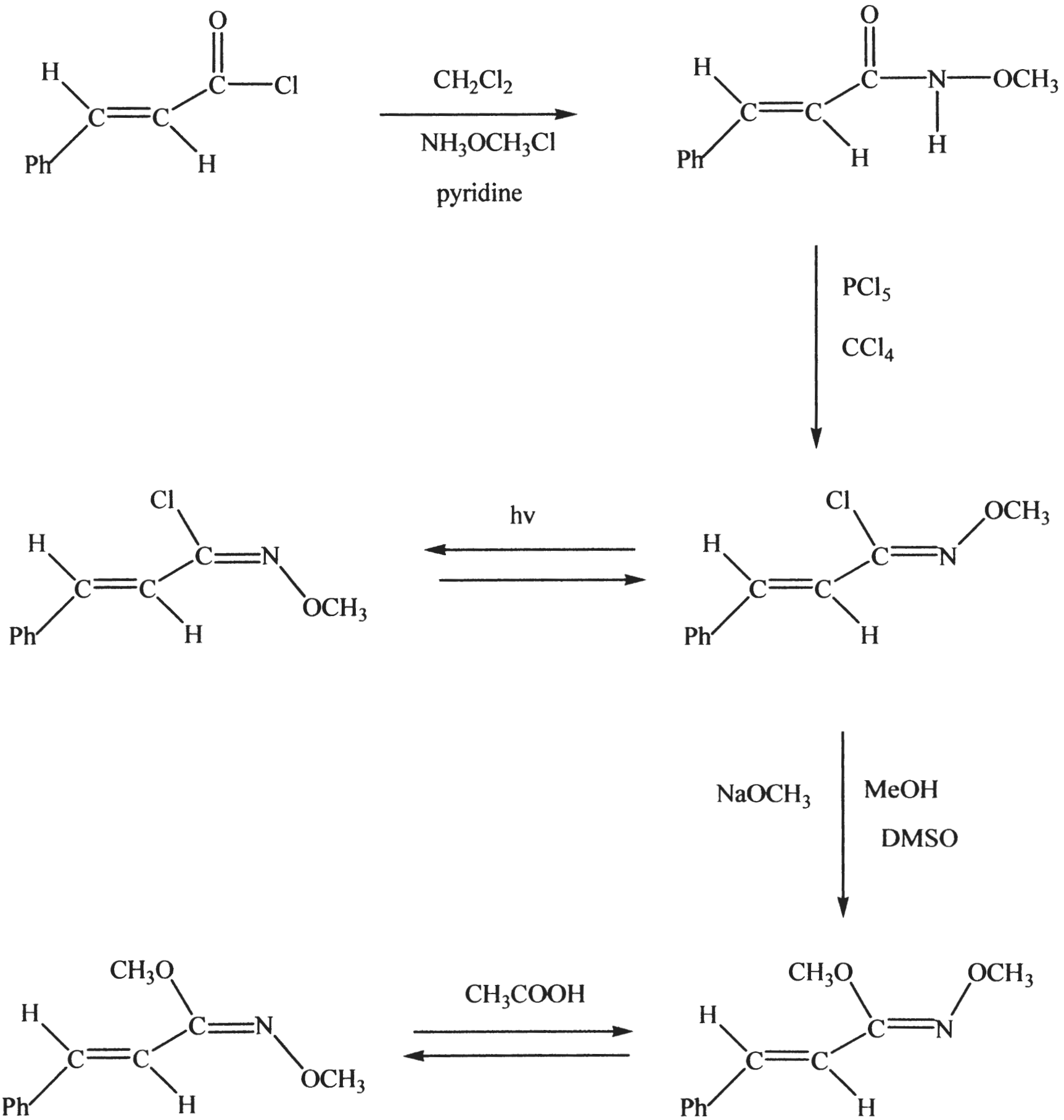


FIGURE 15. Scheme 1

REFERENCES

[1] Childs, R. F.; Shaw, G. S.; and Lock, C. J. L. *J. Am. Chem. Soc.* **1989**, *111*, 5424-5429.

[2] Pankratz, M.; and Childs, R. F. *J. Org. Chem.* **1985**, *50* 4553-4558

[3] Childs, R. F.; and Dickie, B.D. *J. Am. Chem. Soc.,* **1983**, *105*, 5041-5046

[4] Lowry, Thomas H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry* 3rd ed.; Harper and Rowe: New York, 1987, p 491, p 702-709.

[5] Padwa A.; Albrecht, F. *J. Am. Chem. Soc.,* **1974**, *96*, 4849-4857

[6] Satterthwait, A.C.; Jencks, W.P. *J. Am. Chem. Soc.,* **1974**, *96*, 7045-7052

[7] Johnson, J. E..; Nalley, E. A.; Weidig, C.; Arfan, M. *J. Org. Chem.* **1981,** *46,* 3626-3629.

[8] Johnson, J. E.; Riesgo, E. C.; Jano, I. *J. Org. Chem.* **1996,** *61*, 45-50

[9] Conlon, P. R.; Sayer, J. M. *J. Org. Chem.* **1979,** *44*, 262-267.

[10] Johnson, J. E.; Nalley, E. A.; Kunz, Y. K.; Springfield, J. R. *J. Org. Chem.* **1976,** *41,* 252-259.

[11] Walter, W.; Meese, C. O.; Schroder, B. *Liebigs Ann. Chem.* **1975,** 1455-1464

[12] Johnson, J. E.; Silk, N. M.; Arfan, M. *J. Org. Chem.* **1982,** *47,* 1958-1961.

[13] Johnson, J. E.; Ghafouripour, A.; Arfan, M.; Todd, A. L.' Sitz, A. A. *J. Org. Chem.* **1985**, *50,* 3348-3355.

[14] Rowe, J. E.; Lee, K.; Dolliver, D. D.; Johnson, J. E. *Aust. J. Chem.* **1999,** *52*, 807-811.

[15]Miyata, O.; Koizumi, T.; Ninomiya, I.; Naito, T. *J. Org. Chem,* **1996,** *61*, 9078-9079.

[16] Curtin, D. Y.; Crubbs, E. J.; and McCarty, C. G. *J. Am. Chem. Soc.* **1966,** *88* 2775-2786

[17] Kessler H. and Leibfritz, D. *Chem. Ber.* **1971,** *104,* 2143-2157

[18] Yamataka, H.; Ammal, S. C.; Asano, T.; Ohga, Y. *Bull. Chem. Soc. Jpn.* **2005,** *78,* 1851-1855.

[19] Idoux, J. P. and Sikorski, J. A. *J. Am. Chem. Soc., Perkin Trans. 2* **1972,** 921-923.

[20] Jennings, W. B.; Al-Showiman, S.; Tolley, M. S.; Boyd, D. R. *J. Chem. Soc. Perkin Trans. 2* **1975,** 1535-1539.

[21] Holloway, C. E. and Vuik C. P. J. *Tetrahedron Lett.* **1979,** 1017-1020.

[22] Dignam, K. J. and Hegarty, A. F. *J. Chem. Soc. Perkin Trans. 2* **1979,** 1437-1443

[23] Cunningham I. D. and Hegarty, A. F. *J. Chem. Soc. Perkin Trans. 2* **1986,** 537-541

[24] Johnson, J. E.; Silk, N. M.; Nalley, E. A.; and Arfan, M. *J. Org. Chem.* **1981,** *46,* 546-552

[25] Johnson, J. E.; Morales, N. M.; Gorczyca, A. M.; Dolliver, D. D.; McAllister, M. A.; *J. Org. Chem* **2001,** *66,* 7979-7985.

[26] Nsikabaka, S.; Harb, W. and Ruiz-Lopez, M. F. *THERMOCHEM,* **2006,** *764,* 161-166.

[27] Johnson, J. E.; Todd, S. L.; Gardner, J. L.; Gardner, T. M.; Buck, P.; Ghafouripour, A.; Zimmerman, W. *J. Phys. Org. Chem* **1994**, *7,* 352-358.

[28] Johnson, J. E.; Jano, I.; McAllister, M. A. *J. Phys. Org. Chem.* **1999,** *12,* 1-7

[29] Kolthoff, I.M.; Chantooni, M. K. Jr. *J. Chem Eng. Data,* **1999,** *44,* 124-129.

[30] Johnson, J.E and Dia, H.; unpublished work.