SYNTHESIS, HPLC AND NMR STUDIES ON AXIALLY CHIRAL PYRIDINE COMPOUNDS AS POTENTIAL BIDENTATE N,N'-LIGANDS

by

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To my beloved parents, siblings

and to all people who believe in science

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ABSTRACT

SYNTHESIS, HPLC AND NMR STUDIES ON AXIALLY CHIRAL PYRIDINE COMPOUNDS AS POTENTIAL BIDENTATE N, N'-LIGANDS

In this study, axially chiral enantiomeric and diastereomeric 2-arylimino-3-aryl-thiazolidine-4-ones have been synthesized and their stereostructures have been investigated. In these compounds, the rotation around N_3-aryl bond is restricted resulting in axial chirality. Therefore, M and P enantiomers or RM, RP and SM, SP diastereomers exist. Enantiomeric and diastereomeric isomers of the compounds have been investigated by ^{1}H-NMR and HPLC. In 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidine-4-one, it was found that the rotation around N_3-aryl bond is too fast to make the enantiomeric isomer separation observable by enantioselective HPLC. On the other hand, the interconversion rate between the enantiomers of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidine-4-one and the energy barrier for this compound have been determined by thermal racemization of the micropreparatively resolved enantiomers. Rotational barrier of the diastereomers of 5-methyl-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino) thiazolidine-4-one has also been determined by following the interconversion between the unequally populated diastereomers with time by HPLC. Also, 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidine-4-thione was synthesized by converting the C-4 carbonyl oxygen to a sulphur atom via the Lawesson Reagent. It was found that replacing one C-5 proton with a methyl group decreased the rotational barrier by 2.2 kJ/mol. On the other hand, replacing C-4 carbonyl oxygen with a sulphur atom increased the barrier by 18.3 kJ/mol.

ÖZET

POTANSİYEL İKİ DİŞLİ N, N'-LİGANT OLAN EKSENSEL KİRAL PİRİDİN BİLEŞİKLERİ ÜZERİNDE SENTEZ, HPLC VE NMR ÇALIŞMALARI

Bu çalışmada, eksensel kiral enantiomerik ve diastereomerik 2-arilimino-3-aril-tiyoazlidin-4-on türevleri sentezlenmiştir ve bu türevlerin stereoyapıları incelenmiştir. Bu bileşiklerde, N_3-aril bağındaki eksensel kiraliteye neden olan dönme engellidir. Bu nedenle, M ve P enantiomerleri veya RM, RP ve SM, SP diastereomerleri mevcuttur. Bu bileşiklerin enantiomerik ve diastereomerik izomerleri ^{1}H-NMR ve HPLC kullanılarak incelendi. 3-(piridin-2-yl)-2-(piridin-2-ylimino)tiyoazlidin-4-on türevinde, N_3-aril bağı etrafındaki dönmenin enantiomerik izomer ayrışmasının enantio seçici HPLC ile gözlemlenmesini önleyecek derecede hızlı olduğu bulundu. Diğer taraftan, 3-(3-metilpiridin-2-yl)-2-(3-metilpiridin-2-ylimino)tiyoazlidin-4-on bileşiğinde enantiomerlerin birbirlerine dönüşme hızları ve enerji bariyerleri mikro preparatif yöntemle ayrılan enantiomerlerin termal rasemikleşmesi ile bulundu. 5-metil-3-(3-metilpiridin-2-yl)-2-(3-metilpiridin-2-ylimino)tiyoazlidin-4-on diastereomerlerinin rotasyonel bariyeri de eşit dağılmamış diastereomerlerin zamanla kiral kolon üzerinde HPLC ile birbirlerine dönüşmeleri dengeye gelinceye kadar izlenilerek bulundu. Ayrıca, heterosiklik halkanın C-4 pozisyonunda bulunan sübstitüent grupların etkisini anlamak amacıyla, 3-(3-metilpiridin-2-yl)-2-(3-metilpiridin-2-ylimino)tiyoazlidin-4-tiyon ürünü C-4 pozisyonunda bulunan karbonil oksijeninin Lawesson Reaktifi üzerinden sülfür atomu ile değiştirilmesiyle sentezlendi. C-5 protonunu bir metil grubu ile değiştirmenin dönme bariyerini 2.2 kJ/mol düşürdüğü bulundu. Diğer taraftan, C-4 karbonil oksijeninin sülfür atomu ile değiştirilmesiyle dönme bariyerinin 18.3 kJ/mol arttığı saptandı.

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LIST OF SYMBOLS

2D	Two Dimensional
A_m	Amount of the compound in the mobile phase
A_s	Amount of the compound in the stationary phase
C_m	Concentartion of the compound in the mobile phase
C_s	Concentartion of the compound in the stationary phase
F	Flow rate
h	Planck's constant
Hz	Hertz
J	Joule
J	Coupling constant
K	Equilibrium constant
k'	Capacitor factor
k_b	Boltzman constant
k_f	Rate constant for forward reaction
k_r	Rate constant for reverse reaction
s	Second
ms	Milisecond
t	Time
T	Temperature
t_R	Retention time
V_0	Dead volume
V_n	Net retention volume
V_R	Retention volume
α	Separation factor
δ	Chemical shift
$\Delta G^{\#}$	Free energy of activation

LIST OF ACRONYMS/ABBREVIATIONS

$CDCl_3$	Deuterated chloroform
C_6D_6	Deuterated benzene
Chiralcel OD-H	Cellulose tris (3,5-dimethylphenylcarbamate)
Chiralpak AD	Amylose tris (3,5-dimethyl phenyl carbamate)
Chiralpak IB	Cellulose tris(3,5-dimethylphenylcarbamate)
Chiralpak IC	Cellulose tris(3,5 dichlorophenylcarbamate)
HPLC	High pressure liquid chromatography
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Enhancement Spectroscopy
TFA-d_1	Deuterated Trifluoro acetic acid
DMF-d_7	Deuterated Dimethyl formamide
Toluene-d_8	Deuterated Toluene

1. INTRODUCTION

Atropisomerism results from restricted rotation around a single bond, where the rotational barrier is sufficient to allow isolation of enantiopure species. Thus, atropisomers occur among axially chiral molecules. According to Oki, atropisomers are conformers that interconvert with a half-life of more than 1000 seconds at a given temperature [1].

On the other hand, the term atropisomerism was coined by Kuhn, in 1933, to describe molecules that are chiral and exist in enantiomeric forms solely due to hindered rotation around carbon-carbon single bonds. The term is drived from atropos (a Greek word); "a" meaning not and "tropos", meaning turn [2]. Atropisomerism has been a widely applicable area of stereochemistry because unlike other types of chirality, axially chiral compounds can be equilibrated thermally [3].

Atropisomerism was first detected by Christie and Kenner in 1922. They resolved 6,6'-dinitro-2,2'-diphenic acid (Figure 1.1) into its two enantiomers by using a diastereoselective crystallization method. Due to the steric interaction between bulky ortho substituents of 6,6'-dinitro-2,2'-diphenic acid, two aromatic rings of this biphenyl derivative become nonplanar and thus, two axially chiral enantiomers exist [4].

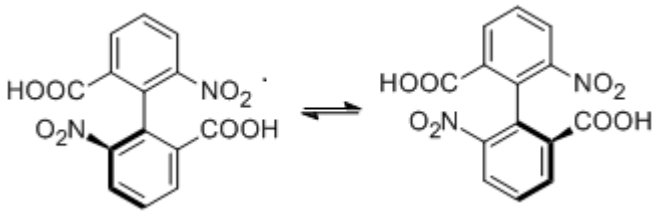


Figure 1.1. Structures of two axially chiral enantiomers of 6,6’-dinitro-2,2’-diphenic acid.

After the studies of Christie and Kenner, axial chirality in heterocyclic analogs of biphenyls was investigated by Adams *et al.*, in 1931. They claimed that the resolution of enantiomers may also occur in substituted N-phenylpyrroles (Figure 1.2) and they proved

the restricted rotation around C-N bond of N-phenylpyrrole derivatives by using the same diastereoselective crystallization method of Christie and Kenner [5-7].

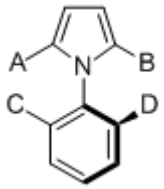


Figure 1.2. General structure of N-phenylpyrroles.

Colebrook *et al.*, in 1970, calculated the activation parameters for hindered rotation around C-N bonds of two heterocyclic compounds; 4,6-diamino-l,2-dihydro-2-methy1-l-(o-toly1)-s-triazine hydrochloride and 5-methyl-3-α-naphthyl-2-thiohydantoin (Figure 1.3), for the first time. In this study, the equilibration of diastereomeric rotational isomers of the heterocyclic compounds was followed by integration of their NMR spectra [8].

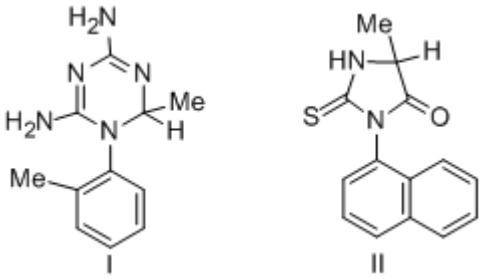


Figure 1.3. Structures of 4,6-diamino-l,2-dihydro-2-methy1-l-(o-toly1)-s-triazine hydrochloride (I) and 5-methyl-3-α-naphthyl-2-thiohydantoin (II).

After reporting high barriers to rotation around aryl C-N bonds in aryl substituted heterocyclic compounds, Colebrook *et al.* investigated some examples of compounds in which there are also barriers to rotation in the absence of bulky ortho substituents, in 1972. They reported that the asymmetric shieldings of the aryl groups may be sufficient to cause chemical shift differences even in the absence of bulky ortho substituents [9].

In 1985, various sterically hindered N-Aryl-pyridone derivatives (Figure 1.4) were synthesized by Mannschreck *et al.* They achieved the enrichment of the enantiomers by liquid chromatography on triacetylcellulose and measured enantiomeric purities by ^{1}H-NMR in the presence of an optically active auxiliary. In these compounds, barriers to partial rotation around the C-N bond were determined by thermal racemization [10].

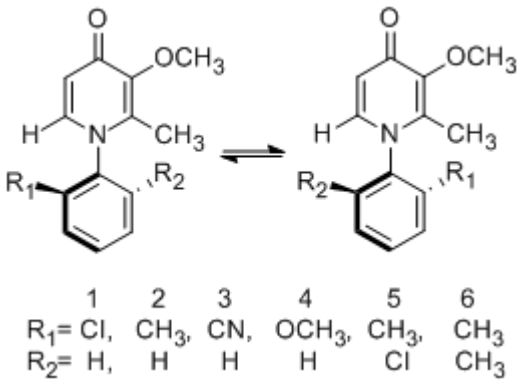


Figure 1.4. Structures of sterically hindered N-Aryl-pyridone derivatives.

Other types of axially chiral molecules which have a hindered rotation around the C-N single bond were synthesized by Doğan *et al.*, in 1992. They synthesized various sterically hindered N-(o-tolyl) and N-(o-chlorophenyl) substituted 2-thioxo-4-oxazolidinones and-thiazolidinones (Figure 1.5). As a result of the partial rotation around the C-N bond, these molecules form M and P enantiomers. Axial chirality of these molecules was proved by ^{1}H-NMR of diastereotopic protons and carbon atoms [11].

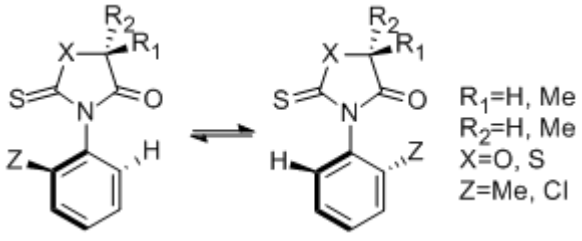


Figure 1.5. Structures of sterically hindered N-(o-tolyl) and N-(o-chlorophenyl) substituted 2-thioxo-4-oxazolidinones and-thiazolidinones.

In 1993, Doğan *et al.* also investigated the enantiomers of different axially chiral heterobiaryls. For the first time, these molecules had been investigated analytically and enriched semi-preparatively by liquid chromatography on triacetyl- and tribenzoylcellulose. Moreover, rotational barriers which stem from the restricted rotation around C-N bond had been determined [12].

Further research studies had been conducted on axially molecules which have a restricted rotation around the C-N single bond. For this purpose, Oğuz and Doğan synthesized 5,5-dimethyl-1-(o-aryl)barbituric and 2-thiobarbituric acid derivatives (Figure 1.6) and separated the enantiomers of these compounds, in 2003. Thermal racemization and temperature dependent NMR studies of these compounds were performed to find the activation barriers for conversion of one enantiomer to its counterpart [13].

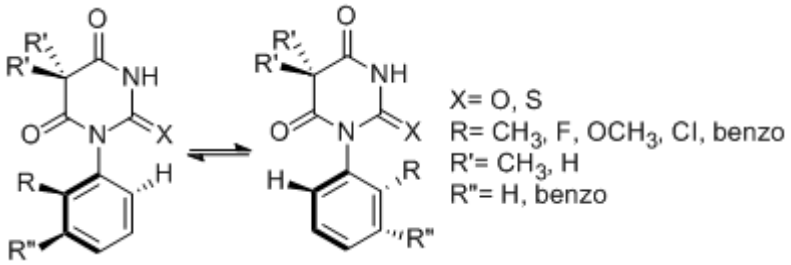


Figure 1.6. Structures of 5,5-dimethyl-1-(o-aryl)barbituric and 2-thiobarbituric acid derivatives.

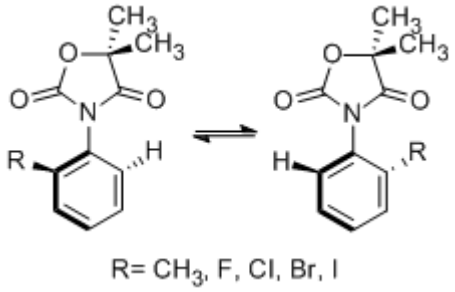
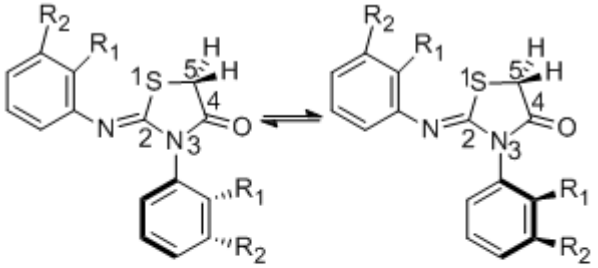


Figure 1.7. Structures of 5,5-dimethyl-3-(o-aryl)-2,4-oxazolidinediones.

Another temperature dependent NMR and thermal racemization study on various axially chiral molecules was conducted by Demir Ordu and Doğan, in 2004. In this study,

the activation barriers for the interconversion between the enantiomers of 5,5-dimethyl-3-(o-aryl)-2,4-oxazolidinediones (Figure 1.7) had been determined. As a consequence of this study, it was found that the activation barriers of these compounds increase linearly with the size of the ortho halogen substituents [14].

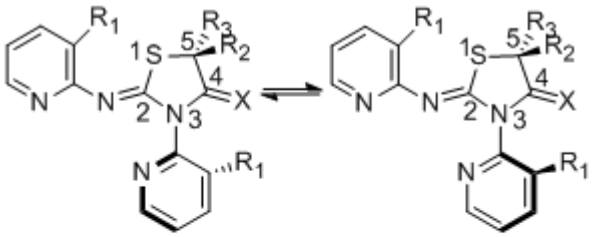
In 2007, various axially chiral 2-arylimino-3-aryl-thiazolidine-4-ones (Figure 1.8) had been synthesized as racemic mixtures by Erol and Doğan. Thermally interconvertible M and P enantiomers of these compounds were seperated by enantioselective HPLC and their rotational barriers were found to be 98.1-114.1 kJ/mol [15].



Compound	R_1	R_2
1	H	H
2	CH_3	H
3	benzo	benzo
4	OCH_3	H
5	Cl	H

Figure 1.8. Structures of axially chiral 2-arylimino-3-aryl-thiazolidine-4-ones.

In the present project, axially chiral enantiomeric and diastereomeric 2-arylimino-3-aryl-thiazolidine-4-ones (Figure 1.9) have been synthesized and their stereostructures have been investigated. Enantiomeric and diastereomeric isomers of these compounds have been investigated by ^{1}H-NMR and HPLC with an optically active sorbent. Also the interconversion rate and the energy barriers have been determined by thermal racemization of the micropreparatively resolved enantiomers. Further rotational barrier studies were conducted in order to understand the effect of substituent groups at the C-4 position of the heterocyclic ring. Chromatographic resolution of the compounds will yield single enantiomers which are expected to be potential N,N'-bidentate ligands in various asymmetric reactions.



Compound	R_1	X	R_2	R_3
1	H	O	H	H
2	CH_3	O	H	H
3	CH_3	O	CH_3	H
4	CH_3	S	H	H
5	CH_3	OH	H	H

Figure 1.9. Structures of axially chiral enantiomeric and diastereomeric 2-arylimino-3-aryl-thiazolidine-4-ones.

In 1991, Salvadori *et al.* reported a new chiral nitrogen bidentate ligand; N,N,N′,N′-tetramethyl-2,2′-diamino-1,1′-binaphthyl (Figure 1.10). A catalytic amount of this ligand was used in the reaction of enantioselective alkylation of aromatic aldehydes by diethylzinc [16]. However, in comparison to other axially chiral compounds, very few axially chiral bidentate nitrogen ligands have been reported [17].

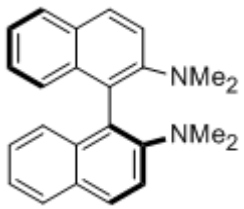


Figure 1.10. Structure of (S)- N,N,N′,N′-tetramethyl-2,2′-diamino-1,1′-binaphthyl.

The purposes of this project are the followings:

- To synthesize axially chiral 2-arylimino-3-aryl-thiazolidine-4-one derivatives.
- To investigate stereostructures of these compounds by NMR techniques.
- To resolve the enantiomers and diastereomers by HPLC on an optically active sorbent.
- To determine the rotational barriers around the C-N bond by thermal racemization and diastereomerization methods.

2. THEORY

2.1. Chirality

The term chirality is derived from cheiro (a Greek word for hand) and it is a mathematical approach to the concept of handedness. Chiral molecules, if non-racemic, are optically active; they rotate the plane of polarization of a beam of polarized light. This property of chiral molecules was first observed by Jean-Baptiste Biot, in 1815 [18]. Later, in 1848, Louis Pasteur deduced that this phenomenon has a molecular basis [19]. However, the term chirality itself was coined by Lord Kelvin, in 1873 [20].

In chemistry, molecules which lack an internal plane of symmetry are identified as chiral and such molecules possess a non-superimposable mirror image. Two non-superimposable mirror images of a chiral molecule are called enantiomers. Enantiomers have identical chemical and physical properties in the absence of an external chiral influence. Stereoisomers that are not mirror images are called diastereomers. Unlike enantiomers, diastereomers can have different physical and chemical properties from one another [21].

There are four different types of chirality namely; central, axial, planar and helical chirality.

Chiral molecules most commonly have central chirality and this type of chirality originates from having four different substituent groups bonded to a central atom. That is why, central atom is called as a stereocenter and the most common example is carbon atom since it can form four bonds to different substituents. Apart from carbon atom, other atoms such as nitrogen, sulfur, and phosphorus can become a stereocenter [22].

On the other hand, all chiral molecules may not possess a stereogenic center. For instance, axially chiral molecules do not have a stereocenter. Since the compounds studied in this project are axially chiral, this type chirality will be discussed later, in detail.

Planar chirality is another special case of chirality. Planarly chiral molecules do not have an asymmetric atom but instead of it, they possess two non-coplanar rings which are dissymmetric and can not easily rotate around the chemical bond connecting them.

The last type of chirality is helical chirality. Molecules which possess helical chirality can have either a right- or left-handed twist [23].

2.2. Axial Chirality

Axial chirality is a special type of chirality in which a molecule has an axis of chirality instead of a stereogenic center. Axis of chirality is an axis about which substituent groups in a spatial arrangement can not superpose on their mirror image [23].

This type of chirality commonly exists in biaryl compounds (Figure 2.1) wherein the rotation about the aryl-aryl bond is restricted.

Figure 2.1. Atropisomerism in biaryl compounds.

In biaryl compounds, the free rotation about the sp^2-sp^2 carbon-carbon bond is restricted if the steric interaction between Y-X and Y-W or Z-X and Z-W is large enough to make the planar conformation an energy maximum. Sterically hindered compounds can then exist as two non-planar, axially chiral enantiomers [24]. BINAP (2,2'-bis(diphenyl phosphino)-1,1'-binaphthyl) and BINOL (1,1'-Bi-2-naphthol) are two of the most important axially chiral biaryl compounds which have been used in various asymmetric reactions [25].

2.3. Axial Chirality in 2-arylimino-3-aryl-thiazolidine-4-ones

In this project, 2-arylimino-3-aryl-thiazolidine-4-ones (Figure 2.2) have been investigated. Due to the steric interaction between the ortho substituent on the N_3-aryl and the exocylic oxygen and imino nitrogen, the rotation around the N_3-aryl bond is restricted. So, just like axially chiral biaryl compounds, 2-arylimino-3-aryl-thiazolidine-4-ones can also exist as two non planar, axially chiral enantiomers.

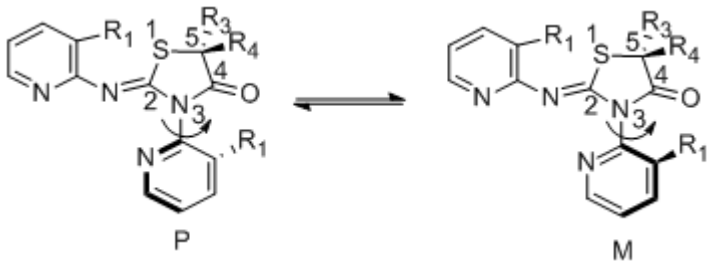


Figure 2.2. Atropisomerism in 2-arylimino-3-aryl-thiazolidine-4-ones.

For the purpose of specifying the absolute configuration of axially chiral molecules, stereochemical descriptors M and P are used according to Cahn-Ingolg-Prelog rules (Figure 2.3) [26]. In this system, first an axis is drawn through the single bond around which conformation is defined and the smallest torsion angle formed between the carbon atoms bearing the groups of the highest priority is used to define helix. A resulting clockwise rotation is denoted as P (plus) and the counter clockwise rotation is denoted as M (minus).

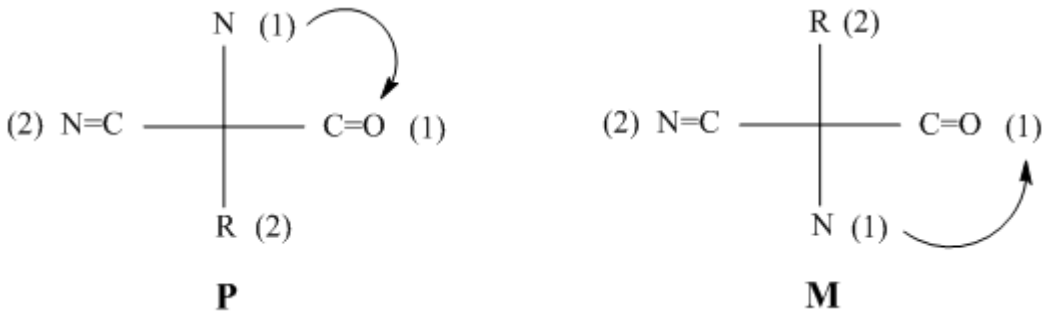


Figure 2.3. Cahn-Ingolg-Prelog rules.

2.4. The E-Z Isomerization of Imines

Isomerization of C=N double bond must be taken into account because 2-arylimino-3-aryl-thiazolidine-4-ones have the imino functional group.

There are two mechanisms by which the imines interconvert between E and Z isomers.

- Rotation about the C=N double bond
- Inversion of nitrogen (Lateral shift mechanism)

2.4.1. Rotation about the C=N Double Bond

Rotation mechanism about the C=N double bond is possible by polarization. In this case, partial negative charge accumulates on nitrogen and C-N single bond forms which make rotation possible. This mechanism has an out of plane transition state (Figure 2.4) [27].

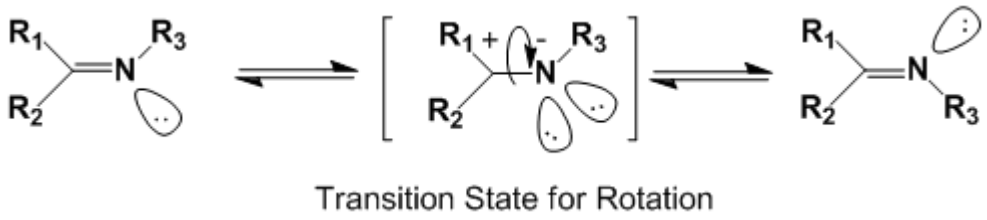


Figure 2.4. Rotation about the C=N double bond mechanism.

In the case of 2-arylimino-3-aryl-thiazolidine-4-ones, lone pair orbital lobe of N_3-nitrogen is perpendicular to the p orbitals of N_3-aryl ring. Thus, N_3- nitrogen can not participate in electron delocalization of aromatic ring. On the other hand, it can go into conjugation with the imino bond and reduce its double bond character so that the rotation can occur (Figure 2.5).

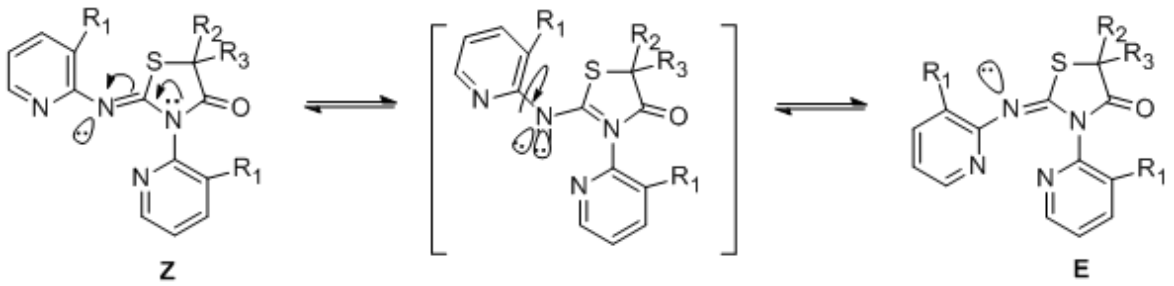


Figure 2.5. The rotation around C=N double bond of 2-arylimino-3-aryl-thiazolidine-4-ones.

2.4.2. Inversion of Nitrogen (Lateral Shift Mechanism)

In lateral shift mechanism, a change of hybridization of the nitrogen from sp^2 to sp orbital takes place. The lone pair of nitrogen atom move from sp^2 orbital to p orbital. This mechanism has an "in plane" transition state (Figure 2.6) [27].

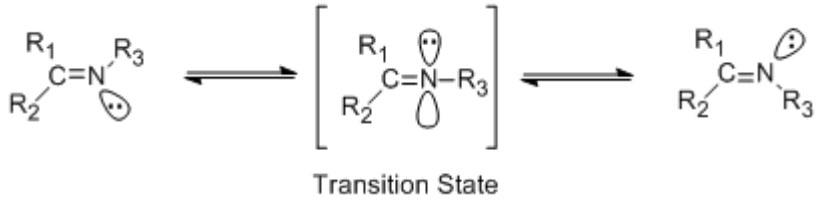


Figure 2.6. Lateral shift mechanism.

It is not clear that whether imines isomerize via rotation or via lateral shift mechanisms. Moreover, both mechanisms may be responsible for isomerization [27, 28].

2.5. Assignment of the E and Z configurations in 2-arylimino-3-aryl-thiazolidine-4-ones

The substituent groups having higher priority are on the same side or on the opposite side of the C=N double bond determines the configuration 2-arylimino-3-aryl-thiazolidine-4-ones. In this case, sulfur atom has higher priority than N_3-nitrogen and aryl ring has higher priority than the lone pair of imino nitrogen. If the substituents having higher

priority are on the same side, then the descriptor Z is used; otherwise, E descriptor is employed (Figure 2.7).

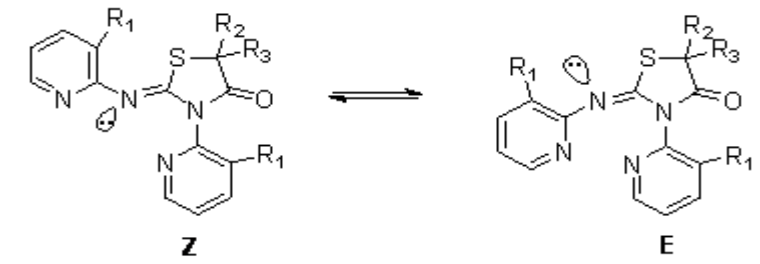


Figure 2.7. E and Z configuration of 2-arylimino-3-aryl-thiazolidine-4-ones.

Due to steric hindrance brought by two pyridine rings, Z configuration may be predominant. On the other hand, E configuration may also be a favorable interaction if we take π-π interaction between two pyridine rings into consideration.

2.6. 2D-NOESY Spectroscopy

2D-NOESY (Nuclear Overhauser effect spectroscopy) experiments can be performed to find out the stereochemistry of the C=N double bond of 2-arylimino-3-aryl-thiazolidine-4-ones. In NOESY, the cross peaks connect resonances from nuclei that are spatially close to each other. So, this technique indicates which protons are close enough in space if the through space distance is smaller than 4 A° [29]. If 2-arylimino-3-aryl-thiazolidine-4-one derivatives possess E configuration (Figure 2.7), then the crosspeaks must be observed for the protons of the two pyridine rings.

2.7. The AB Spin System

In the AB spin system the chemical shift difference $\Delta\nu = \nu_A - \nu_B$ is of the same order of magnitude as the coupling constant J_{AB}. Analysis of the AB spectrum is done by numbering the resonance frequencies of the four lines of the AB spectrum from left to right as f_1, f_2, f_3 and f_4 (Figure 2.8).

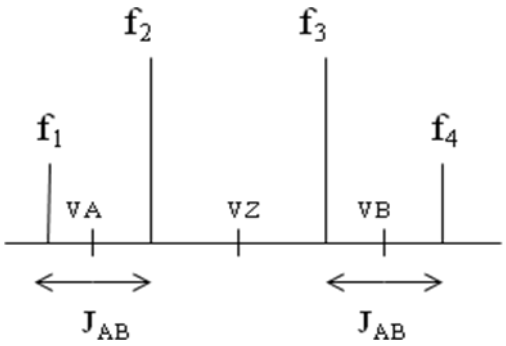


Figure 2.8. Sketch for analyzing a two-spin AB system.

The coupling constant J_{AB} is equal to the frequency intervals between lines 1 and 2 or between 3 and 4.

$$J_{AB} = f_1 - f_2 = f_3 - f_4 \text{ [Hz]} \tag{2.1}$$

$\Delta\nu$ is in fact the geometrical mean of the distances between the two outer and the two inner signals.

$$\Delta\nu = [(f_1 - f_4)(f_2 - f_3)]^{1/2} \tag{2.2}$$

From $\Delta\nu$ and the center frequency ν_Z, the following equation is obtained [29].

$$\nu_A = \nu_Z + \Delta\nu/2 \text{ and } \nu_B = \nu_Z - \Delta\nu/2 \tag{2.3}$$

2.8. Dynamic NMR

The technique, where NMR is used in obtaining information about time-dependent phenomena, is called dynamic NMR. The main requirement for use of dynamic NMR is to have a sample where the dynamics occurs in the NMR timescale (ms range) [29]. In this project, Dynamic NMR can be used on compounds which have molecular dynamics occurring with rate constants between approximately 10 and 10000 sec^{-1} to reveal detectable changes in an NMR property (chemical shift or coupling constant).

2.9. Determination of the Barriers to Rotation by Thermal Racemization

2.9.1. A Review of High Performans Liquid Chromatography

Chromatography is the term for a set of laboratory techniques which are used for separation and it involves a sample being dissolved in a mobile phase which may be a gas, a liquid or a supercritical fluid. Mobile phase simply carries dissolved sample through a structure holding another material called the stationary phase. The various constituents of the solute travel at different speeds, causing them to separate. The separation depends on the differential distribution of solute between the mobile and stationary phases. Depending on the nature of the mobile and the stationary phases, there are different types of chromatography.

High performance or high pressure liquid chromatography (HPLC) is one of the liquid chromatographic techniques. It is widely used for chromatographic separation and identification of compounds. HPLC instruments consist of different types of stationary phases, a pump and a detector. With HPLC, a pump provides the higher pressure required to move the mobile phase and analyte through the stationary phase which contains a special solid packing material. Analyte is separated by injecting the sample mixture onto column. Analyte retention time depends on the strength of its interactions with the stationary phase, the ratio/composition of solvent(s) used, and the flow rate of the mobile phase. Simply, the components of analyte which are strongly retained by the stationary phase move slowly or vice versa.

The retention of a compound on a column can be expressed by its retention time (t_R), retention volume ($V_R = t_R F$; F: flow rate) or the capacity ratio (k'), which is directly related to its equilibrium distribution constant (K) in the stationary–mobile phase system. The capacity ratio is defined by:

$$k' = A_s / A_m \qquad (2.4)$$

Where A_S and A_m denote the amount of the compound in the stationary and the mobile phase, respectively. Let V_S and V_m be the volumes of the respective phases; then

$$k'=CsVs/C_mV_m=KV_S/V_m \quad (2.5)$$

V_m is commonly writen as V_0 and represents the dead volume in the column, which does not contribute to the separation. Consequently, the net retention volume, V_n, can be written as $V_n=V_R-V_0$, since $K=V_n/V_s$, combination with Equation 2.5 gives:

$$k'=(V_R-V_0)/V_0 \quad (2.6)$$

These expressions permit the determination of the capacity factor from the chromatogram. The chromatographic separation of two components (1 and 2) depends on the separation factor (α) of a column. It can be written as $k_2'/k_1'=K_2/K_1=\alpha$. From Equation 2.6, α can be formulated as:

$$\alpha = (V_{R2}-V_0)/(V_{R1}-V_0) \quad (2.7)$$

Thus the separation factor is simply the ratio of the net retention volumes of the two components. If the dead volume V_0, has been determined, the separation factor is easly calculated from Equation 2.7 [30].

2.9.2. Separation of Stereoisomers by Chiral HPLC

Enantiomers have identical chemical and physical properties in the absence of an external chiral influence. It is impossible to separate enantiomers by ordinary HPLC because they retained by the stationary phases to the same extent. On the other hand, enantiomers can behave chemically and physically in different manner in the presence of an external chiral influence. That is why; enantiomers can be separated by using chiral HPLC columns packed with chiral stationary phases (CSPs).

Resolution in chiral HPLC columns depends on the formation of transient diastereoisomers on the surface of the column packing. Simply, the compounds which form the most stable diastereoisomer will be most retained or vice versa. There needs to be at least three points of interaction to achieve separation between enantiomers. Since the forces that lead to this interaction are very weak, careful optimization must be applied to

maximize selectivity. Optimization can be done by adjustment of the mobile phase, temperature and flow rate. The separation in chiral HPLC is a result of the sum of a large number of interactions. Generally, a free energy of interaction difference of only 0.03 kJ/mol between the enantiomers and chiral stationary phase will lead to resolution [30].

There are various types of chiral stationary phases present in the market such as cellulose, pirkle (brush), ligand-exchange and protein type. In this study, resolution of the stereoisomers was attempted on Chiralcel OD-H, Chiralpak AD-H, Chiralpak IC and Chiralpak IB columns. These columns are packed with cellulose tris-3,5-dimethylphenyl carbamate, amylose tris-3,5-dimethylphenyl carbamate, tris-3,5-dichlorophenylcarbamate and tris-3,5-dimethylphenylcarbamate as chiral stationary phases, respectively.

2.9.3. Determination of the Kinetic and Thermodynamic Constants of the Internal Rotation Process for 2-arylimino-3-aryl-thiazolidine-4-ones

Atropisomers can be equilibrated thermally whereas in the other forms of chirality isomerization is usually only possible chemically. That is why; if one of the stereisomers of 2-arylimino-3-aryl-thiazolidine-4-one derivatives is separated or enriched from the other one by enantioselective HPLC, it can be interconverted to its counterpart. This interconversion takes place through the rotation around the N_3-aryl bond and finally reaches the equilibrium (Figure 2.9).

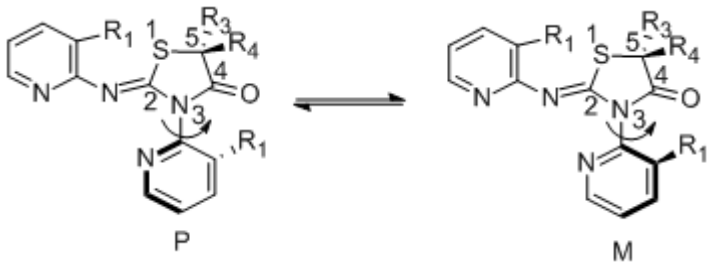


Figure 2.9. Internal rotation between two rotamers.

The process follows reversible first-order kinetics, the theory of which is given below:

The reversible reaction M $\rightleftharpoons$ P is first order in both the forward (f) and the reverse direction (r), so that $r_f = k_f [M]$ and $r_r = k_r [P]$. If $(d[M]/dt)_f$ denotes the rate of change of [M] due to forward reaction, then $-(d[M]/dt)_f = r_f = k_f[M]$. The rate of formation of [M] by reverse reaction is $(d[M]/dt)_r = r_r = k_f[P]$. Then,

$$(d[M]/dt) = -k_f[M]+k_r[P] \tag{2.8}$$

We have $\Delta[P]=-\Delta[M]$, so $[P]-[P]_0=-([M]-[M]_0)$. Substitution of $[P]=[P]_0+[M]_o-[M]$ into Equation 2.8 gives

$$d[M]/dt=k_r[P]_0+k_r[M]_0-(k_f+k_r)[M] \tag{2.9}$$

At equilibrium, the rates of the forward and reverse reactions become equal, the concentration of each species being constant, thus d[M]/dt is 0. Let $[M]_{eq}$ be the equilibrium concentration of M. Setting d[M]/dt=0 and $[M]=[M]_{eq}$ in Equation 2.9, we get

$$k_r[P]_0+k_r[M]_0= (k_f+k_r)[M]_{eq} \tag{2.10}$$

The use of Equation 2.10 in Equation 2.9 gives $d[M]/dt= (k_f+k_r) ([M]_{eq}-[M])$. Using the identity $\int(x + s)^{-1}dx= \ln(x + s)$ to integrate this equation, we get,

$$\ln ([M]-[M]_{eq}/[M]_0-[M]_{eq})= -(k_f+k_r)t \tag{2.11}$$

Since $k_f=k_r$ for the racemization of enantiomers, Equation 2.11 could be written as Equation 2.12 for the racemization of enantiomers

$$\ln ([M]-[M]_{eq}/[M]_0-[M]_{eq})=-2kt \tag{2.12}$$

By using Equation 2.12, a plot of $\ln ([M]-[M]_{eq}/[M]_0-[M]_{eq})$ versus time gives a straight line, the slope being equal to -2k. Having determined k, the free energy of activation can be calculated using the Eyring Equation 2.13,

$$\Delta G^{\#}=RTln(k_b.T/k.h) \quad (2.13)$$

Where R=8.3143 J/mol.K, T=temperatue (Kelvin) at which the interconversion takes place, k_b(Boltzmann constant)=$1.3805.10^{-23}$J/K, h (Planck's constant)=$6.6256.10^{-34}$J.s, k=the rate constant for the racemization reaction [30].

3. ORGANIC SYNTHESIS

3.1. Synthesis of N,N'-diarylthioureas

3.1.1. General Procedure

The N,N'-diarylthioureas were used as starting materials to synthesize 2-arylimino-3-aryl-thiazolidine-4-ones. They were synthesized by the reaction of corresponding anilines with carbon disulfide in the presence of pyridine as solvent (Figure 3.1).

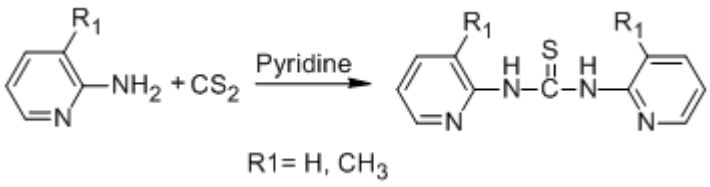


Figure 3.1. The synthesis of N,N'-diarylthioureas.

The appropriate aniline derivative (50 mmol) was dissolved in 20 ml pyridine and then, CS_2 was added. The mixture was refluxed overnight under N_2. Later, the solution was concentrated by evaporating the solvent and cooled producing a precipitate. The precipitated product was isolated by vacuum filtration, stirred in water overnight and dried in vacuo. The crude N,N'-diarylthiourea was purified by recrystallization from ethanol.

3.1.1.1. 1,3-di(pyridin-2-yl)thiourea. The compound was synthesized according to the general procedure.

Starting materials:

- 2-Amino pyridine: 4.71 g (0.05 mole)
- Carbon disulfide: 7.61 g (0.1 mole)
- Pyridine: 20 ml

Yield: 1.92 g (33.4%)
Melting point: 156-158 °C

^{1}H NMR (400 MHz) data (ppm):
Solvent: $CDCl_3$
Aromatic protons: 9.40-7.10 ppm
NH proton (H-bonded): 14.30 ppm
NH proton: 6.92 ppm

3.1.1.2. 1,3-bis(3-methylpyridin-2-yl)thiourea. The compound was synthesized according to the general procedure.

Starting materials:

- 2-amino-picoline: 5.03 ml (0.05 mole)
- Carbon disulfide: 7.61 g (0.1 mole)
- Pyridine: 20 ml

Yield: 2.45 g (38%)
Melting point: 166-168 °C

^{1}H NMR (400 MHz) data (ppm):
Solvent: $CDCl_3$
Aromatic protons: 8.42-7.20 ppm
NH proton (H-bonded): 13.80 ppm
NH proton: 6.96 ppm
Methyl protons (on N_3 pyridine): 2.51 ppm
Methyl protons (on imino pyridine): 2.31 ppm

3.2. Synthesis of 1,3-bis((R)-1-cyclohexylethyl)thiourea

3.2.1. General Procedure

Apart from N,N'-diarylthiourea derivatives, 1,3-bis((R)-1-cyclohexylethyl)thiourea (Figure 3.2) was also synthesized according to general procedure.

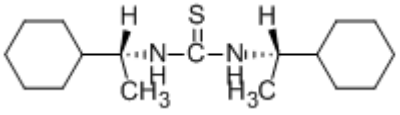


Figure 3.2. Structure of 1,3-bis((R)-1-cyclohexylethyl)thiourea.

Starting materials:

- (R)-1-cyclohexylethanamine: 6.36 ml (0.05 mole)
- Carbon disulfide: 7.61 g (0.1 mole)
- Pyridine: 20 ml

Yield: 6.37 g (86%)
Melting point: 186-188 °C

^{1}H NMR (400 MHz) data (ppm):
Solvent: $CDCl_3$
NH protons: 5.51 ppm
CH protons: 3.91 ppm
CH_3 and Cyclohexyl protons: 1.85-0.90 ppm

3.3. Synthesis of 2-arylimino-3-aryl-thiazolidine-4-ones

3.3.1. General Procedure

The 2-arylimino-3-aryl-thiazolidine-4-ones were synthesized by the reaction of the corresponding N,N'-diarylthioureas and α-bromoacetic acid in the presence of sodium acetate (Figure 3.3). In these reactions, ethanol was used as solvent.

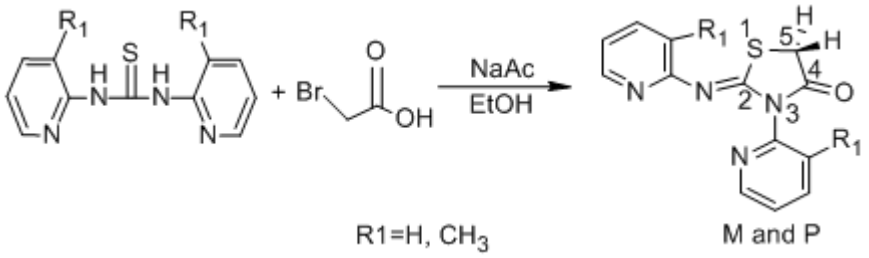


Figure 3.3. Synthesis of 2-arylimino-3-aryl-thiazolidine-4-ones.

The appropriate N,N'-diarylthiourea and α-bromoacetic acid were refluxed for 4 hours in absolute ethanol in the presence of sodium acetate. At the end of this period, the excess of ethanol was distilled out and the reaction mixture was poured in cold water. Then a precipitate was obtained and it was collected and washed several times with hot water to remove unreacted α-bromoacetic acid and sodium acetate. After drying, the product was purified by recrystallization from ethanol.

3.3.1.1. 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one. This compound was synthesized according to the general procedure.

Starting materials:

- 1,3-di(pyridin-2-yl)thiourea: 1.15g (0.005 mole)
- α-bromoacetic acid: 0.69 g (0.005 mole)
- Sodium acetate: 0.49 g (0.006 mole)
- Ethanol: 30 ml

Yield: 0.71 g (53%)
Melting point: 210-212 °C

^{1}H NMR (400 MHz) data (ppm):
Solvent: $CDCl_3$
Methylene protons at C-5: 3.84 ppm
Aromatic protons: 8.64-6.88 ppm

^{13}C NMR (400MHz) data (ppm):
Solvent: $CDCl_3$
C-2 carbon of the thiazolidine ring: 148.9 ppm
C-4 carbon of the thiazolidine ring: 171.8 ppm
C-5 carbon of the thiazolidine ring: 33.8 ppm
Aromatic carbons: 120.0-157.9 ppm

3.3.1.2. 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one. This compound was synthesized according to the general procedure.

Starting materials:

- 1,3-bis(3-methylpyridin-2-yl)thiourea: 1.29 g (0.005 mole)
- α-bromoacetic acid: 0.69 g (0.005 mole)
- Sodium acetate: 0.49 g (0.006 mole)
- Ethanol: 30 ml

Yield: 0.54 g (36%)
Melting point: 134-136 °C

^{1}H NMR (400 MHz) data (ppm):
Solvent: $CDCl_3$
Methylene protons at C-5: 3.96 ppm
CH_3 protons (on N_3 pyridine ring): 2.29 ppm

CH_3 protons (on C=N pyridine ring): 1.93 ppm
Aromatic protons: 8.53-6.91 ppm

^1H NMR (400 MHz) data (ppm):
Solvent: C_6D_6
Methylene protons at C-5: 2.72 ppm
CH_3 protons (on N_3 pyridine ring): 1.69 ppm
CH_3 protons (on C=N pyridine ring): 1.58 ppm
Aromatic protons: 8.03-6.16 ppm

^{13}C NMR (400MHz) data (ppm):
Solvent: $CDCl_3$
C-2 carbon of the thiazolidine ring: 147.3 ppm
C-4 carbon of the thiazolidine ring: 170.4 ppm
C-5 carbon of the thiazolidine ring: 32.9 ppm
CH_3 carbon (on N_3 pyridine ring): 16.0 ppm
CH_3 carbon (on C=N pyridine ring): 15.7 ppm
Aromatic carbons: 119.1-155.1 ppm

3.4. Synthesis of 5-methyl-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one

3.4.1. General Procedure

5-methyl-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one (Figure 3.4) was synthesized according to general procedure of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one except; 2-bromo-propionic acid was used instead of α-bromoacetic acid.

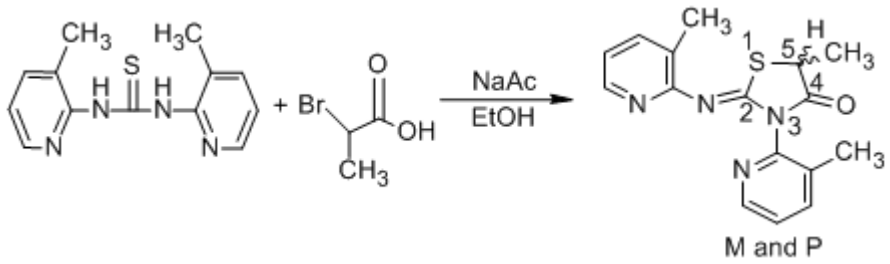


Figure 3.4. Synthesis of 5-methyl-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one.

Starting materials:

- 1,3-bis(3-methylpyridin-2-yl)thiourea: 1.29g (0.005 mole)
- 2-bromo-propionic acid: 0.76 g (0.005 mole)
- Sodium acetate: 0.49 g (0.006 mole)
- Ethanol: 30 ml

Yield: 0.41 g (26%)

Melting point: 130-132 °C

^{1}H NMR (400 MHz) data (ppm):

Solvent: $CDCl_3$

CH_3 protons at C-5: 1.76 ppm

CH protons at C-5: 4.17 ppm

CH_3 protons (on N_3 pyridine ring): 2.26 ppm

CH_3 protons (on C=N pyridine ring): 1.93 ppm

Aromatic protons: 8.53-6.91 ppm

^{1}H NMR (400 MHz) data (ppm):

Solvent: C_6D_6

CH_3 protons at C-5: 1.03 and 1.00 ppm

CH protons at C-5: 3.27 and 3.13 ppm

CH_3 protons (on N_3 pyridine ring): 1.73 and 1.68 ppm

CH_3 protons (on C=N pyridine ring): 1.60 and 1.58 ppm

Aromatic protons: 8.04-6.17 ppm

^{13}C NMR (400MHz) data (ppm):
Solvent: $CDCl_3$
C-2 carbon of the thiazolidine ring: 148.4 ppm
C-4 carbon of the thiazolidine ring: 174.8 ppm
C-5 carbon of the thiazolidine ring: 42.6 ppm
CH_3 carbon at C-5 position: 19.1 ppm
CH_3 carbon (on N_3 pyridine ring): 16.9 ppm
CH_3 carbon (on C=N pyridine ring): 16.8 ppm
Aromatic carbons: 120.1-156.2 ppm

3.5. Synthesis of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidine-4-thione

3.5.1. General Procedure

The compound was synthesized by the reaction of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one and Lawesson Reagent in the presence of toluene (Figure 3.5).

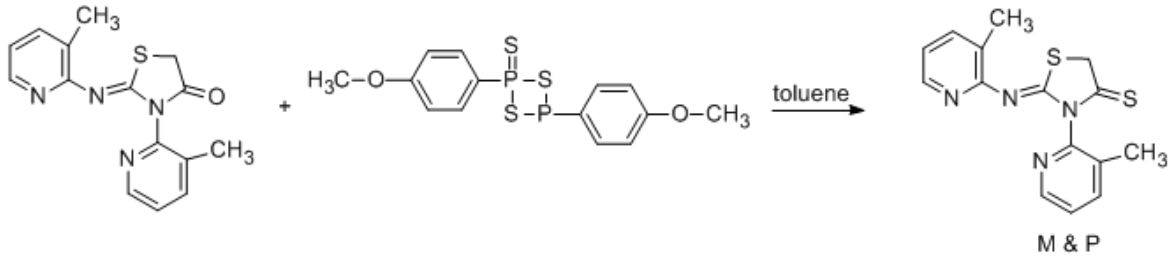


Figure 3.5. Synthesis of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidine-4-thione.

The reaction mixture was refluxed for 6 hours and then, the solvent was removed under reduced pressure. The crude product was purified by column chromatography which

was packed with silica gel and eluted with n-hexane/ethyl acetate mixture (EtOAc/Hexane; 1/5).

Starting materials:

- 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one: 1.85 g (6.2 mmole)
- Lawesson Reagent: 1.25 g (3.1 mmole)
- Toluene: 15 ml

Yield: 4%.
Melting point: 130-132 °C

^{1}H NMR (400 MHz) data (ppm):
Solvent: $CDCl_3$
Methylene protons at C-5: 4.42 ppm
CH_3 protons (on N_3 pyridine ring): 2.17 ppm
CH_3 protons (on C=N pyridine ring): 1.83 ppm
Aromatic protons: 8.48-6.88 ppm

^{1}H NMR (400 MHz) data (ppm):
Solvent: C_6D_6
Methylene protons at C-5: 3.36 ppm
CH_3 protons (on N_3 pyridine ring): 1.66 ppm
CH_3 protons (on C=N pyridine ring): 1.52 ppm
Aromatic protons: 8.06 – 6.13 ppm

^{13}C NMR (400MHz) data (ppm):
Solvent: $CDCl_3$
C-2 carbon of the heterocyclic ring: 154.5 ppm
C-4 carbon of the heterocyclic ring: 199.7 ppm
C-5 carbon of the heterocyclic ring: 45.1 ppm
CH_3 carbon (on N_3 pyridine ring): 15.7 ppm

CH_3 carbon (on C=N pyridine ring): 15.6 ppm
Aromatic carbons: 119.5-158.4 ppm

3.6. Synthesis of 3-((R)-1-cyclohexylethyl)-2-((R)-1-cyclohexylethylimino)thiazolidin-4-one

3.6.1. General Procedure

The compound was synthesized according to the general procedure of 2-arylimino-3-aryl-thiazolidine-4-ones (Figure 3.6).

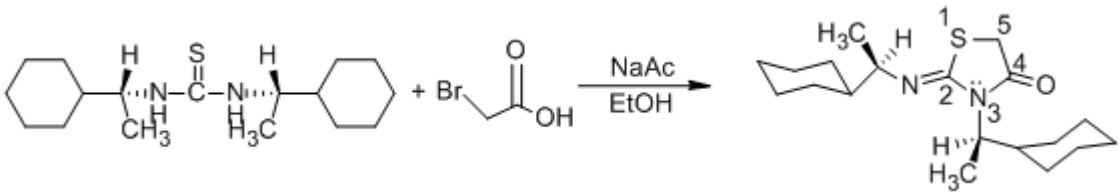


Figure 3.6. Synthesis of 3-((R)-1-cyclohexylethyl)-2-((R)-1-cyclohexylethylimino) thiazolidin-4-one..

After reaction, the crude product was purified by column chromatography which was packed with silica gel and eluted with n-hexane/dichloromethane mixture (CH_2CI_2/Hexane; 1/1).

Starting materials:

- 1-((R)-1-cyclohexylethyl)-3-((S)-1-cyclohexylethyl)thiourea: 1.48g (0.005 mole)
- α-bromoacetic acid: 0.69 g (0.005 mole)
- Sodium acetate: 0.49 g (0.006 mole)
- Ethanol: 30 ml

Yield: 0.40 g (24%).
Melting point: Oily.

^{1}H NMR (400 MHz) data (ppm):

Solvent: $CDCI_3$

NH protons: 4.13 ppm

CH protons: 2.89 ppm

Methylene protons: 3.67 ppm

CH_3 and Cyclohexyl protons: 2.17-0.73 ppm

^{13}C NMR (400MHz) data (ppm):

Solvent: $CDCl_3$

C-2 carbon of the heterocyclic ring: 148.4 ppm

C-4 carbon of the heterocyclic ring: 171.8 ppm

Cyclohexyl, -CH3 and –CH2 and –CH carbons: 63.6 – 15.4 ppm

3.7. Apparatus

- ^{1}H NMR and ^{13}C NMR spectra were recorded on the Varian-Mercury VX-400 MHz-BB.
- Melting points were recorded using a Bibby Stuart Scientific melting point apparatus.
- The IR analyses were performed on a Perkin Elmer 1600 FTIR using KBr windows.
- Liquid chromatography analyses were performed using Chiralpak IC column (Daicel Ltd., partical size: 5µm, column size:250×4.6 mm), Chiralpak IB column (Daicel Ltd., partical size: 5µm, column size:250×4.6 mm), Chiralcel OD-H column (Daicel Ltd., partical size: 5µm, column size:250×4.6 mm) or Chiralpak AD column (Daicel Ltd., partical size: 5µm, column size:250×4.6 mm), Lab Alliance Series III pump and Water Assoc. UV absorbance detector.

3.8. List of Chemicals

Table 3.1. Chemicals used in this study.

Name	Formula	Supplier	% Purity
2-Amino pyridine	$C_5H_6N_2$	Aldrich	99
Carbon disulfide	CS_2	Merck	99.5
Pyridine	C_5H_5N	Merck	99
2-Amino picoline	$C_6H_8N_2$	Aldrich	95
(R)-1-cyclohexylethanamine	$C_8H_{17}N$	Aldrich	98
α-bromoacetic acid	$BrCH_2COOH$	Fluka	99
Absolute ethanol	CH_2OH	Merck	99
Sodium acetate	CH_3COONa	Merck	99
Ethanol for HPLC	CH_2OH	J.T.Baker	99.5
Hexane for HPLC	$CH_3(CH_2)_4CH_3$	J:T:Baker	95
2-Propanol for HPLC	$CH_3CH(OH)CH_3$	Merck	99.9
2-bromopropionic acid	$CH_3CHBrCOOH$	Aldrich	99
Lawesson Reagent	$C_{14}H_{14}O_2P_2S_4$	Aldrich	99
Toluene	$C_6H_5CH_3$	Merck	99

4. RESULTS AND DISCUSSIONS

4.1. N,N'-diarylthioureas

4.1.1. 1,3-di(pyridin-2-yl)thiourea

There are four possible conformational isomers for 1,3-di(pyridin-2-yl)thiourea (Figure 4.1).

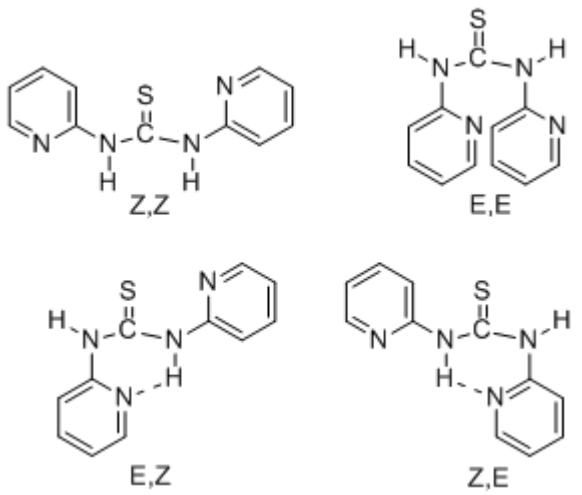


Figure 4.1. Conformational isomers for 1,3-di(pyridin-2-yl)thiourea.

Due to steric reasons, formation of the E,E conformational isomer is not favored. Also, there is an intramolecular H-bonding in E,Z and Z,E conformers. In these isomers, nitrogen of the pyridine ring forms an intramolecular H-bonding with thioamide group hydrogen. That is why; E,Z and Z,E conformers possess extra stability imparted by the internal hydrogen bonding which results in formation of a six membered ring. Since E,Z and Z,E conformers are more stable than Z,Z conformer, it is not populated to any significant extent [31].

The interconversion of the E,Z and Z,E conformers takes place very rapidly at room temperature (Figure 4.2). During this interconversion, rapid formation and deformation of

intramolecular H-bonding occurs and because of this fact, the ^{1}H-NMR spectrum of 1,3-di(pyridin-2-yl)thiourea displays broad peaks at room temperature.

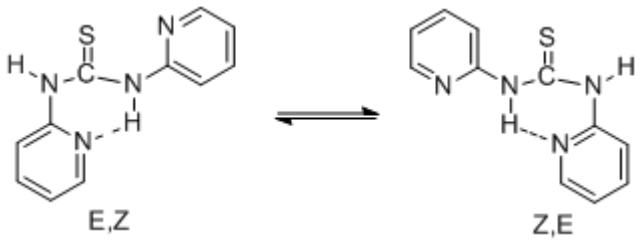


Figure 4.2. Interconverting conformers of 1,3-di(pyridin-2-yl)thiourea.

At room temperature, the ^{1}H-NMR spectrum of 1,3-di(pyridin-2-yl)thiourea (Figure 4.3) displays two different -NH proton signals at 14.31 and 9.02 ppm. The –NH proton which participates in intramolecular H-bonding is desielded up to 14.31 ppm and the other one, which does not participate in H-bonding, displays a signal at 9.02 ppm.

Since proton peaks of 1,3-di(pyridin-2-yl)thiourea are broad at room temperature, ^{1}H-NMR spectra were also taken at lower temperatures, at -5 °C and -15 °C (Figure 4.4 and 4.5).

At room temperature, aromatic ring protons are in the range between 8.88 and 6.83 ppm and, they display broad signals due to the characteristic exchange occuring between two interconverting conformers of 1,3-di(pyridin-2-yl)thiourea (Figure 4.2). However, these protons become sharper and distinguishable at lower temperatures.

These facts prove that the low-field –NH signal results from a strong intramolecular H-bonding and the interconversion of conformers slows down at lower temperatures. The low-field –NH proton was assigned to the –NH in the E orientation (NH_E) with respect to the thioamide group. The high-field –NH group, on the other hand, has a Z orientation (NH_Z) (Figure 4.1).

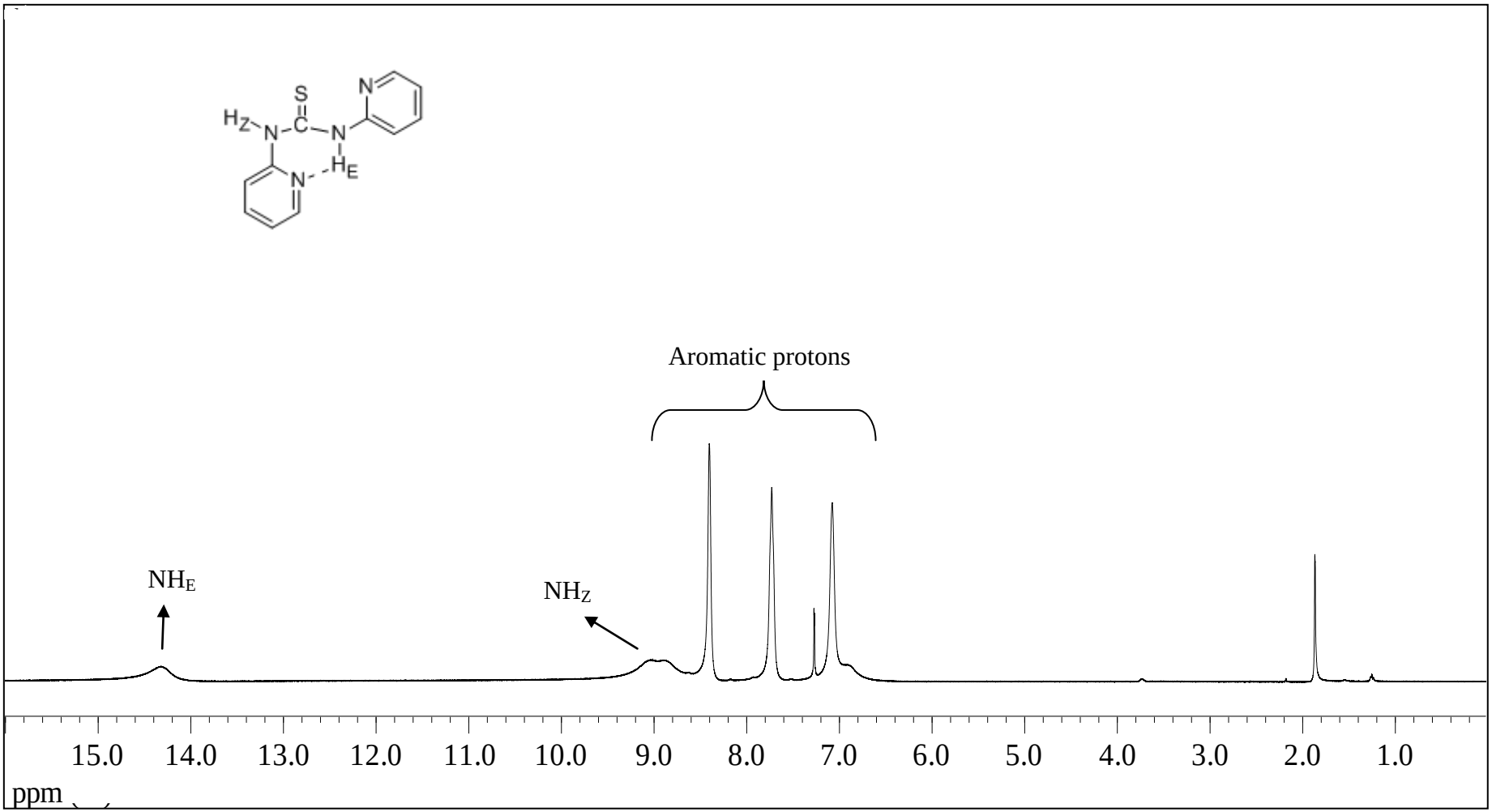


Figure 4.3. The 400 MHz ^{1}H-NMR spectrum of 1,3-di(pyridin-2-yl)thiourea in $CHCl_3$-d_1 at room temperature.

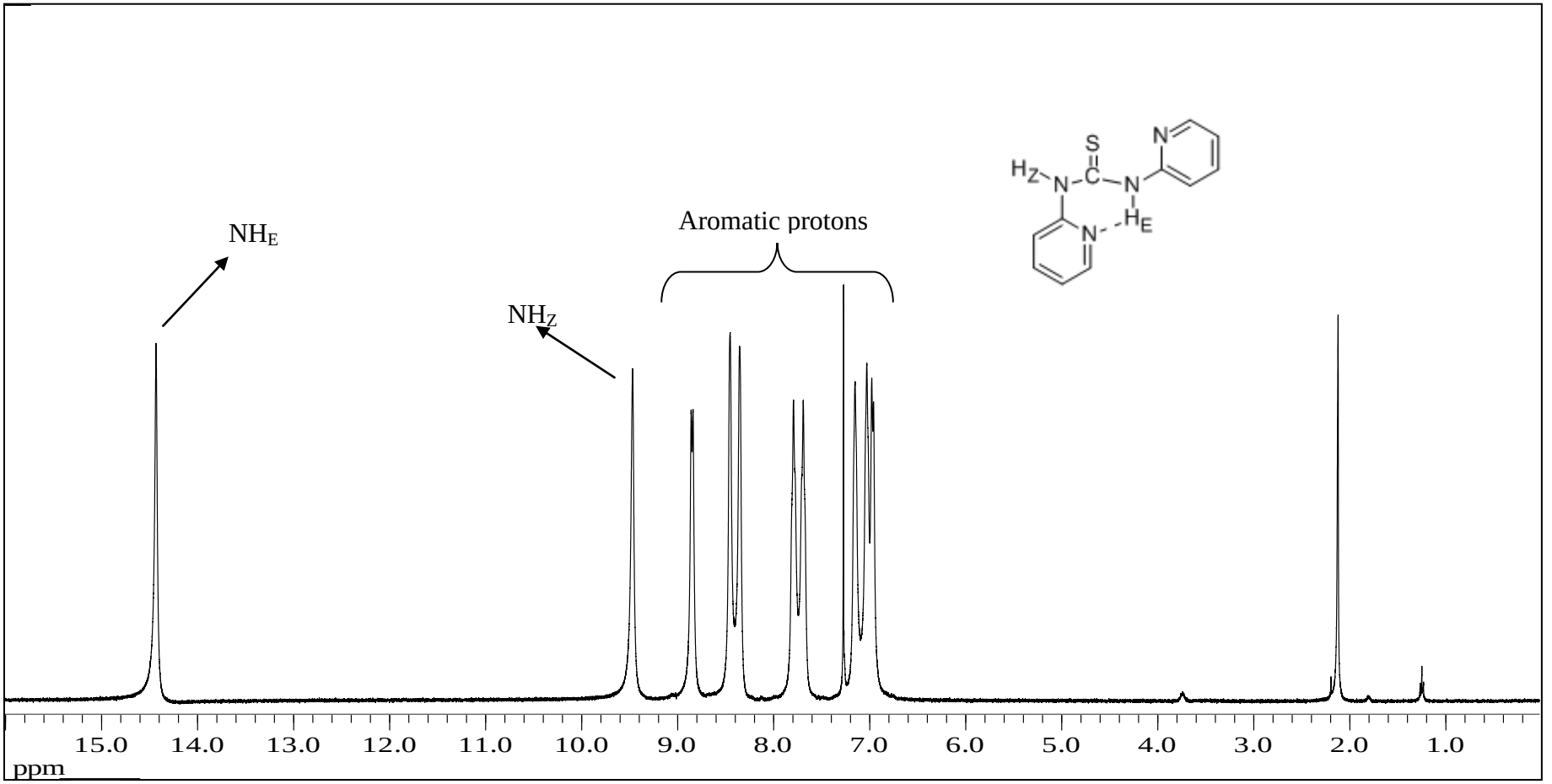


Figure 4.4. The 400 MHz ^{1}H-NMR spectrum of 1,3-di(pyridin-2-yl)thiourea in $CHCl_3$-d_1 at -5 °C.

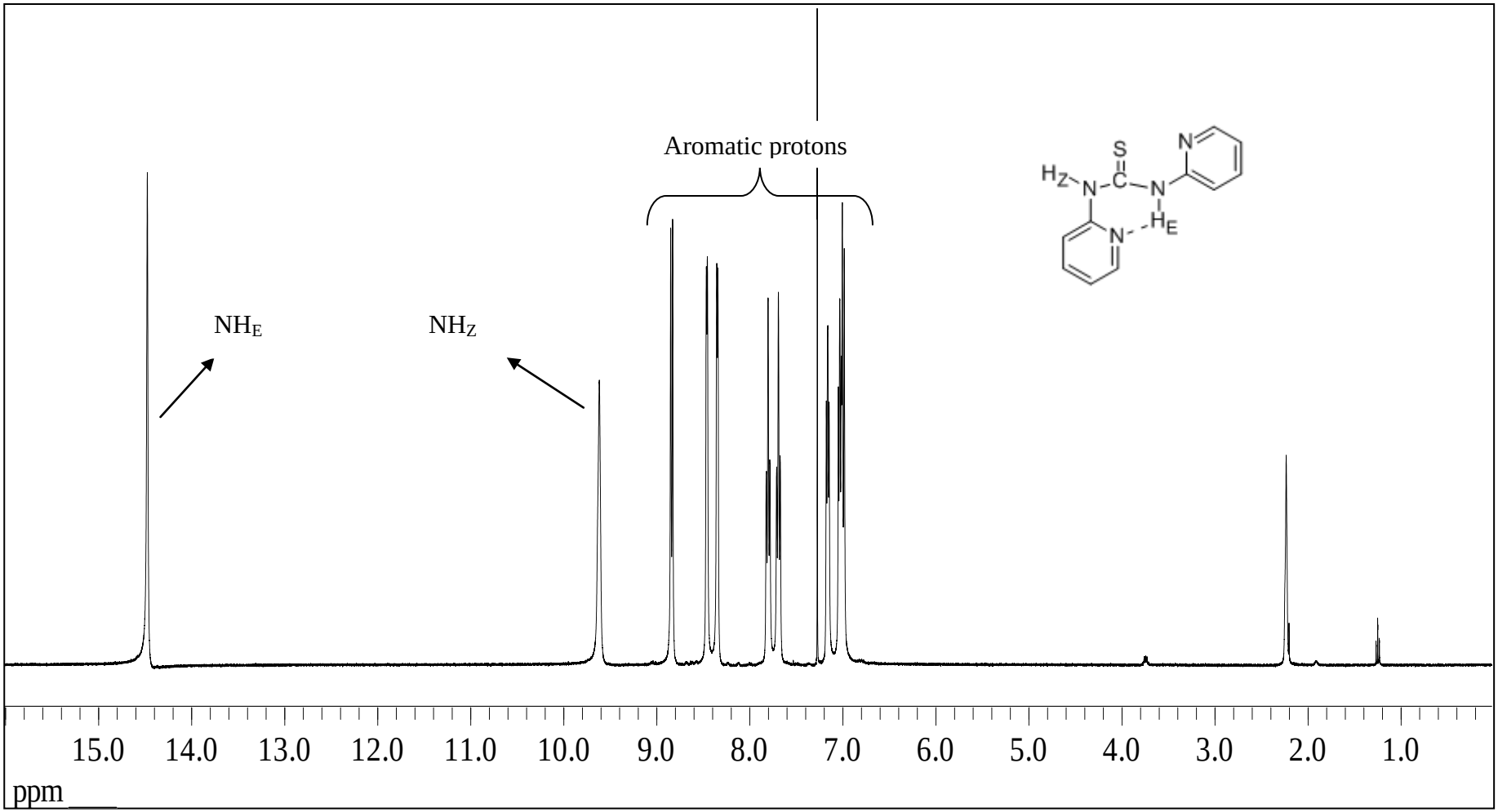


Figure 4.5. The 400 MHz ^{1}H-NMR spectrum of 1,3-di(pyridin-2-yl)thiourea in $CHCl_3$-d_1 at -15 °C.

4.1.2. 1,3-bis(3-methylpyridin-2-yl)thiourea

Like 1,3-di(pyridin-2-yl)thiourea, 1,3-bis(3-methylpyridin-2-yl)thiourea also have two interconverting E,Z and Z,E conformers (Figure 4.6).

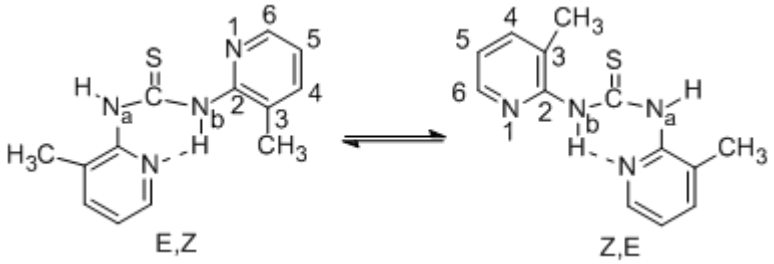


Figure 4.6. Interconverting conformers of 1,3-bis(3-methylpyridin-2-yl)thiourea.

The ^{1}H-NMR spectra of this compound in $CHCl_3$-d_1 and in C_6H_6-d_6 also display broad peaks due to rapid interconversion between the E,Z and Z,E conformers at room temperature (Figure 4.7 and 4.8). The $–NH_E$ proton, which participates in intramolecular hydrogen bonding, appears at 13.79 ppm and $–NH_Z$ proton gives a signal at 8.43 ppm in $CDCl_3$.

Aromatic protons are broad at room temperatue and appear in the range between 8.11 and 6.95 ppm in $CDCl_3$. Due to intramolecular hydrogen bonding, the two methyl groups of 1,3-bis(3-methylpyridin-2-yl)thiourea become different and thus, they give separate signals. The $–CH_3$ group on the pyridine ring, which participates in hydrogen bonding, is more deshielded than the other $–CH_3$ group. In $CDCl_3$, the two methyl groups are not base line separated and they give different singlets at 2.42 and 2.46 ppm at room temperature. On the other hand, they become quite separable at room temperature in C_6D_6; low field $–CH_{3(E)}$ group signals at 2.15 ppm and high field $–CH_{3(Z)}$ group gives a signal at 0.90 ppm in (Figure 4.7 and 4.8).

At low enough temperatures, N_b-C_2 bond in this compound is expected to be a chiral axis due to slow rotation around this bond. Low temperature NMR studies will be performed as a future work to reveal the possible chiral axis in N_b-C_2 bond.

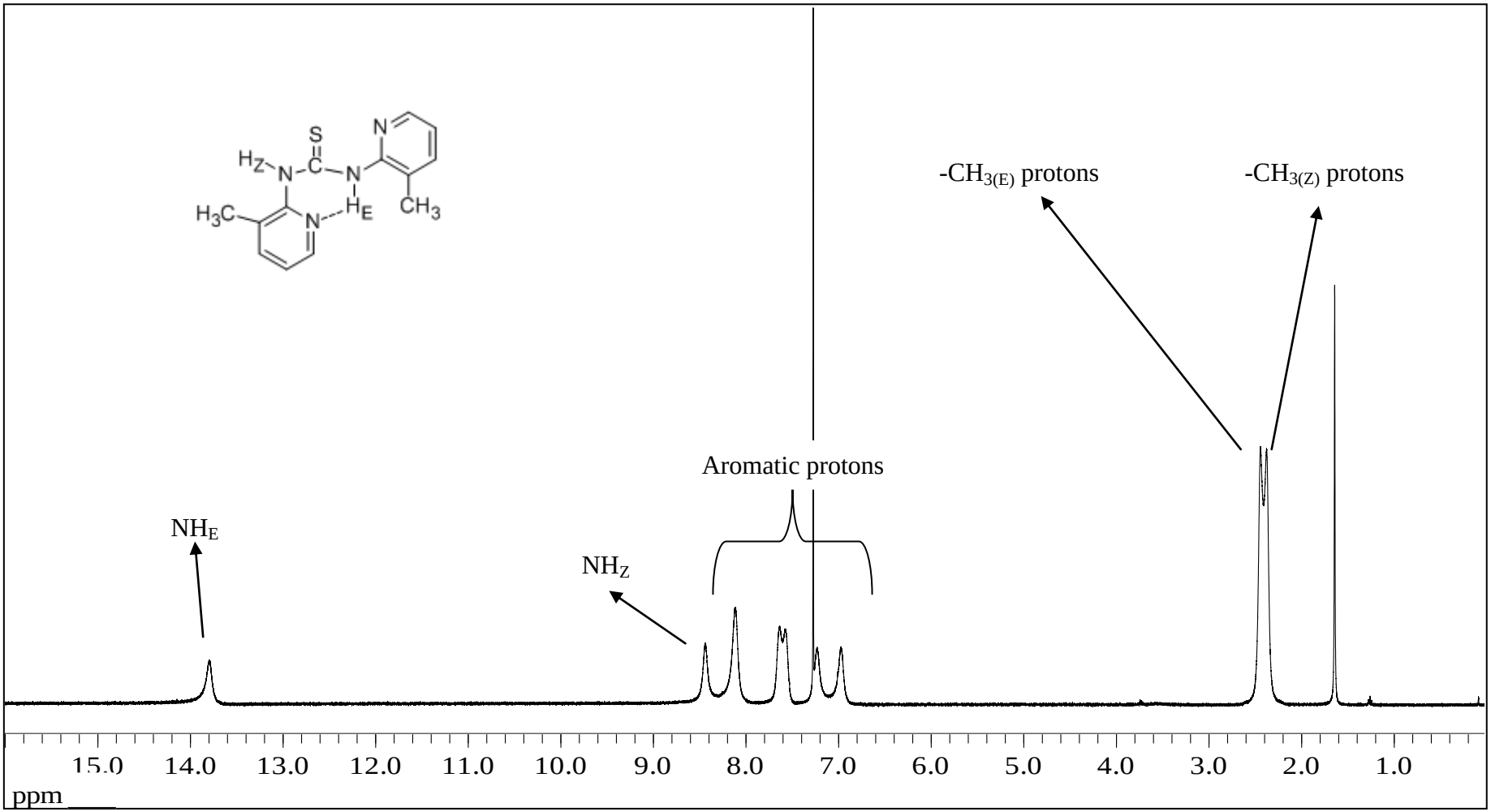


Figure 4.7. The 400 MHz ^{1}H-NMR spectrum of 1,3-bis(3-methylpyridin-2-yl)thiourea in $CHCl_3$-d_1.

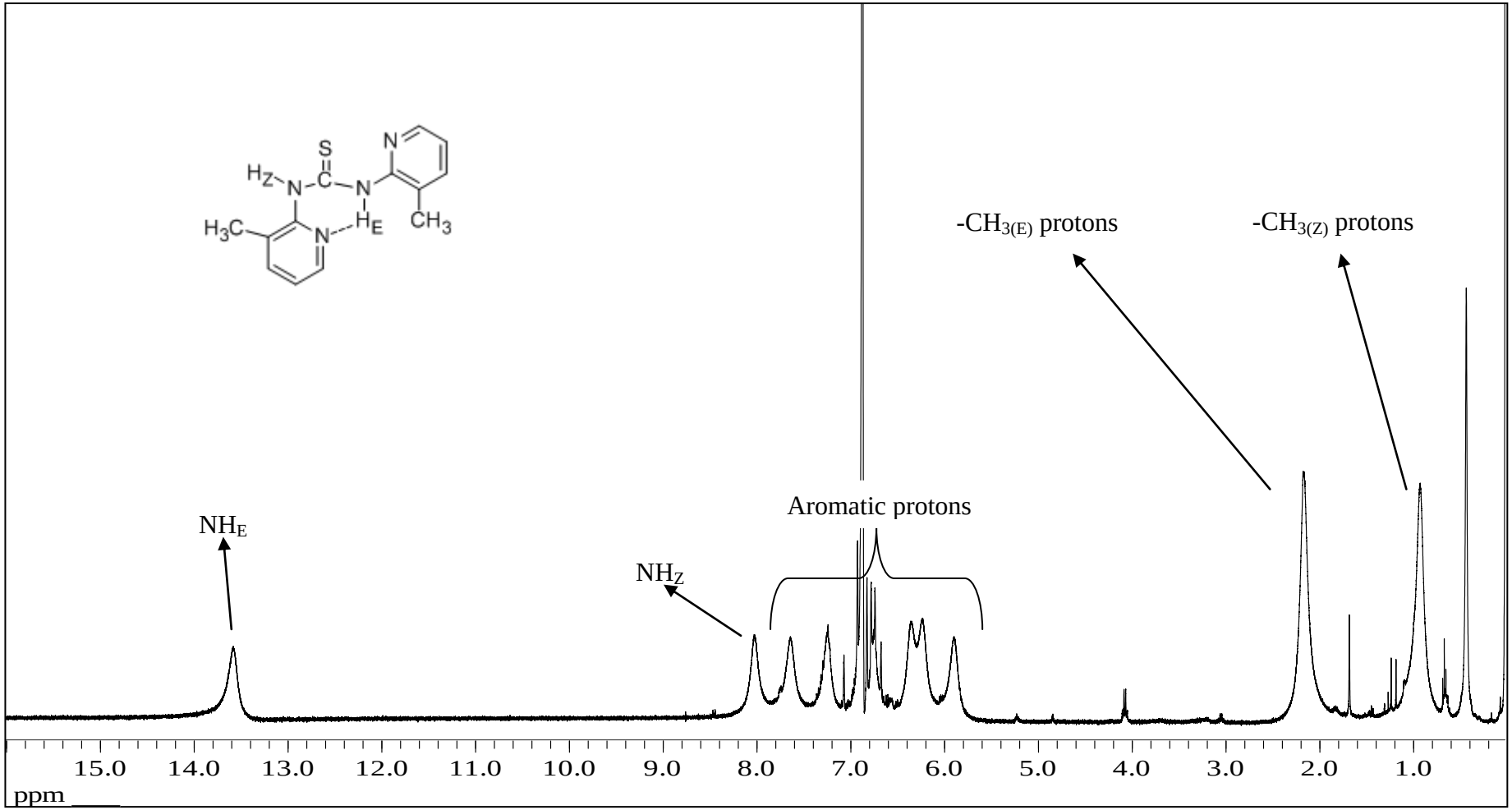


Figure 4.8. The 400 MHz ^{1}H-NMR spectrum of 1,3-bis(3-methylpyridin-2-yl)thiourea in C_6D_6.

4.2. 1,3-bis((R)-1-cyclohexylethyl)thiourea

Recently, various enantiomerically pure thioureas have been synthesized and used as catalysts in the addition of nitromethanes to aldehydes (Henry reaction) [32]. Since 1,3-bis((R)-1-cyclohexylethyl)thiourea has two chiral centers, this compound was synthesized to be used as catalyst in Henry reaction. The two –NH protons are expected to coordinate to the nitro group of nitromethanes and then, coordinated thiourea will asymmetrically direct the addition of nitromethanes to aldehydes (Figure 4.9).

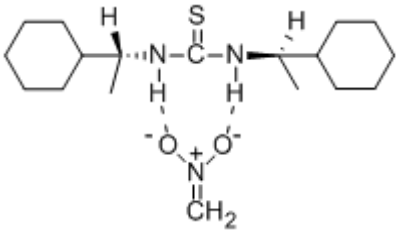


Figure 4.9. Coordination of 1,3-bis((R)-1-cyclohexylethyl)thiourea to nitromethane.

Enantiomerically pure 1,3-bis((R)-1-cyclohexylethyl)thiourea was synthesized; however, its usage as catalyst will be performed as a future work. This thiourea showed only one peak by HPLC on cellulose tris(3,5-dichlorophenylcarbamate)-Chiralpak IC column (Mobile solvent: n-Hexane/Ethanol, 95/5, flow rate 0.6 ml/min).

The ^{1}H-NMR spectrum of the compound in $CHCl_3$-d_1 (Figure 4.10) displayed a broad signal for the two –NH protons at 5.52 ppm. –CH protons at chiral centers also gave a broad signal at 3.92 ppm. This compound may be expected to make intermolecular H-bonding between the nitrogen and hydrogen of different 1,3-bis((R)-1-cyclohexylethyl) thiourea molecules and the -CH protons can give a broad signal due to this H-bonding. The cyclohexyl protons appear in the range between 1.78 and 0.95 ppm and the $–CH_3$ group gave a doublet at 1.14 ppm.

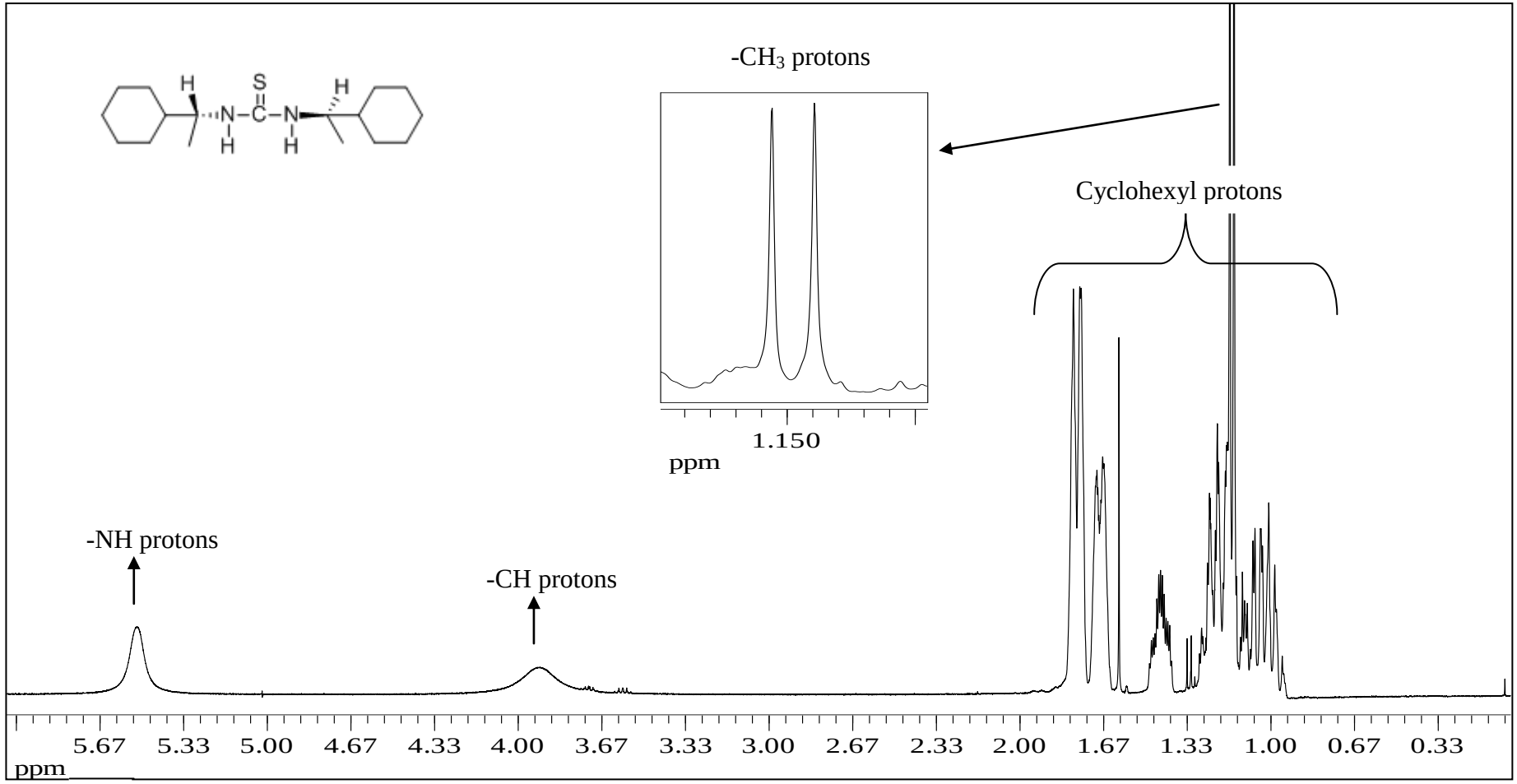


Figure 4.10. The 400 MHz ^{1}H-NMR spectrum of 1,3-bis((R)-1-cyclohexylethyl)thiourea in $CHCl_3$-d_1.

4.3. 2-arylimino-3-aryl-thiazolidine-4-ones

4.3.1. 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one

Due to the steric interaction between the lone pair on the nitrogen of the pyridine ring bonded to N_3 and, the exocylic oxygen and the imino nitrogen atoms, the rotation around the N_3-aryl bond in 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one may be restricted (Figure 4.11).

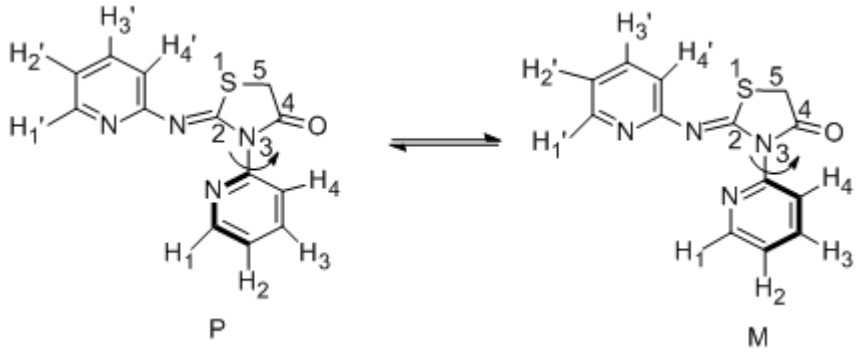


Figure 4.11. The restricted rotation around the N_3-aryl bond in 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one.

The restricted rotation creates two thermally interconvertible enantiomers; P and M (Figure 4.11). These enantiomers were investigated by HPLC on Cellulose tris(3,5-dimethylphenylcarbamate)-Chiralpak IB colum and Amylose tris (3,5-dimethyl phenyl carbamate)-Chiralpak AD column (Figure 4.12). n-Hexane/2-Propanol (95/5, flow rate: 0.5 ml/min) and n-Hexane/2-Propanol (70/30, flow rate: 0.6 ml/min) were used as mobile solvent mixtures for Chiralpak IB and AD columns, respectively. Different HPLC peaks for P and M enantiomers were not observed due to the fast rotation around the N_3-aryl bond.

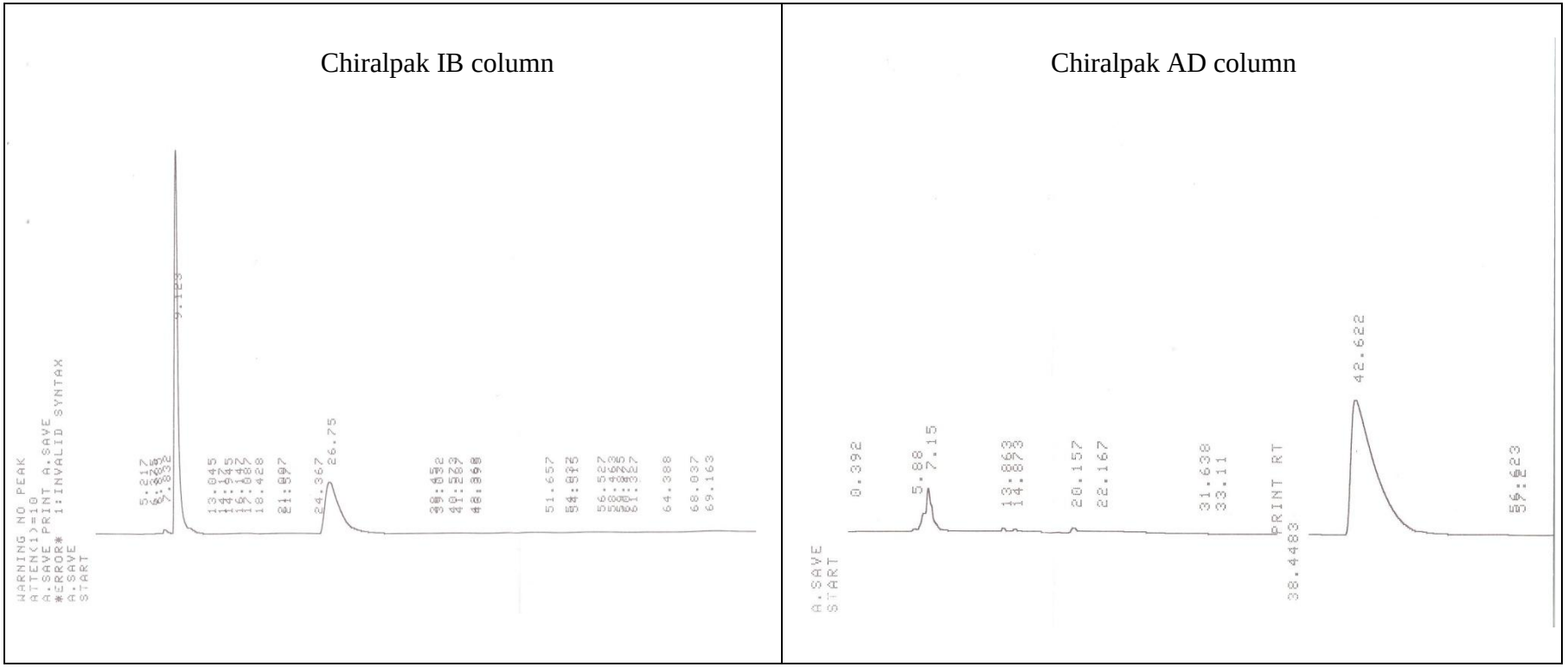


Figure 4.12. HPLC chromatogram of 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one on Cellulose tris(3,5-dimethylphenylcarbamate)-Chiralpak IB column and Amylose tris (3,5-dimethyl phenyl carbamate)-Chiralpak AD column.

Also due to the fast rotation, the ^{1}H-NMR signal of $–CH_2$ protons of this compound appeared as a singlet at room temperature in $CHCl_3$-d_1. An AB type splitting would have been observed if the rotation was slow (Figure 4.14).

The ^{1}H-NMR spectra of this compound were taken in different NMR solvents; DMF-d_7 and TFA-d_1 (Figure 4.15 and 4.16). AB splitting of the $–CH_2$ protons could not be observed in these solvents too. For this reason, the ^{1}H-NMR spectra of the compound were taken at lower temperatures in $CHCl_3$-d_1 (-5 °C, -15 °C, -30 °C and -45 °C) for the purpose of slowing down the interconversion rate of enantiomers and observing the AB splitting of $–CH_2$ protons (Figures 4.17-20). However, even at -45 °C the AB splitting could not be observed and this situation proves that the interconversion of the enantiomers is fast on the NMR timescale even at -45 °C.

In 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one compound, N_3-nitrogen has no contribution to the resonance structure of its neighbour pyridine group because lone pair electrons of N_3-nitrogen are not on the same plane with the N_3-pyridine with. On the other hand, lone pair electrons of N_3-nitrogen can increase the electron density of pyridine ring on the imino group by forming the resonance structure shown in Figure 4.13.

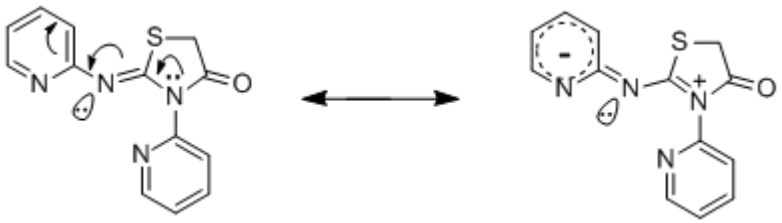


Figure 4.13. The resonance structure of 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one.

Due to this resonance structure, ^{1}H-NMR signals of the pyridine ring on the imino group is more shielded than those of the other pyridine ring. The aromatic protons of 3-(pyridin-2-yl)-2-(pyridin-2-ylimino) thiazolidin-4-one can be observed seperately due to the shielding difference the two pyridine rings. Chemical shift values of protons in different solvents are given in Table 4.1.

Table 4.1. 400 MHz ^{1}H-NMR spectral data for 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one in various solvents.

Solvents	**$CHCl_3$-d_1**	**TFA-d_1**	**DMF-d_7**	**Toluene-d_8**
Protons on C-5 (ppm)	3.88	4.56	4.34	2.95
Aromatic protons (ppm)	8.65-6.88	9.06-7.78	8.86-7.04	8.36-6.41

According to the ^{13}C-NMR spectrum of the compound, carbonyl and imino group carbons give signal at 171.8 and 148.9 ppm, respectively. $-CH_2$ carbon displays a signal at 33.8 ppm and aromatic carbons signals in the range between 157.9 and 120.1 ppm (Figure 4.21).

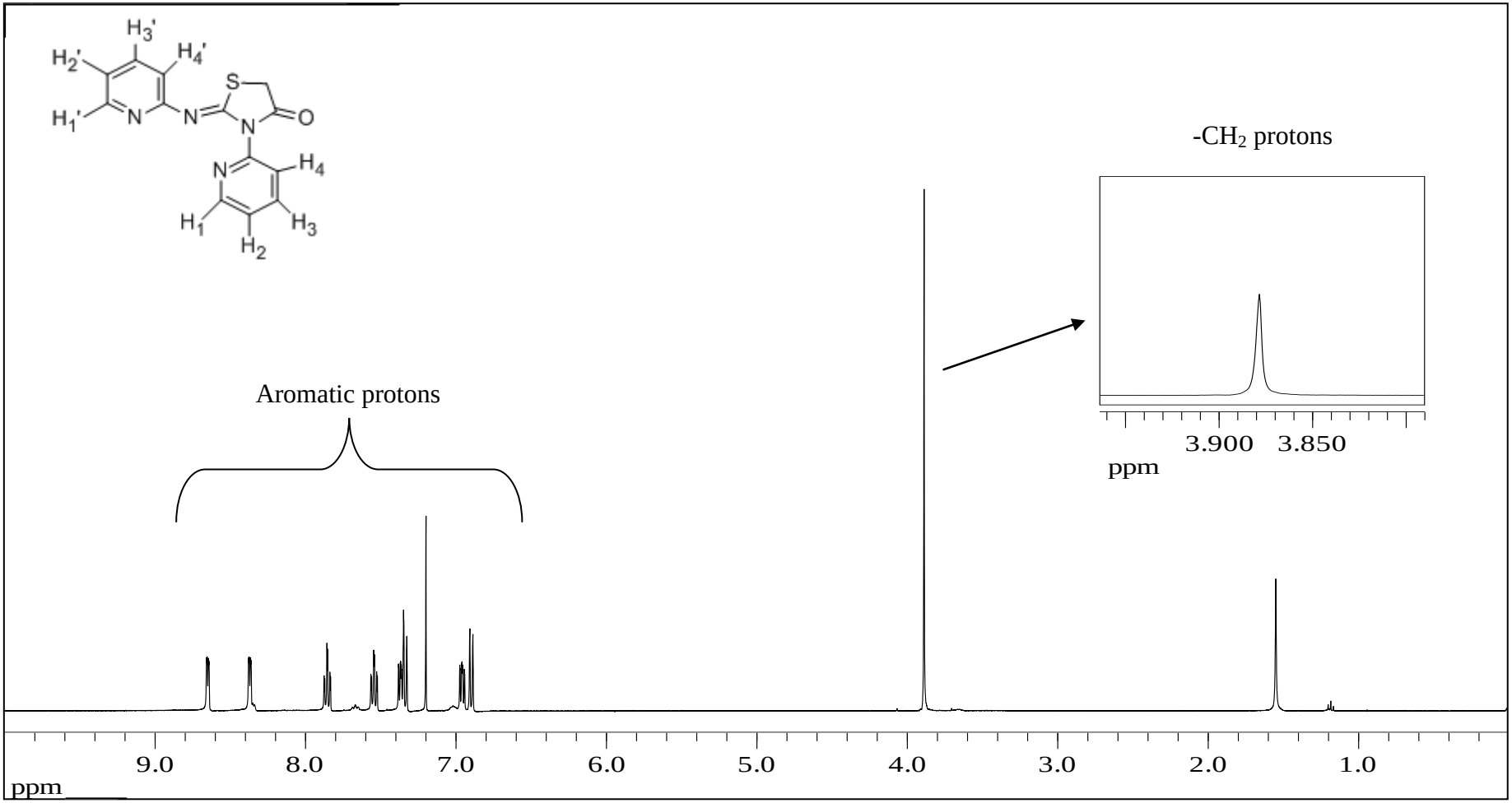


Figure 4.14. The 400 MHz ^{1}H-NMR spectrum of 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one in $CHCl_3$-d_1.

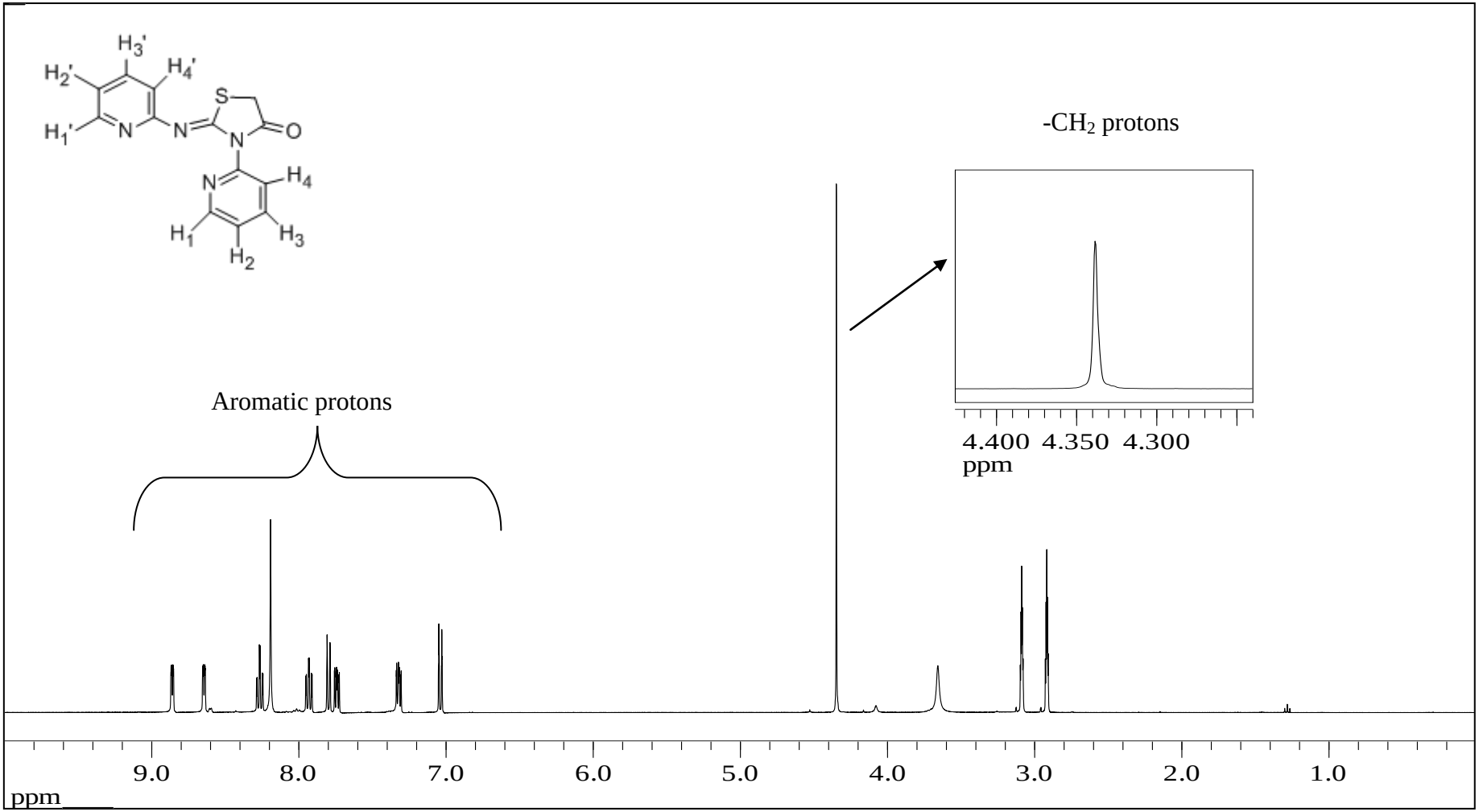


Figure 4.15. The 400 MHz ^{1}H-NMR spectrum of 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one in DMF-d_7.

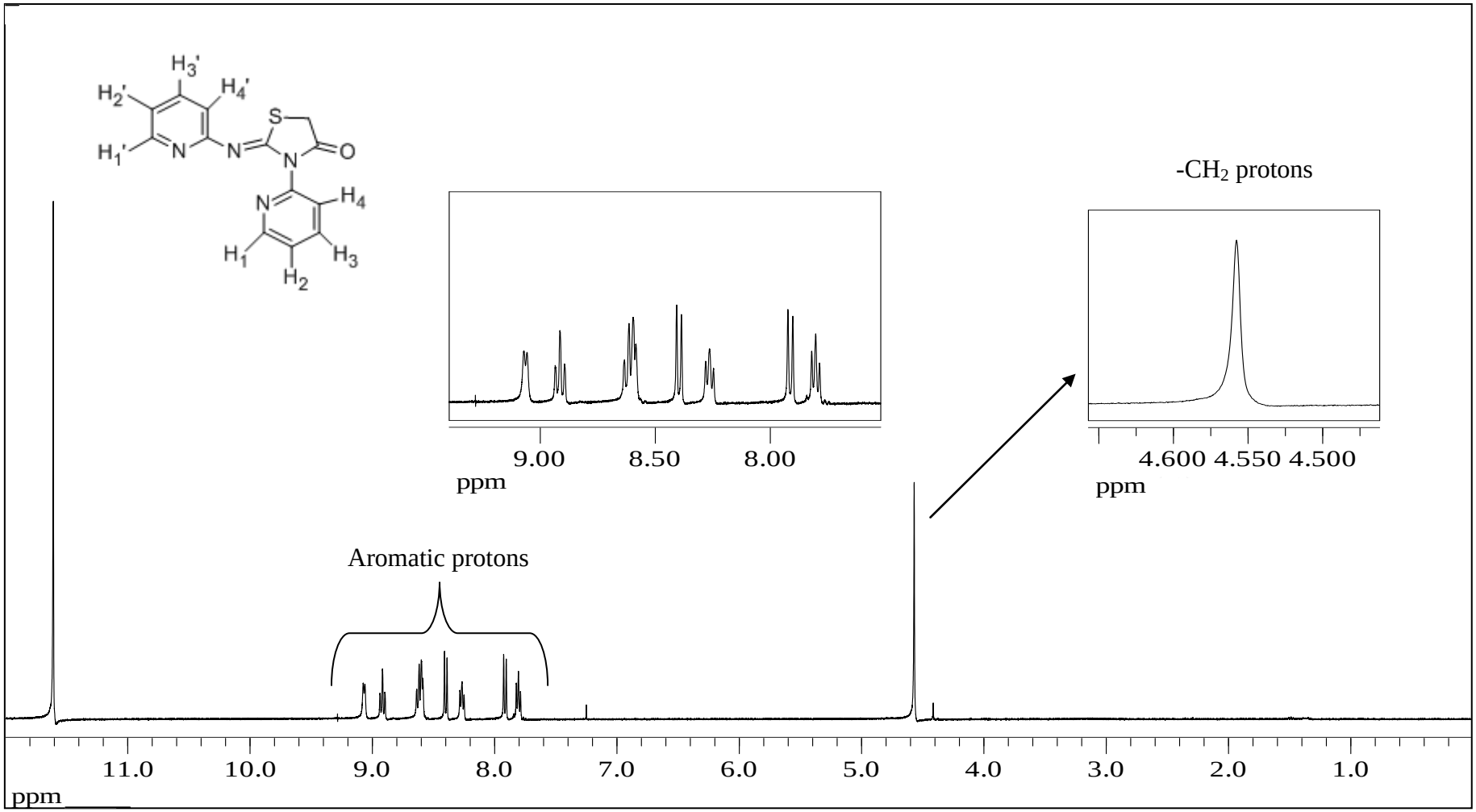


Figure 4.16. The 400 MHz ^{1}H-NMR spectrum of 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one in TFA-d_1.

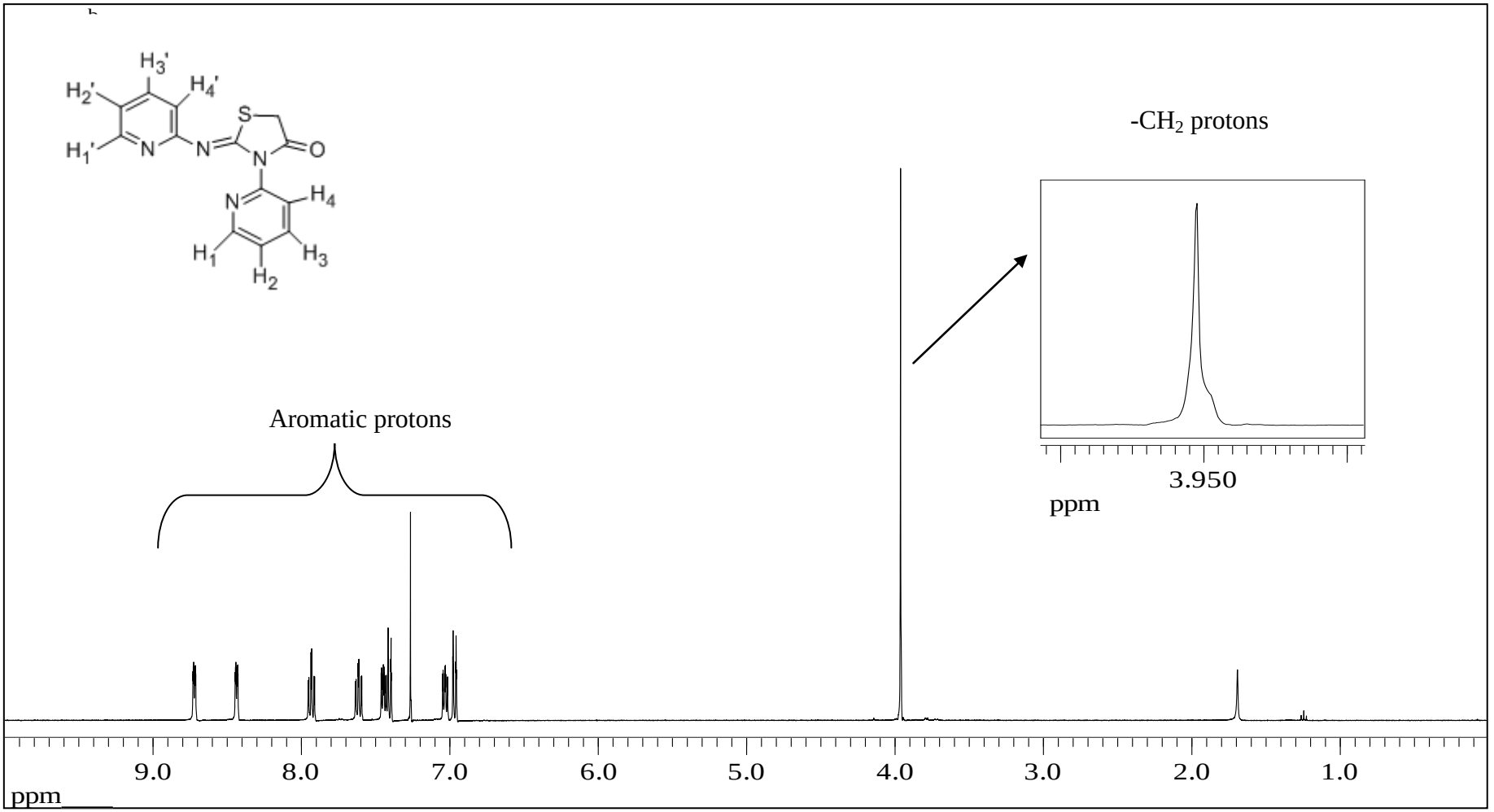


Figure 4.17. The 400 MHz ^{1}H-NMR spectrum of 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one in $CHCl_3$-d_1 at -5 °C.

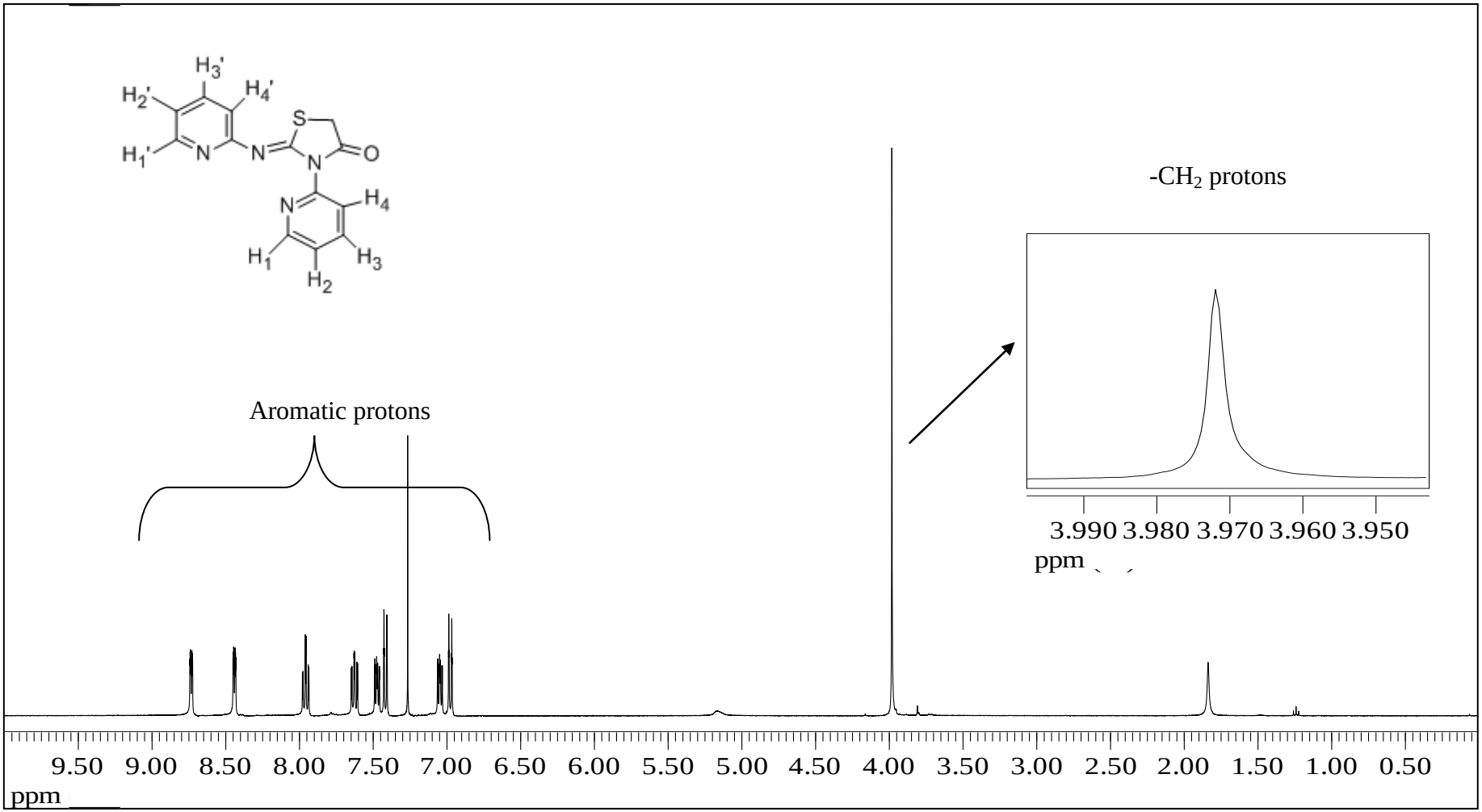


Figure 4.18. The 400 MHz ^{1}H-NMR spectrum of 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one in $CHCl_3$-d_1 at -15 °C.

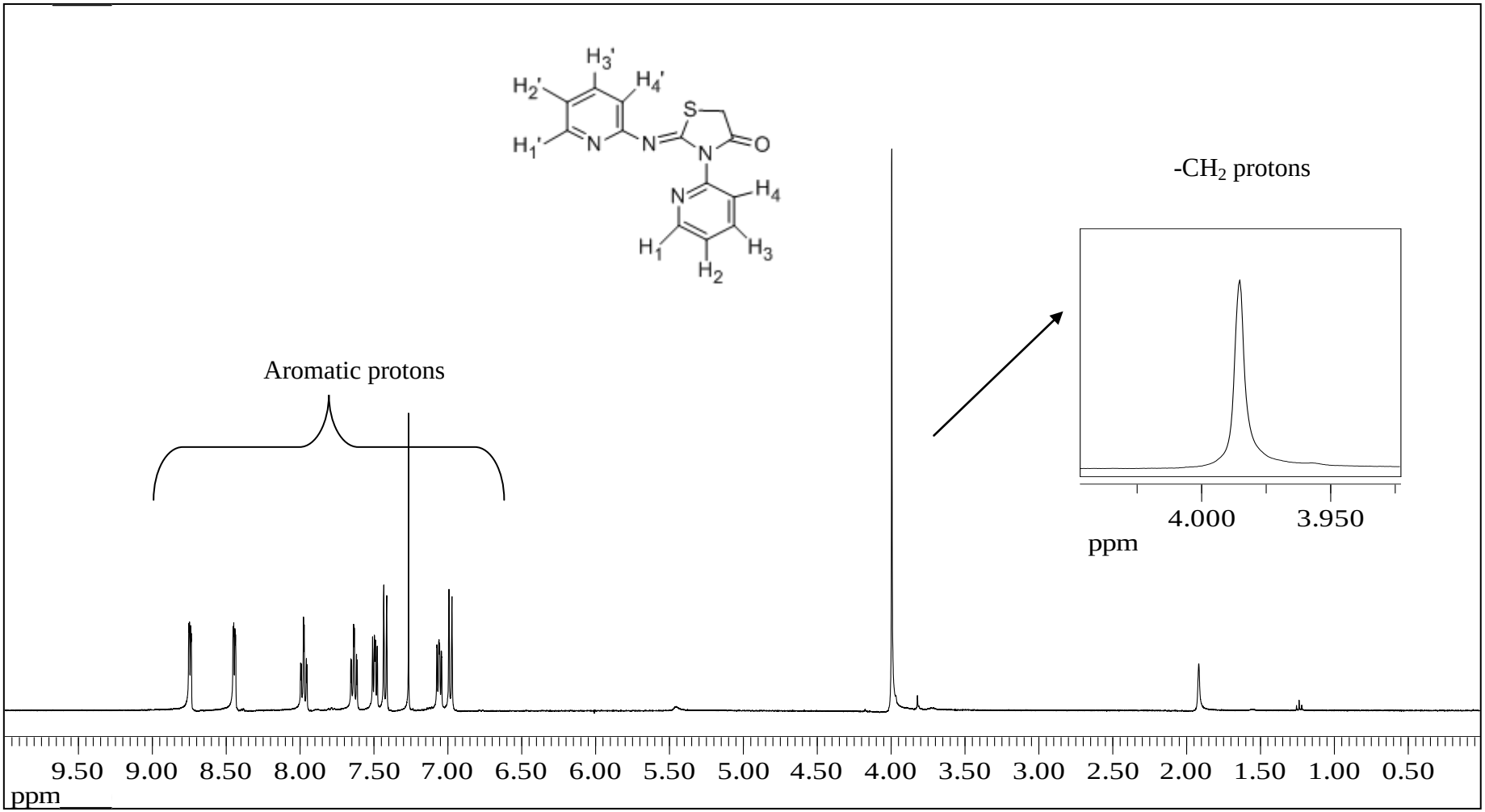


Figure 4.19. The 400 MHz ^{1}H-NMR spectrum of 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one in $CHCl_3$-d_1 at -30 °C.

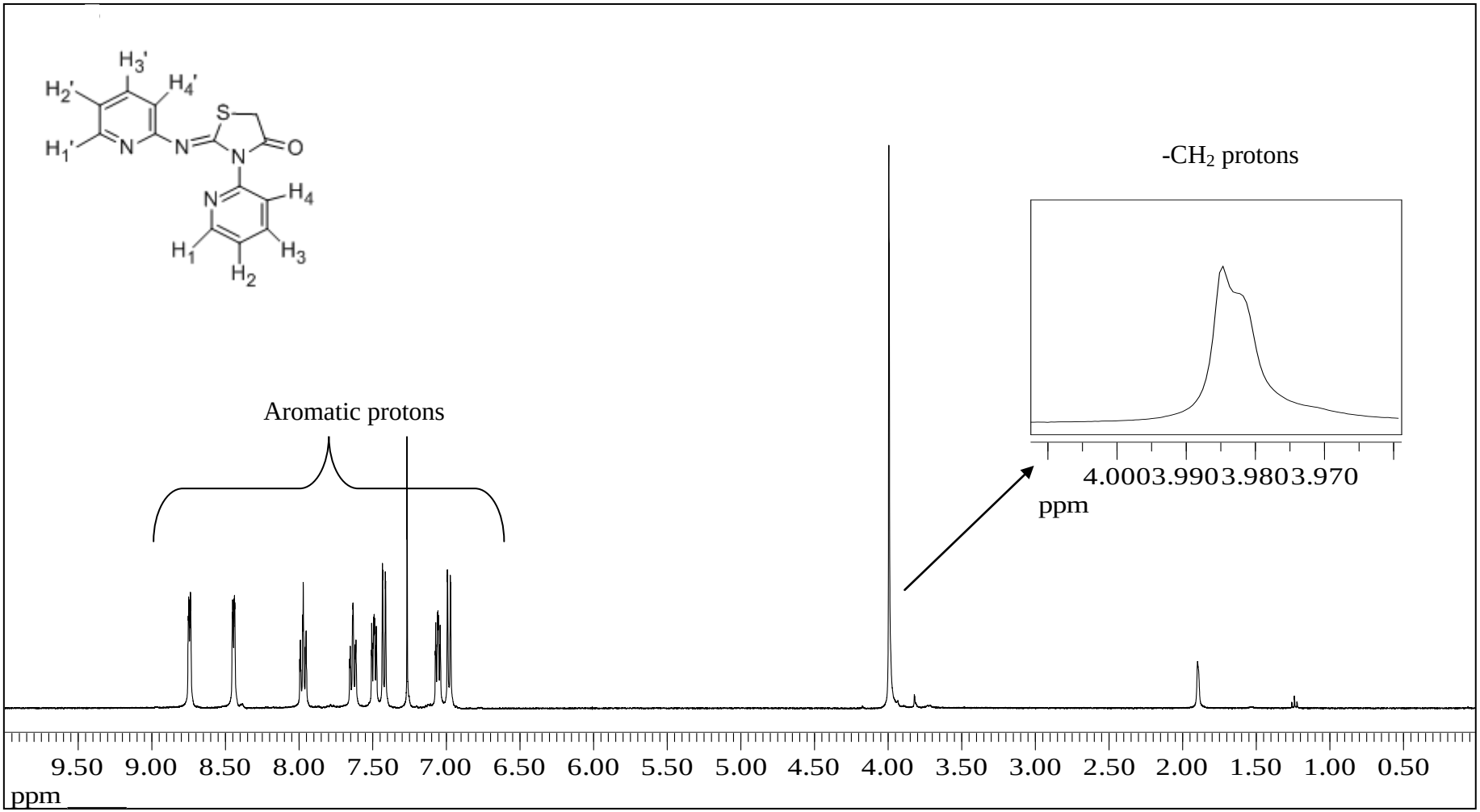


Figure 4.20. The 400 MHz ^{1}H-NMR spectrum of 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one in $CHCl_3$-d_1 at -45°C.

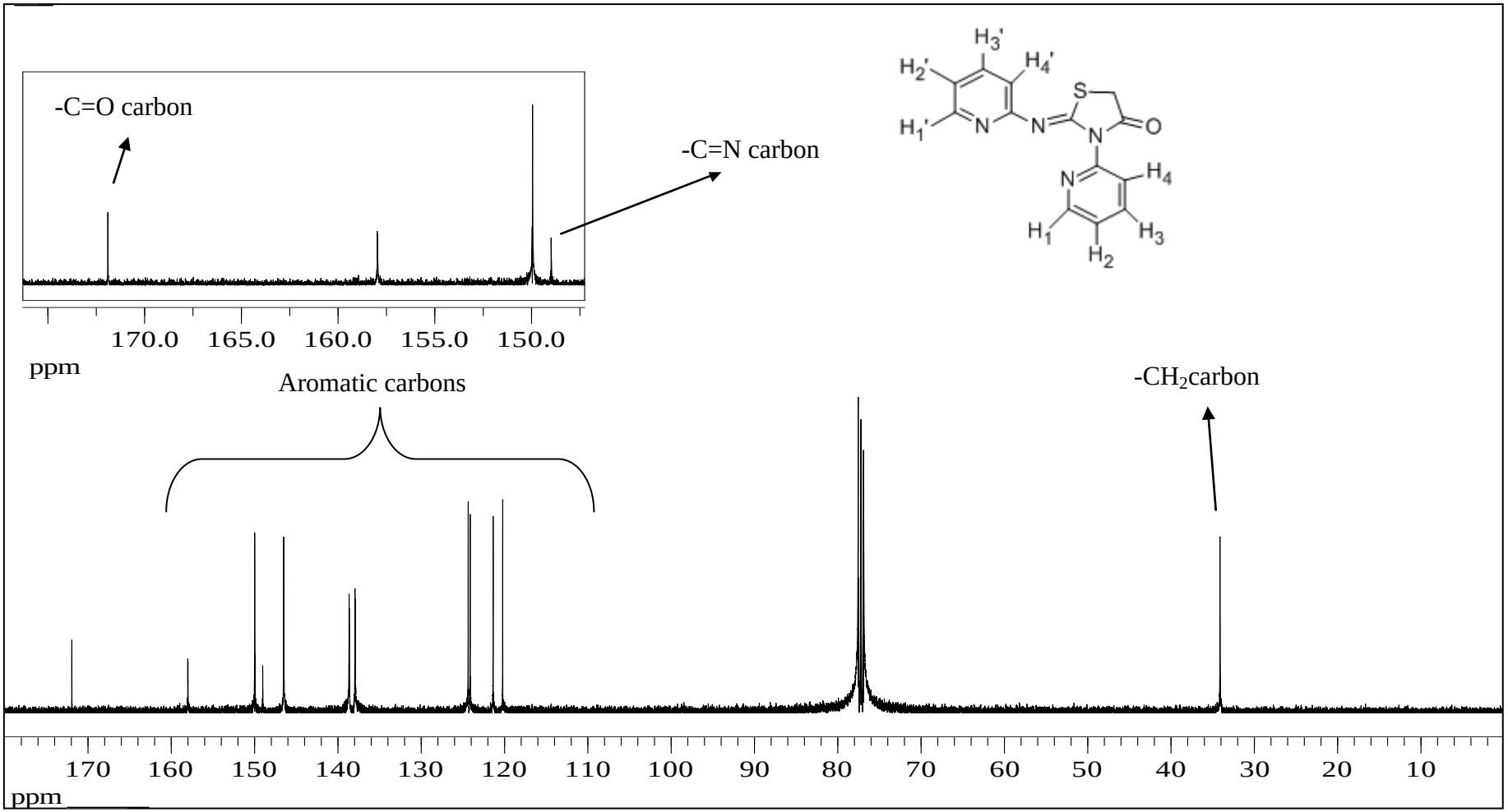


Figure 4.21. The ^{13}C-NMR spectrum of 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one in $CHCl_3$-d_1.

4.3.2. 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one

It is possible that 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one compound may have both E and Z configurations since the compound have a C=N double bond (Figure 4.22).

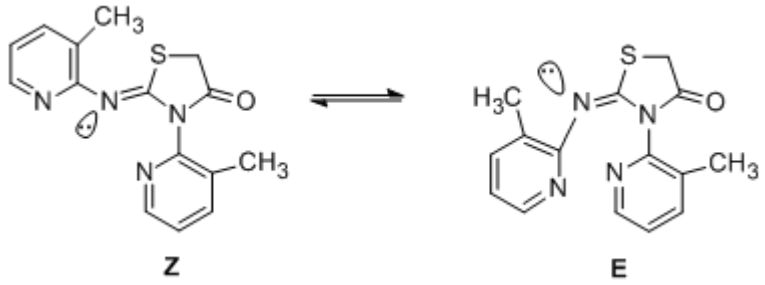


Figure 4.22. Possible E and Z configurations of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one.

A 2D-NOESY (Nuclear Overhauser effect spectroscopy) experiment was performed to find out the stereochemistry of the C=N double bond (Figure 4.26). 2D-NOESY NMR technique indicates which protons are close in space. If the through space distance between the two protons is smaller than 4 A°, a crosspeak is seen in the spectrum. It was found that 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one has a Z configuration because 2D-NOESY crosspeaks could not be observed for the protons of the two pyridine rings. Although 2D-NOESY experiments were not performed for other 2-arylimino-3-aryl-thiazolidine-4-ones and its derivatives, they are also expected to have a Z configuration due to the steric hindrance between two pyridine rings.

3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one product has a restricted rotation around N_3-aryl single bond as a result of the steric interaction between the *ortho* substituent on the N_3-pyridine ring and, the exocylic oxygen and the imino nitrogen (Figure 4.23).

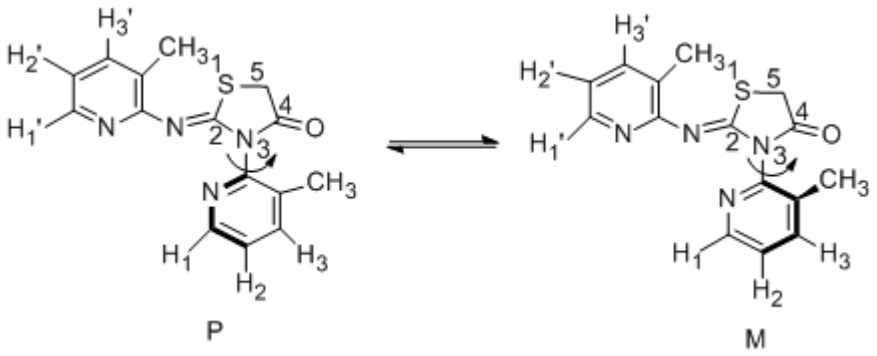


Figure 4.23. The restricted rotation around the N_3-aryl bond in 3-(3-methyl pyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one.

As a consequence of the restricted rotation, thermally interconvertible **P** and **M** enantiomers were formed. These isomers were investigated by HPLC on Cellulose tris(3,5-dimethylphenylcarbamate)-Chiralpak IB column (Figue 4.27). For the analysis, n-Hexane/2-Propanol (95/5, flow rate: 0.6 ml/min) were used as mobile solvent mixture. Under these conditions retention times of the enantiomers were 22.5 min and 38.6 min and ratio of the enantiomers was found to be 50% each .

Since the two enantiomers were separable, determination of the rotational barrier to hindered rotation was done by thermally interconverting the micropreparatively separated enantiomer to its counterpart. For this process, the enantiomers of the compound were separated by HPLC on Cellulose tris(3,5-dimethylphenylcarbamate)-Chiralpak IB column. The mobile solvent was n-Hexane/2-Propanol (95/5, flow rate: 0.6 ml/min) and the column temperature was 7 °C. As soon as each enantiomer was collected, the mobile solvent was evaporated immediately. This process was repeated successively until collecting 0.2 mg of each isomer. Then, one of the enantiomers was dissolved in about 200 µl of HPLC absolute ethanol and 40 µl of this solution was injected into the column to determine the initial concentration. The solution was kept in an oil bath at a constant temperature of 40 °C. The thermal racemization process was followed by taking 40 µl of the separated sample at certain time intervals. This process was repeated until enough data (Table 4.2), which shows the change of the relative percent composition of each enantiomer according to time, was recorded.

Table 4.2. Time vs relative percent composition of enantiomers of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one at 40 °C.

Time	**Enantiomer 1 (Percent ratio)**	**Enantiomer 2 (Percent ratio)**
0 s	69.36 %	30.64 %
2760 s	59.12 %	40.88 %
6060 s	53.80 %	46.20 %
8880 s	53.10 %	46.90 %
11700 s	51.84 %	48.16 %

The relative percent composition values were substituted into Equation 2.12 and a graph of the obtained results versus time (Figure 4.25) was plotted.

$$\ln ([M]-[M]_{eq}/[M]_0-[M]_{eq})=-2kt \qquad (2.12)$$

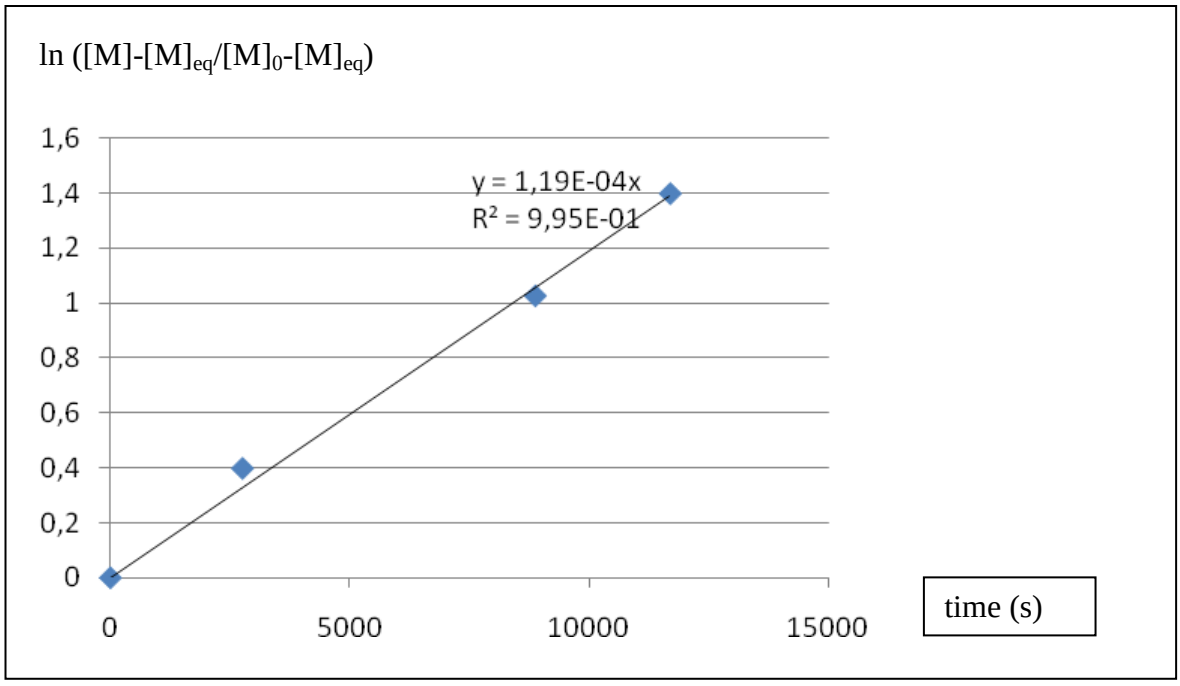


Figure 4.24. The plot of $\ln(([M]_0-[M]_{eq}/[M]-[M]_{eq}))$ versus time at 313 K for 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one.

From the slope of the graph ($y=1,19\times10^{-4}x$), the first order rate constant (k) was calculated and it was found to be $0,595\times10^{-4}$ s^{-1}. This value of the rate constant was substituted into Equation 2.13 and the energy barrier of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one was found to be 102.106 kJ/mole.

$$\Delta G^{\#}=RT\ln(k_b.T/k.h) \qquad (2.13)$$

In 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidine-4-one derivative, it was found that the rotation around N_3-aryl bond is too fast to make the enantiomeric isomer separation observable by enantioselective HPLC. On the other hand, 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one has a rotational barrier of 102.106 kJ/mole. By taking these findings into consideration, it can be concluded that inserting a methyl group into the C_3 position of pyridine ring in 2-arylimino-3-aryl-thiazolidine-4-one efficiently increases the rotational barrier around the N_3-aryl bond.

The restricted rotation around the N_3-aryl bond giving rise to axial chirality can be proved by observing an AB splitting pattern for the ^{1}H-NMR signal of the $-CH_2$ protons at C_5 position of the thiazolidinone ring. However, an AB type splitting could not be observed for this compound $CHCl_3$-d_1; the ^{1}H-NMR signal of $-CH_2$ protons of the compound appeared as a singlet at room temperature (Figure 4.28). On the other hand, AB type splitting of the $-CH_2$ protons was observed in different solvents such as benzene-d_6, TFA-d_1 and toluene-d_8 (Figure 4.29–31). For these solvents, the chemical shift values of the two $-CH_2$ protons were calculated according to Equations 2.2 and 2.3 and they were presented in Table 4.3.

Since chemical shift (ν) is a solvent dependent NMR parameter, the chemical shift difference ($\Delta\nu$) between two protons can vary in different NMR solvents. If the chemical shift difference between two AB type protons approaches to zero in a specific solvent, then the inner peaks of the AB type splitting of these protons start to coalescence and the outer ones tend to vanish [33]. This is the situation in $CHCl_3$-d_1. The inner peaks of the AB splitting coalescence and the outer ones vanish so that the ^{1}H-NMR signal of $-CH_2$ protons looks like as a singlet (Figure 4.28). On the other hand, the chemical shift difference

between the two $-CH_2$ protons is large enough in benzene-d_6, TFA-d_1 and toluene-d_8 and this situation allows these protons to give an AB splitting (Figures 4.29–31).

Like 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one compound, N_3-nitrogen of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one also increases the electron density of pyridine ring on the imino group by forming a resonance structure as shown in Figure 4.25.

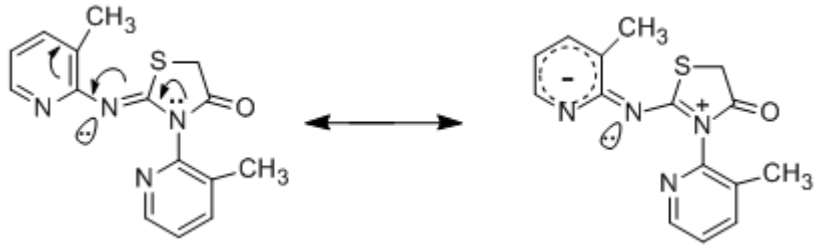


Figure 4.25. The resonance structure of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one.

Table 4.3. 400 MHz ^{1}H-NMR spectral data for 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one in various solvents.

Solvents	**$CHCl_3$-d_1**	**TFA-d_1**	**Benzene- d_6**	**Toluene-d_8**
Protons on C-5 (ppm)	3.96	4.62 and 4.56	2.76 and 2.68	3.08 and 3.00
Aromatic protons (ppm)	8.53-6.91	8.98-7.70	8.03-6.16	8.29-6.46
-CH_3 protons (on the N_3 pyridine ring) (ppm)	2.29	2.70	1.69	1.99
CH_3 protons (on the imino pyridine ring) (ppm)	1.93	2.47	1.58	1.84

Due to this resonance structure, the pyridine ring protons on the imino group become more shielded than those of the other pyridine ring protons. So, aromatic protons of the compound can be observed separately due to the shielding difference between the two pyridine rings. Chemical shift values of protons in different solvents are given in Table 4.3.

According to the ^{13}C-NMR spectrum of the compound, carbonyl and imino group carbons give signal at 170.4 and 147.3 ppm, respectively. $–CH_2$ carbon gives a signal at 32.9 ppm and aromatic carbons are in the range between 155.1 and 119.1 ppm. $–CH_3$ group on the N_3 pyridine ring and the other one on the imino pyridine ring display a signal at 16.0 and 15.7, respectively (Figure 4.32).

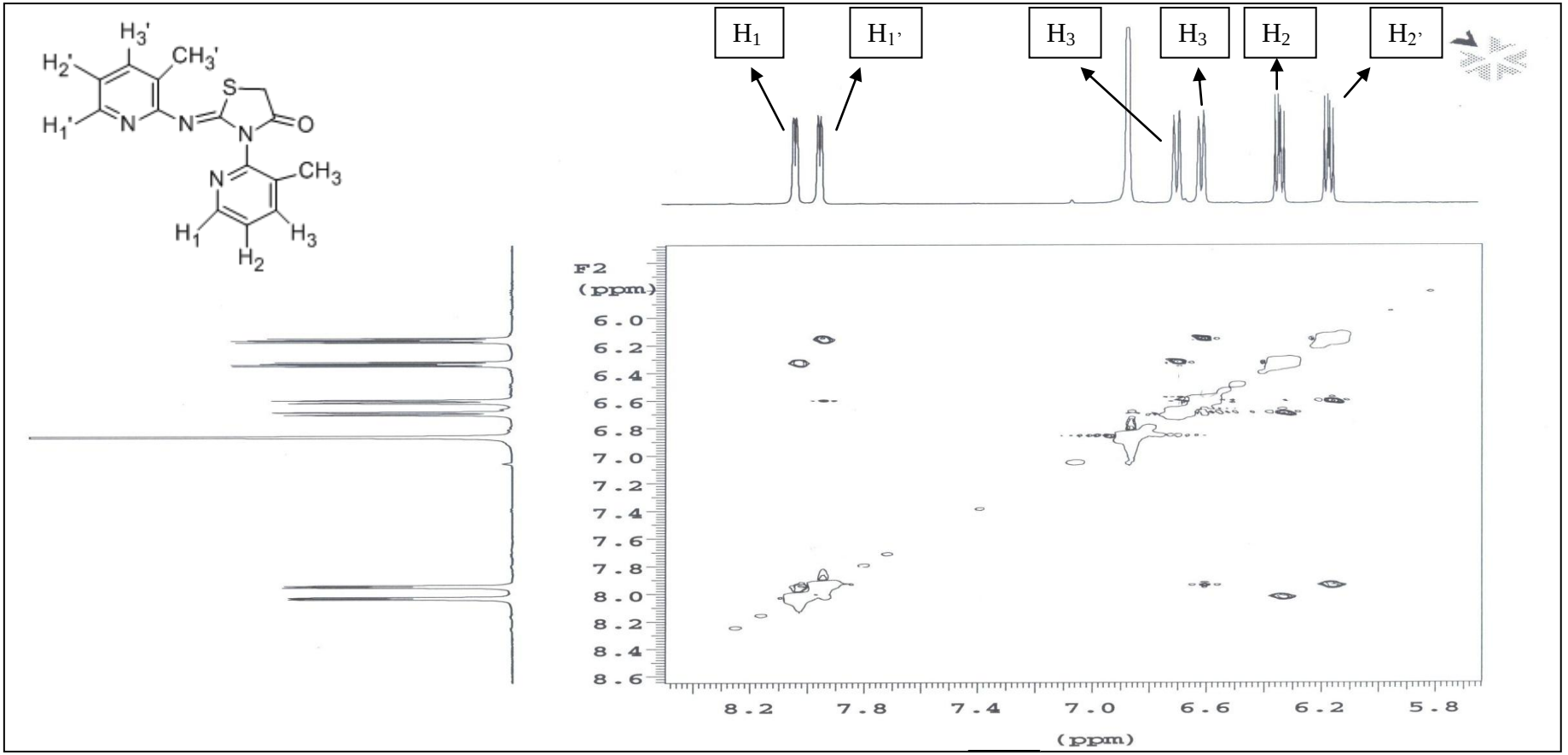


Figure 4.26. Aromatic part of 2D-NOESY spectrum of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one in $CHCl_3$-d_1.

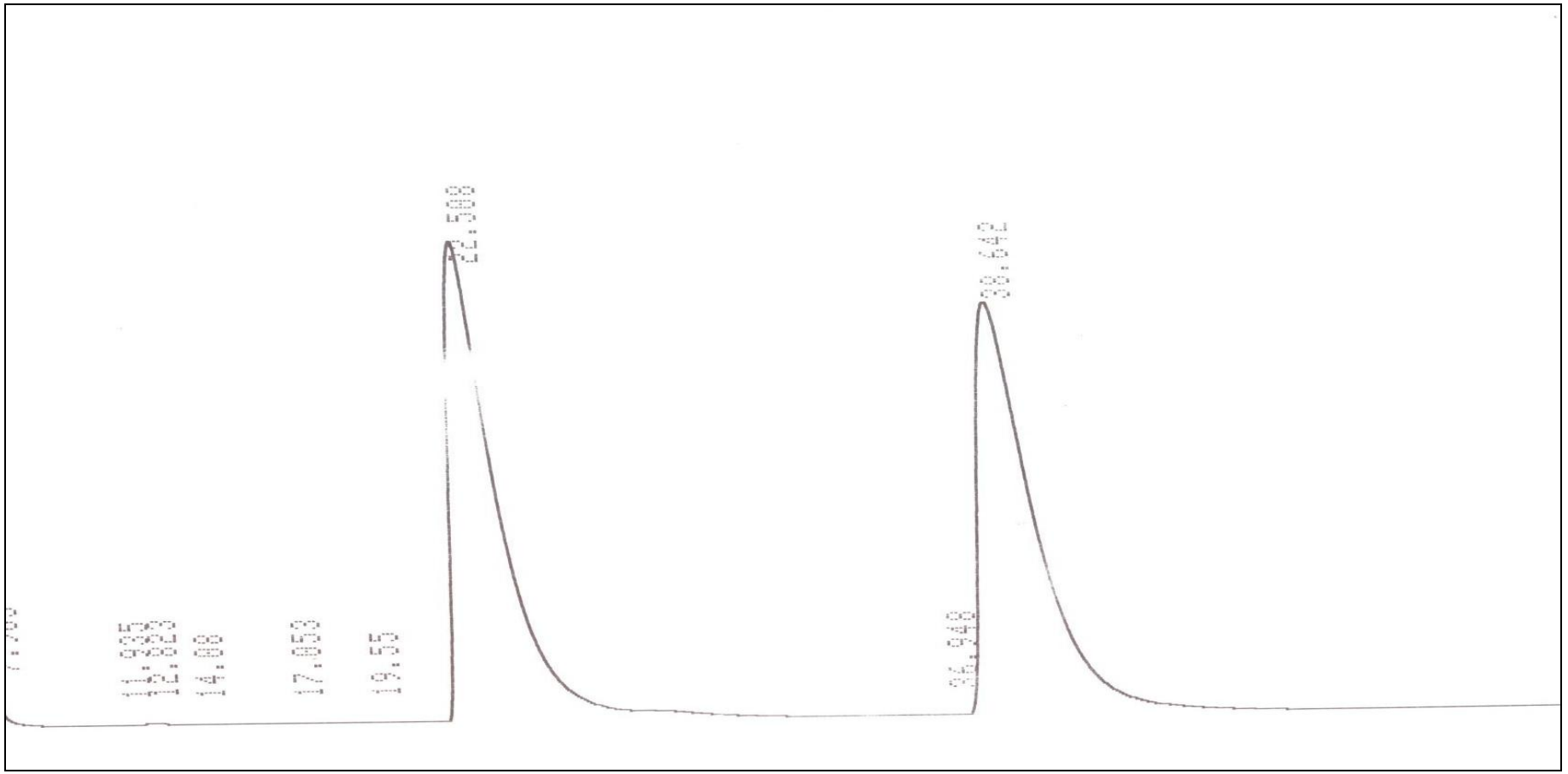


Figure 4.27. HPLC chromatogram of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one on Cellulose tris(3,5-dimethylphenylcarbamate)-Chiralpak IB column. (Mobile solvent: n-Hexane/2-Propanol; 95/5; flow rate: 0.6 ml/min).

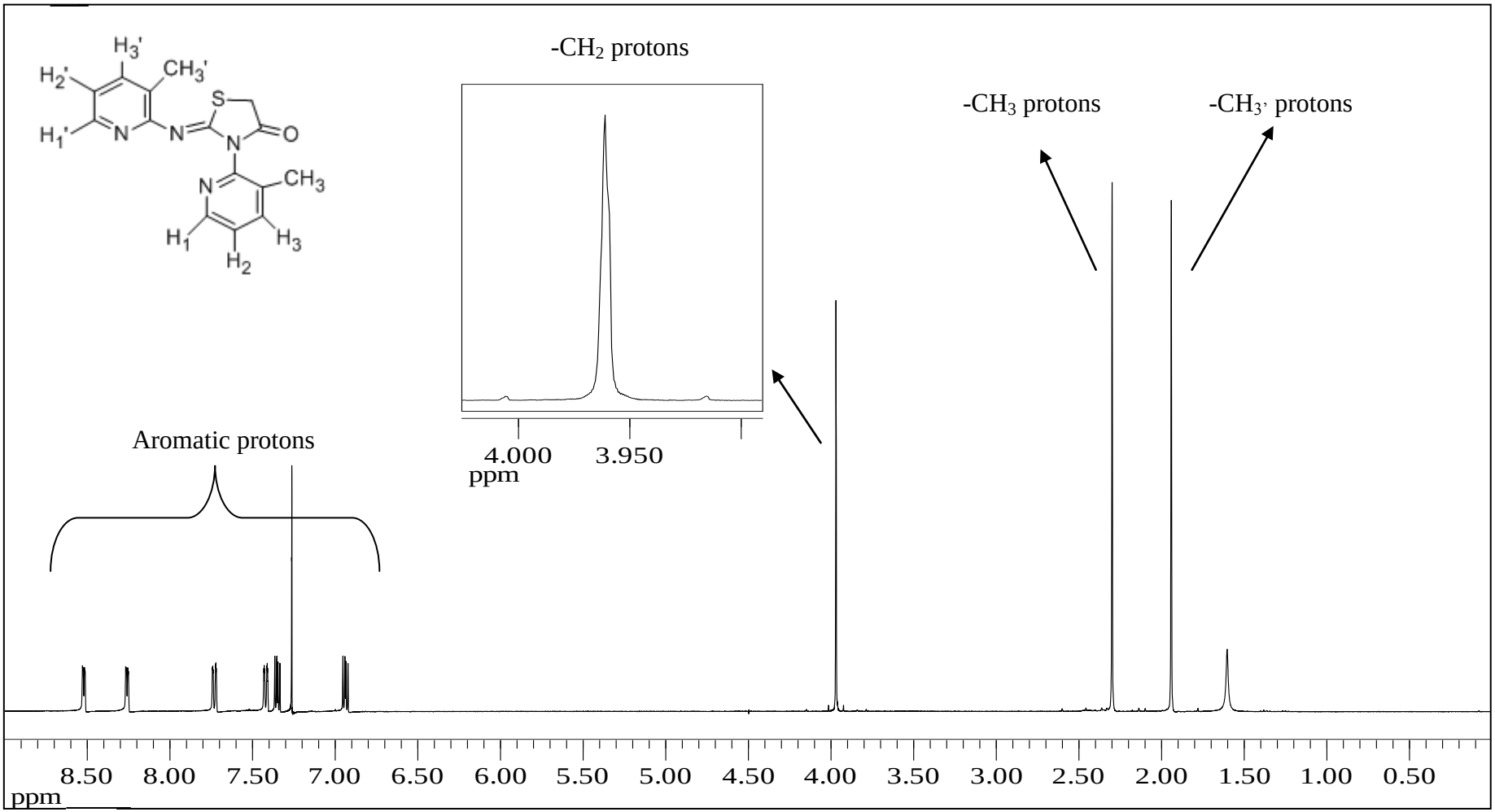


Figure 4.28. The 400 MHz ^{1}H-NMR spectrum of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one in $CHCl_3$-d_1.

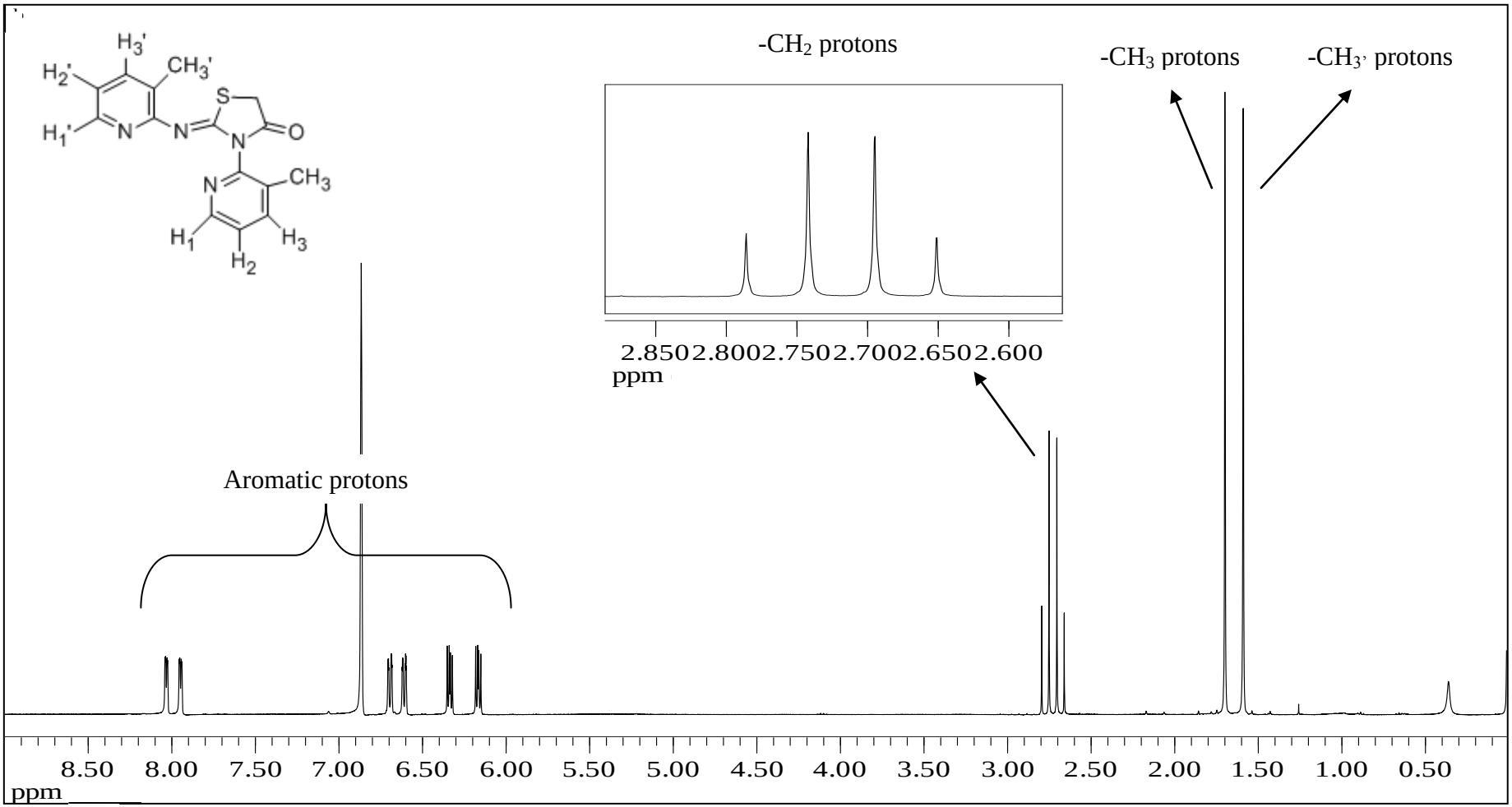


Figure 4.29. The 400 MHz ^{1}H-NMR spectrum of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one in benzene-d_6.

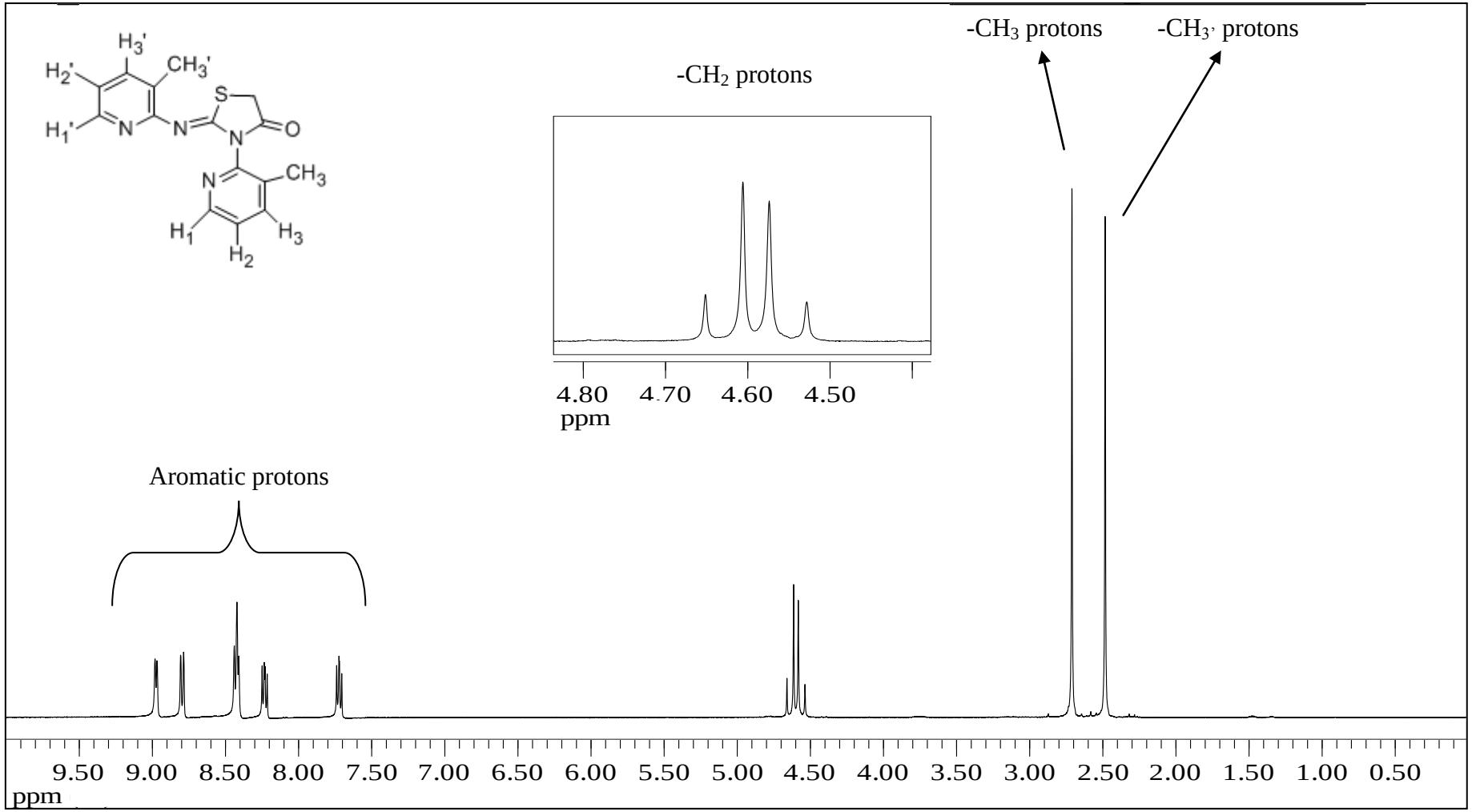


Figure 4.30. The 400 MHz ^{1}H-NMR spectrum of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one in TFA-d_1.

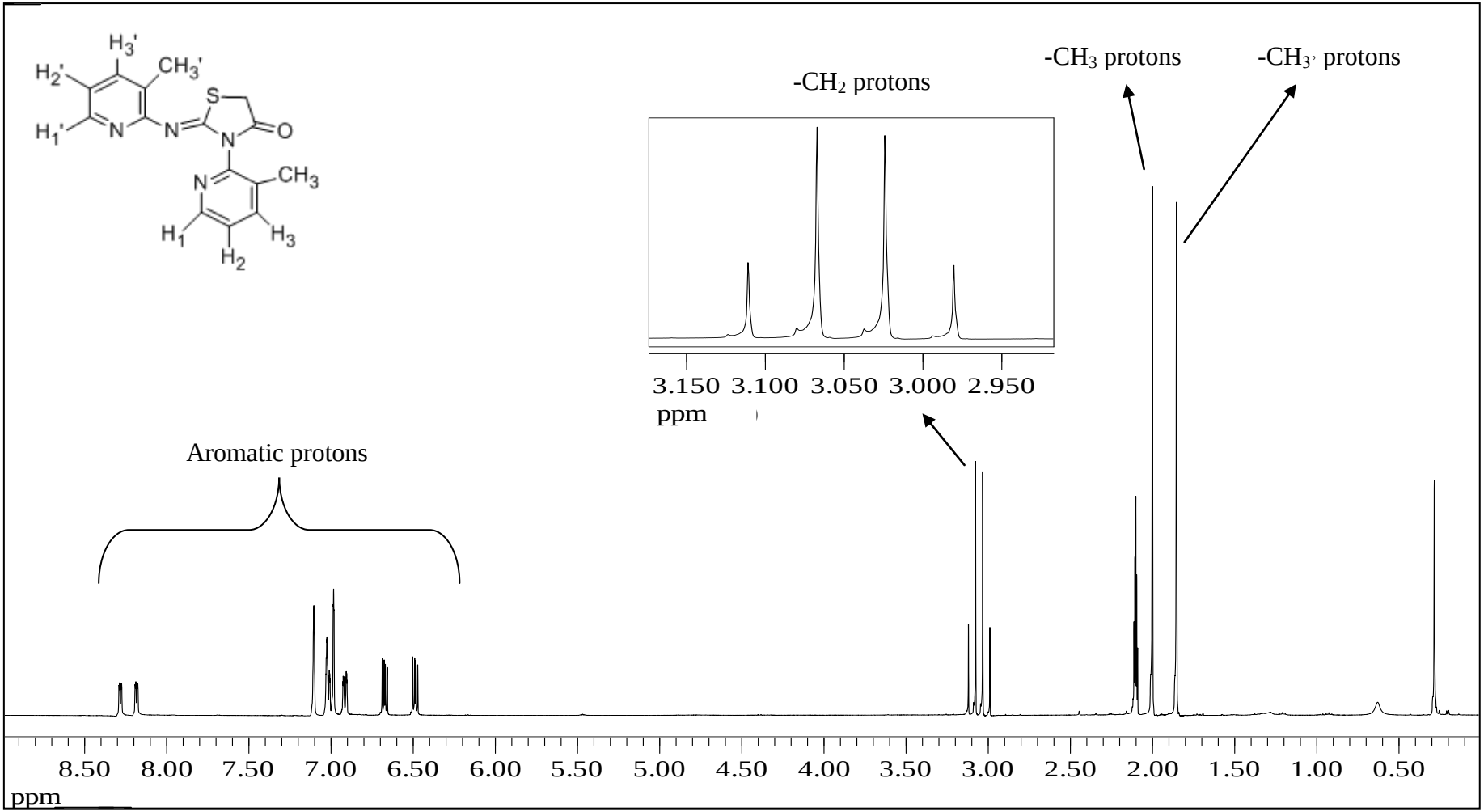


Figure 4.31. The 400 MHz ^{1}H-NMR spectrum of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one in toluene-d_8.

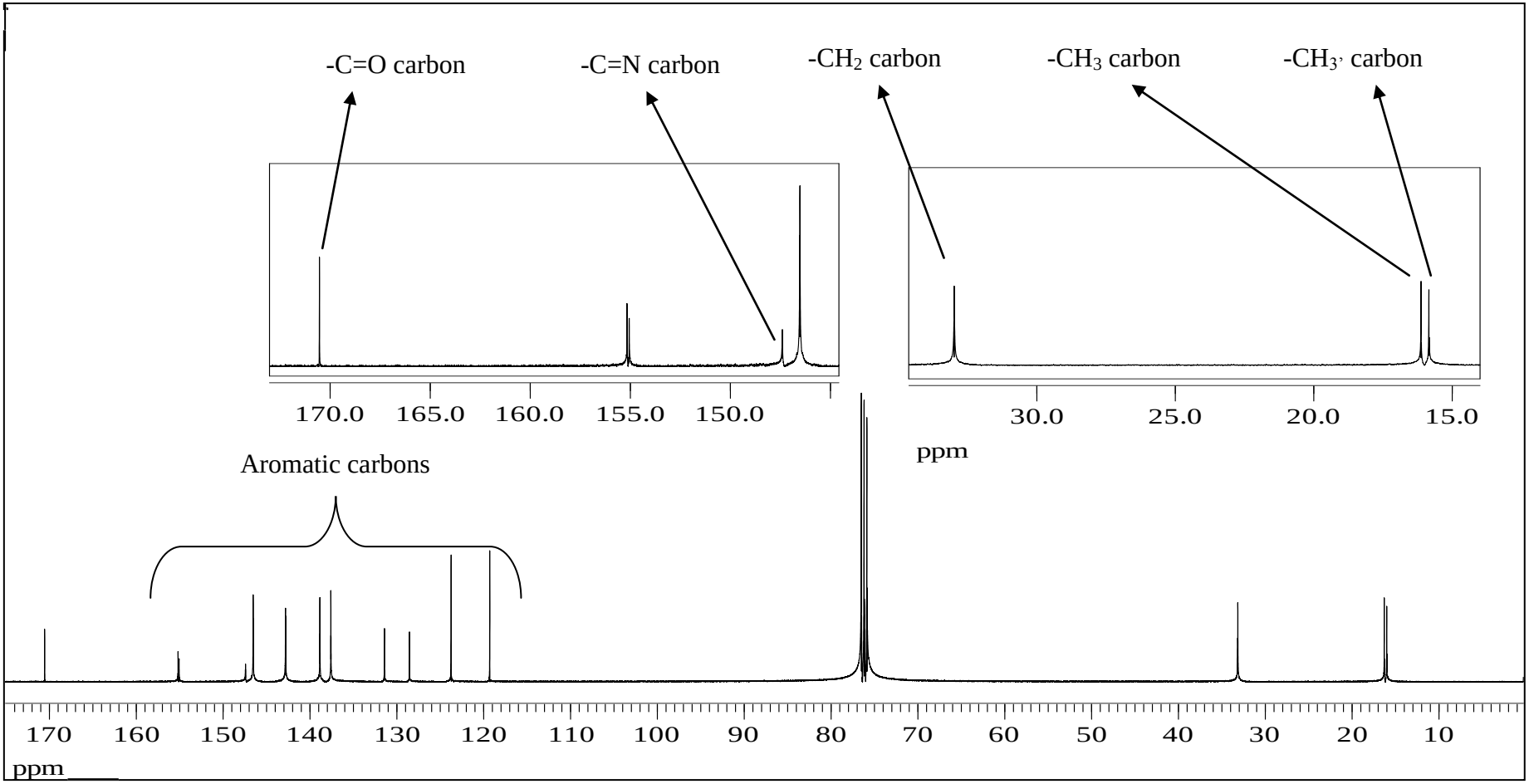


Figure 4.32. The ^{13}C-NMR spectrum of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one in $CHCl_3$-d_1.

4.4. 5-methyl-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one

Like 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one, this compound also have a resticted rotation around the N_3-aryl single bond due to the steric interaction between the *ortho* substituent on the N_3 pyridine ring and, the exocylic oxygen and the imino nitrogen. Also, the compound has a central chirality at C_5 position. That is why, there are 4 possible isomers (PS, MS, PR and MR) of 5-methyl-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one. PS-MR and PR-MS are enantiomers of each other and PS-PR and MS-MR are diastereomers of each other (Figure 4.33).

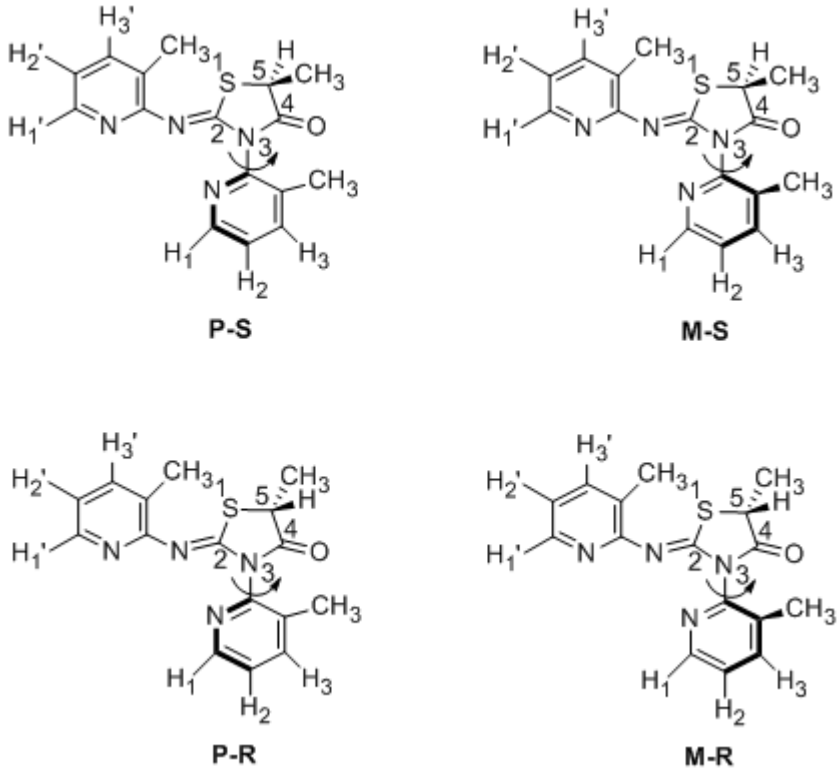


Figure 4.33. Possible isomers of 5-methyl-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one.

These isomers were investigated by HPLC on Cellulose tris(3,5-dimethylphenylcarbamate)-Chiralpak IB column (Figue 4.34). For the analysis, n-Hexane/2-Propanol (60/40, flow rate: 0.6 ml/min) were used as mobile solvent mixture.

Under these conditions, diastereomeric percent ratio of the isomers were found as 12.8% and 87.2% after recrystallization from ethanol (Figure 4.34).

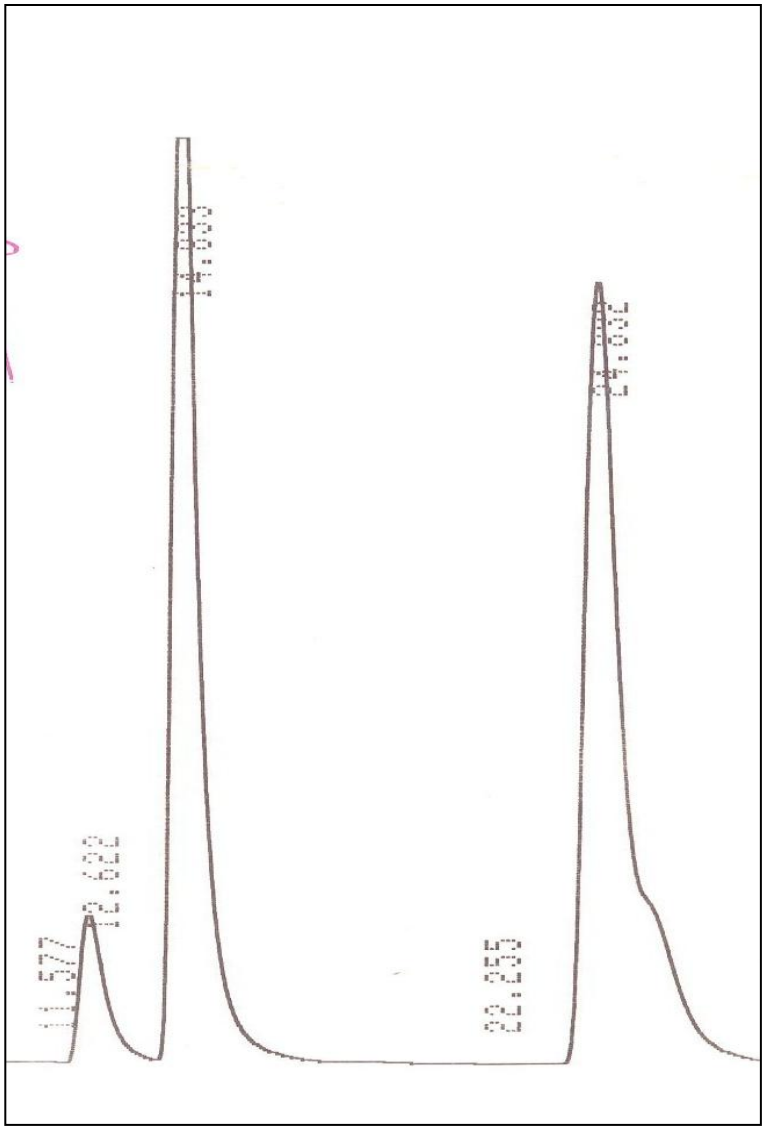


Figure 4.34. HPLC chromatogram of 5-methyl-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one on Cellulose tris(3,5-dimethylphenylcarbamate)-Chiralpak IB column. (Mobile solvent: n-Hexane/2-Propanol; 60/40; flow rate: 0.6 ml/min).

Determination of the rotational barrier to hindered rotation was done by thermally interconverting the micropreparatively separated one enantiomer to its counterpart. For this

process, the isomers of the compound were seperated by HPLC on Cellulose tris(3,5-dimethylphenylcarbamate)-Chiralpak IB column. The mobile solvent was n-Hexane/2-Propanol (60/40, flow rate: 0.6 ml/min) and the column temperature was 7 °C. Then, one of the isomers was dissolved in about 200 µl of HPLC absolute ethanol and 40 µl of the solution was injected into the column to determine the initial concentration. The solution was kept in an oil bath at a constant temperature of 40 °C. The thermal racemization process was followed by taking 40 µl of the separated sample at certain time intervals. This process was repeated until enough data (Table 4.4), which shows the change of the relative per cent composition of each enantiomer according to time, was recorded.

Table 4.4. Time vs relative percent composition of enantiomers of 5-methyl-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one at 40 °C.

Time	**Diastereomer 1 (Retention time: 14.86 min) (Percent ratio)**	**Diastereomer 2 (Retention time: 12.48 min) (Percent ratio)**
0 s	43.84 %	6.41 %
1860 s	36.74 %	13.37 %
4380 s	31.40 %	19.07 %
6240 s	28.85 %	21.17 %
10140 s	27.81 %	22.50 %

The relative percent composition values were substituted into Equation 2.11 and a graph of the obtained results versus time (Figure 4.4.3) was plotted. Equilibrium percents of the enantiomers were found to be 26.59% and 23.84%, respectively.

$$\ln ([M]-[M]_{eq}/[M]_0-[M]_{eq})= -(k_f+k_r)t \qquad (2.11)$$

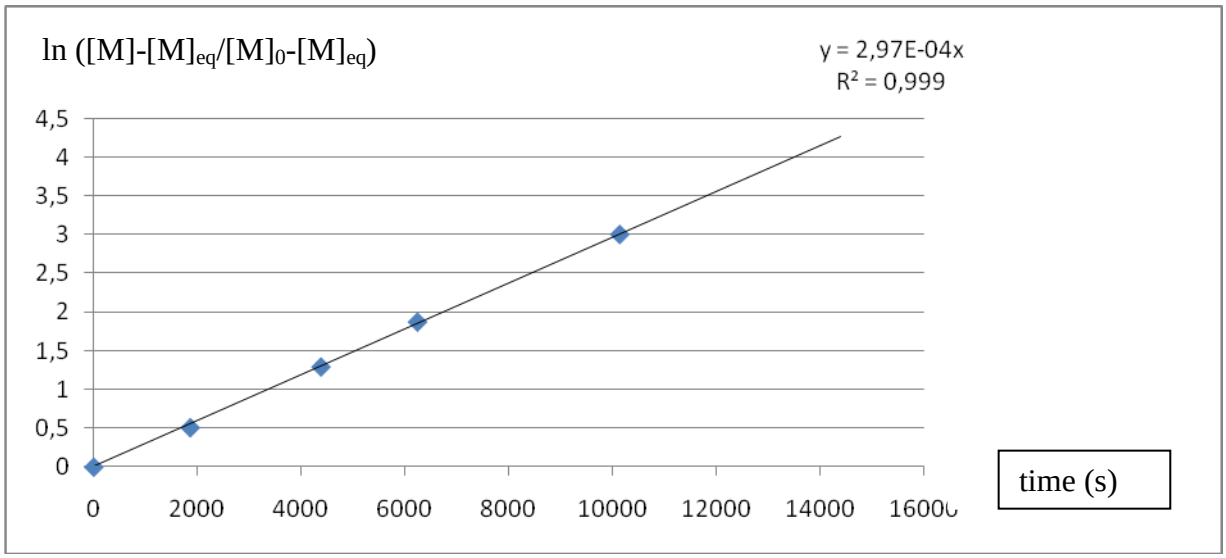


Figure 4.35. The plot of ln(([M]$_0$-[M]$_{eq}$/[M]-[M]$_{eq}$)) versus time at 313 K for 5-methyl-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one.

Slope of the graph was found to be $y=2.97\times10^{-4}x$. The first order forward (k_f) and reverse (k_r) rate constants were calculated as the following way:

K (equilibrium ratio of the diastereomers)= 23.84 % / 25.59 % = 0.8966 = k_f / k_r (1)

$k_f + k_r = y / x = 1.19\times10^{-4}$ (2)

From (1) and (2); $k_f = 1.40\times10^{-4}$ s^{-1} and $k_r = 1.57\times10^{-4}$ s^{-1}

These values of the rate constants were substituted into Equation 2.13. The forward ($\Delta G^{\#}_f$) and reverse ($\Delta G^{\#}_r$) energy barriers of 5-methyl-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one were found to be 99.88 kJ/mole and 99.58 kJ/mole, respectively.

$$\Delta G^{\#}=RT\ln(k_b.T/k.h) \quad (2.13)$$

Like 2-arylimino-3-aryl-thiazolidine-4-ones, N_3 nitrogen of this compound increases the electron density of pyridine ring on the imino group by forming a resonance structure

(Figure 4.13). So, aromatic protons of this compound can be observed separately. The ^{1}H-NMR spectrum of the compound in benzene-d_6 (Figure 4.37) was investigated and it was found that hydrogen atom of the compound at C_5 position gives two sets of quartets. This situation simply proves the presence of the diastereomeric pair. According to the ^{1}H-NMR spectrum of the compound in benzene-d_6, the percent diastereomeric ratio was found to be 12.98% to 87.02%. This result shows that one of the diastereomers crystallized out prefentially in a higher amount than the other one.

On the other hand, the two sets of quartets of the hydrogen atom at C_5 position could not be observed in the ^{1}H-NMR spectrum of the compound in $CHCl_3$-d_1 (Figure 4.38). It is expected that the chemical shift difference ($\Delta\nu$) between the two sets of quartets of this hydrogen must be very small in $CHCl_3$-d_1. That is why, a distorted quarted was observed instead of two sets of different quartets.

Interestingly, ^{1}H-NMR spectrum of the compound in TFA-d_1 (Figure 4.39) displays the two sets of quartets with the percent ratios of 47.30% and 52.70%. Thus, the diastereomers of the compound nearly have the same ratio. Deuterium atom of the TFA-d_1 can form a hyrogen bond with the nitrogen of the N_3 pyridine ring and oxygen of the carbonyl group at C_4 position. Also, a hydrogen bond can be formed by the deuterium atom of the TFA-d_1 and, the nitrogen of the N_3 pyridine ring and the nitrogen of the imino group (Figure 4.36).

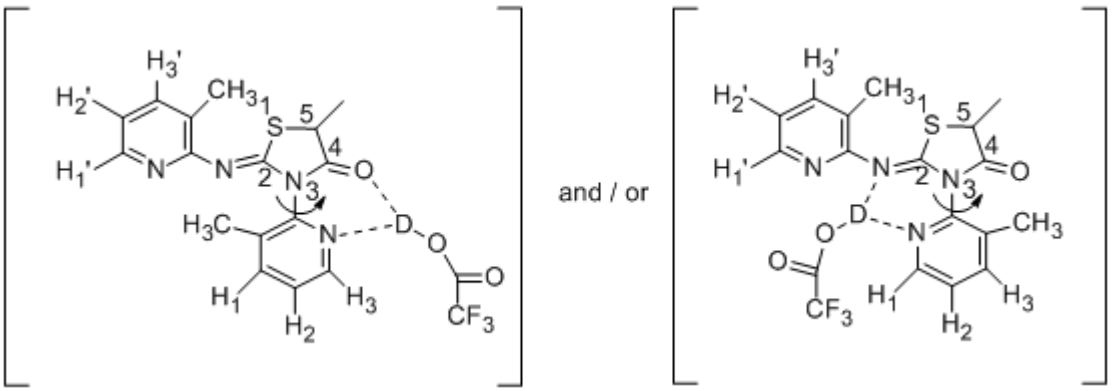


Figure 4.36. Possible hydrogen bonding network between TFA-d_1 and 5-methyl-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one.

As a result of this hydrogen bonding, transition state energy of the compound for rotation decreases very rapidly so that the compound can rotate around the N_3-aryl single bond very easily. Because of this fact, the percent difference between the diastereomers of the compound decreases and approaches to equilibrium rapidly in TFA-d_1 (Figure 4.36).

The chemical shift values of the two $–CH_2$ protons which belong to the different sets of quartets were calculated according to Equations 2.2 and 2.3 and they were presented in Table 4.5.

Table 4.5. 400 MHz ^{1}H-NMR spectral data for 5-methyl-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one in various solvents.

Solvents	**TFA-d_1**		**Benzene- d_6**	
Percent ratios of the diastereomers	47. 30 %	52.70 %	12.98 %	87.02 %
Protons on C-5 (ppm)	4.88 and 4.84	4.81 and 4.77	3.29 and 3.26	3.15 and 3.11

According to the ^{13}C-NMR spectrum of the compound, carbonyl and imino group carbon atoms give signals at 175.0 and 148.4 ppm, respectively. Carbon atom of the compound at C_5 position gives a signal at 42.6 ppm and aromatic carbons signals in the range between 156.2 and 120.1 ppm. The $–CH_3$ group on the N_3 pyridine ring and the other one on the imino pyridine ring display signals at 16.9 and 16.8, respectively Finally, the $–CH_3$ group at C_5 position of the compound gives a signal at 19.1 ppm (Figure 4.40).

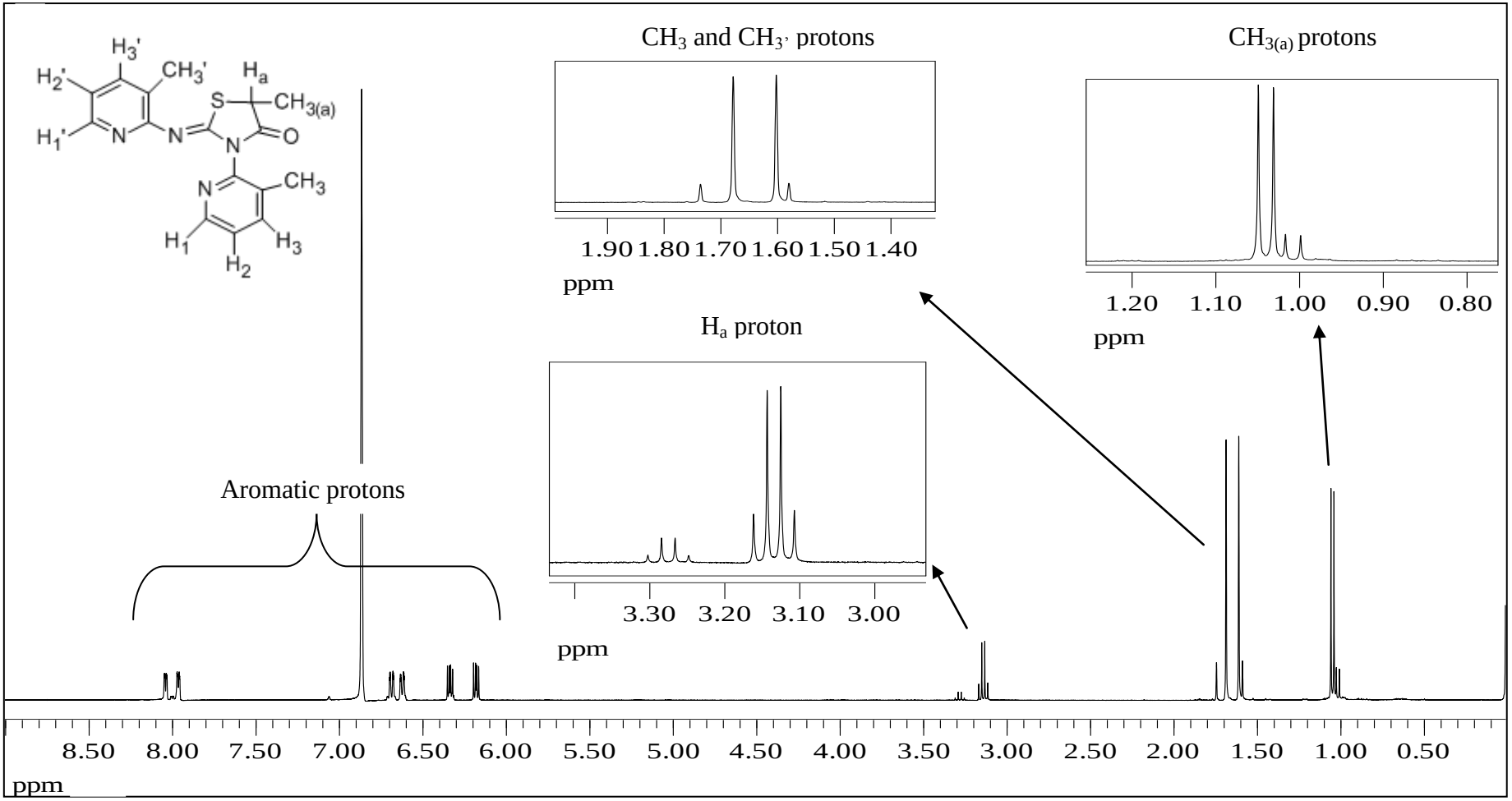


Figure 4.37. The 400 MHz ^{1}H-NMR spectrum of 5-methyl-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one in C_6D_6.

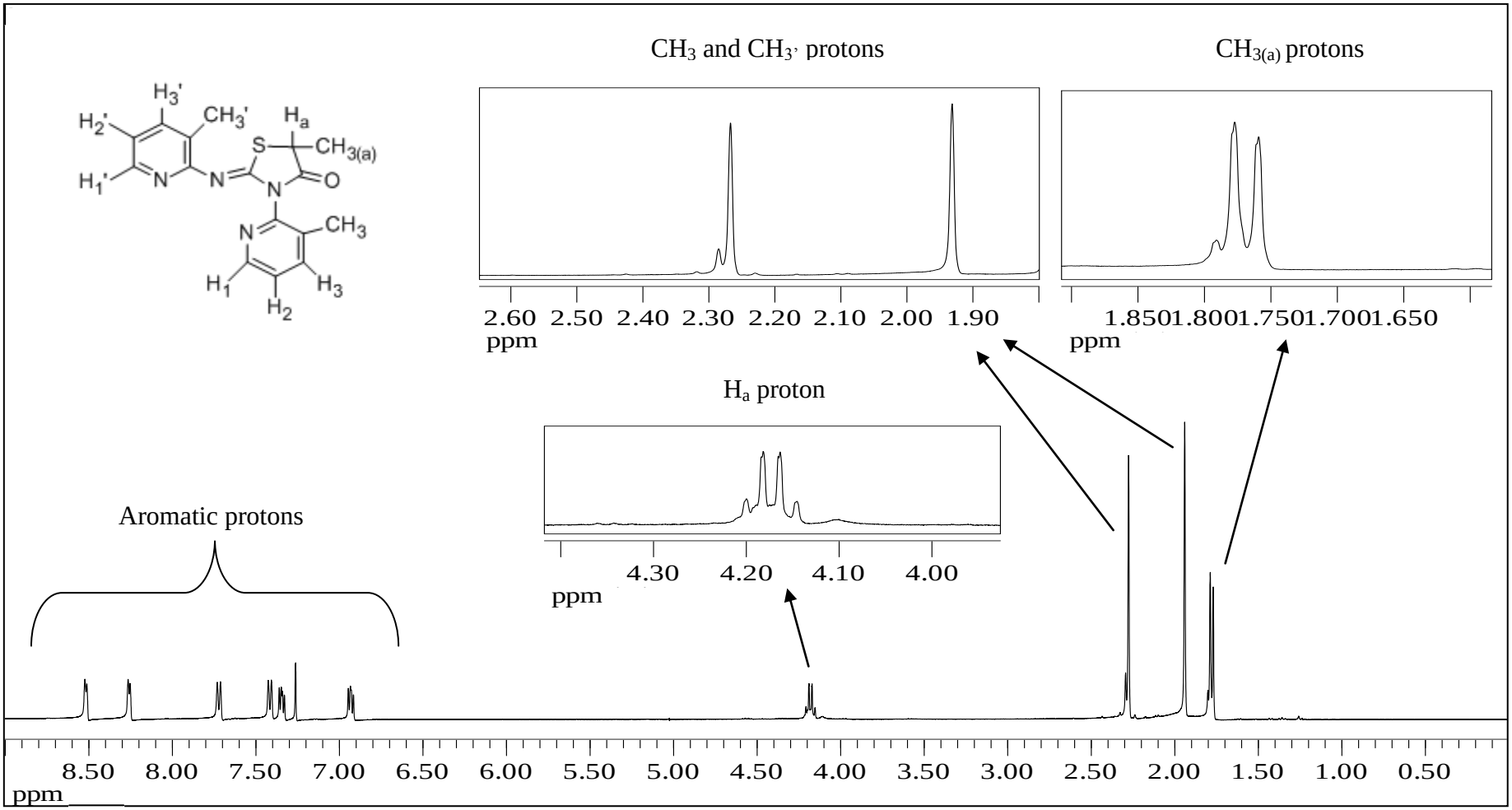


Figure 4.38. The 400 MHz ^{1}H-NMR spectrum of 5-methyl-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one in $CDCl_3$.

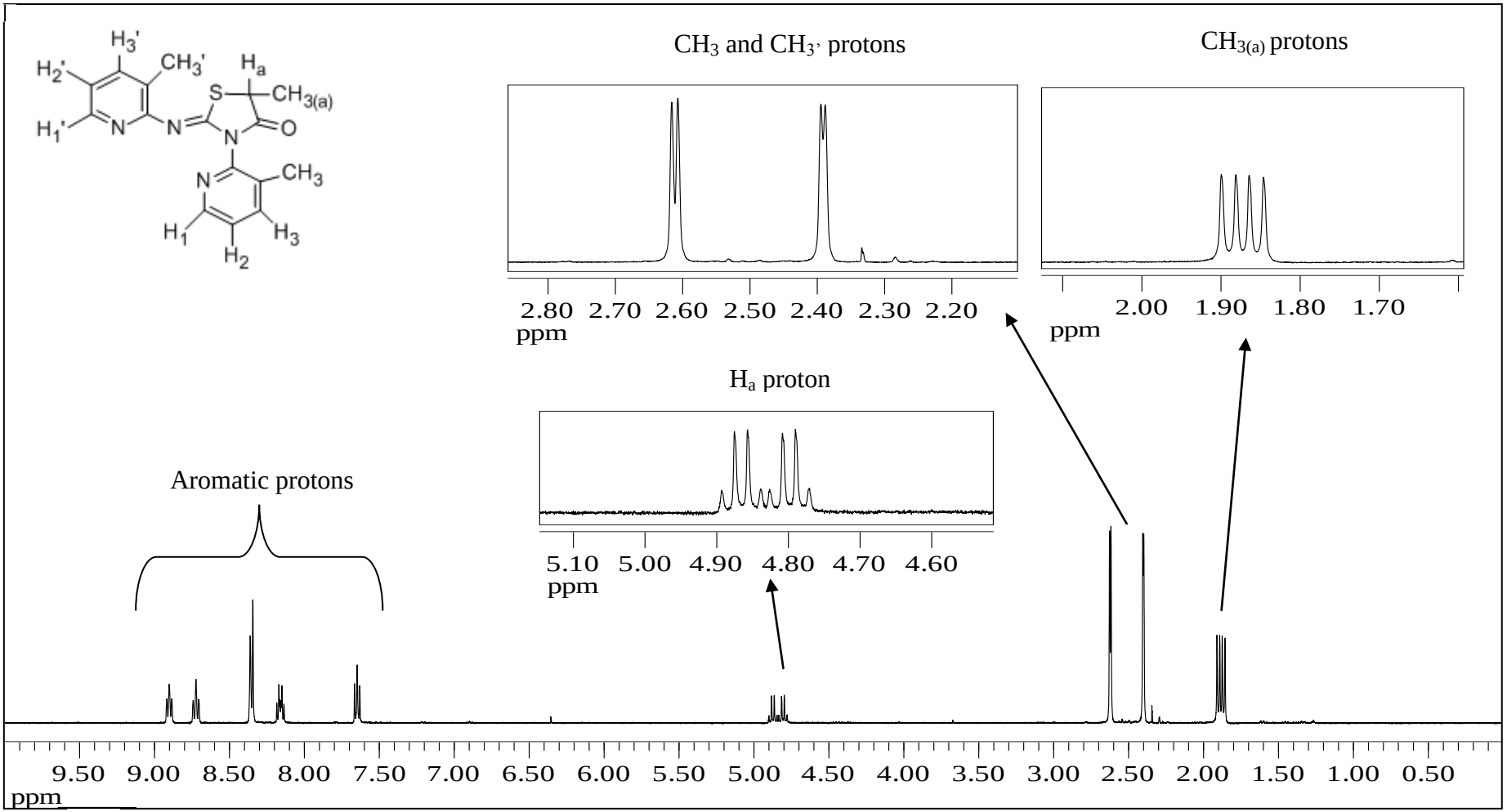


Figure 4.39. The 400 MHz ^{1}H-NMR spectrum of 5-methyl-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one in TFD.

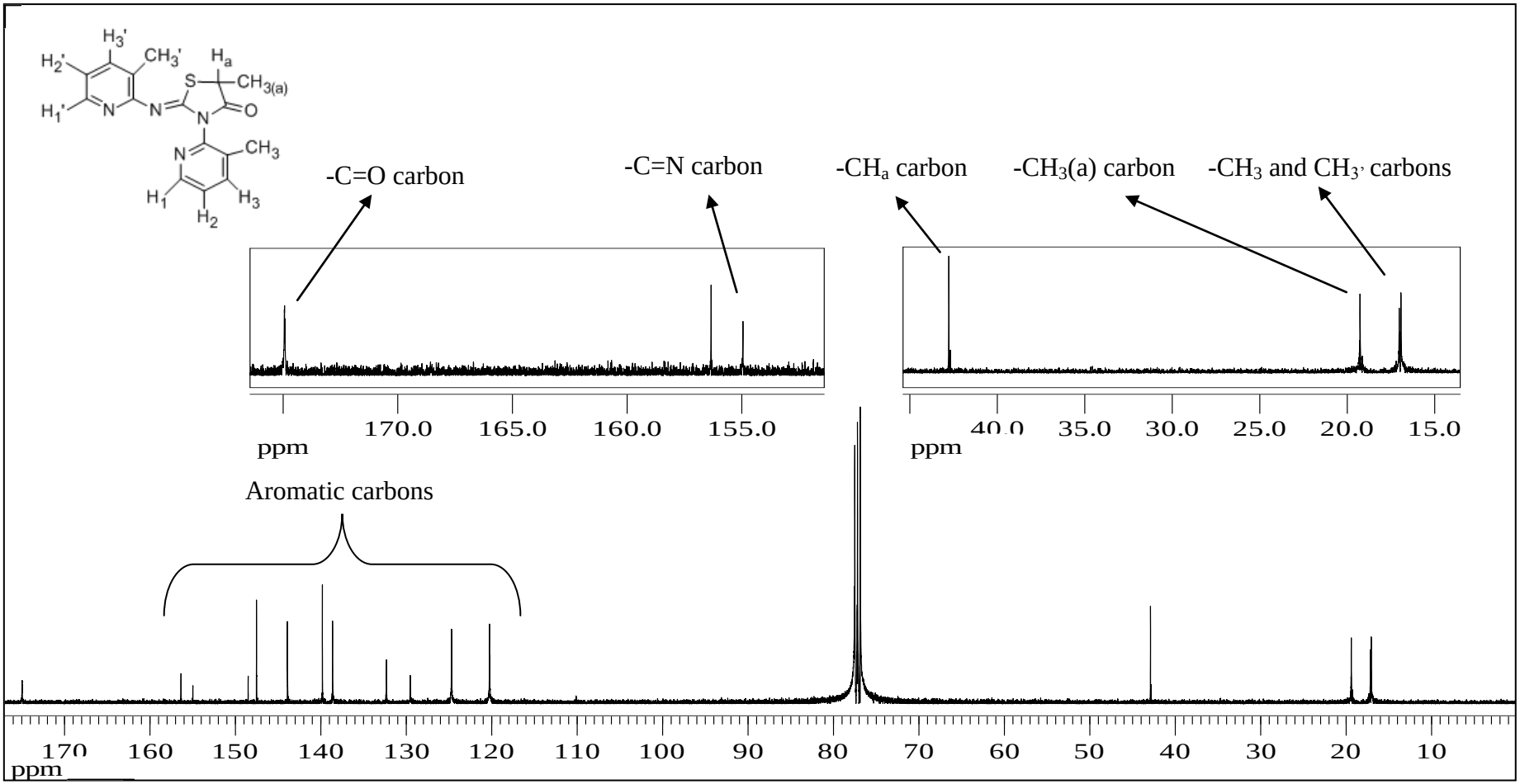


Figure 4.40. The ^{13}C-NMR spectrum of 5-methyl-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one in $CDCl_3$.

4.5. 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidine-4-thione

This product was synthesized by converting the C-4 carbonyl oxygen of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidine-4-one to a sulphur atom via the Lawesson Reagent. The reaction product was monitored by IR (Infrared Spectroscopy) and the formation of the product was proved by the disapperance of the characteristic carbonyl peak at 1718 cm^{-1} and the formation of the thiocarbonyl peak at 1122 cm^{-1} on the IR spectrum (Figure 4.41 and 4.42).

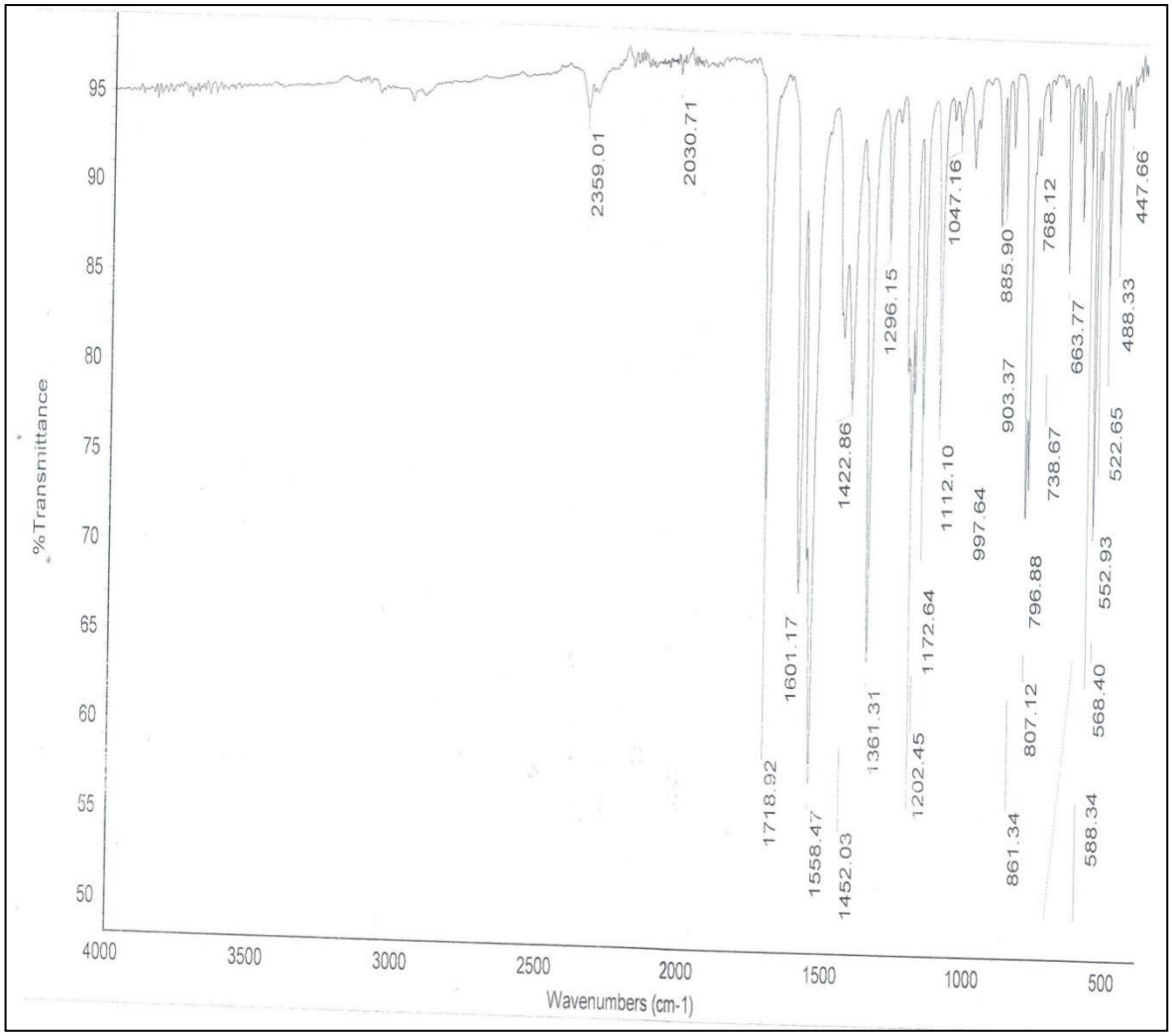


Figure 4.41. IR spectrum of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidine-4-one.

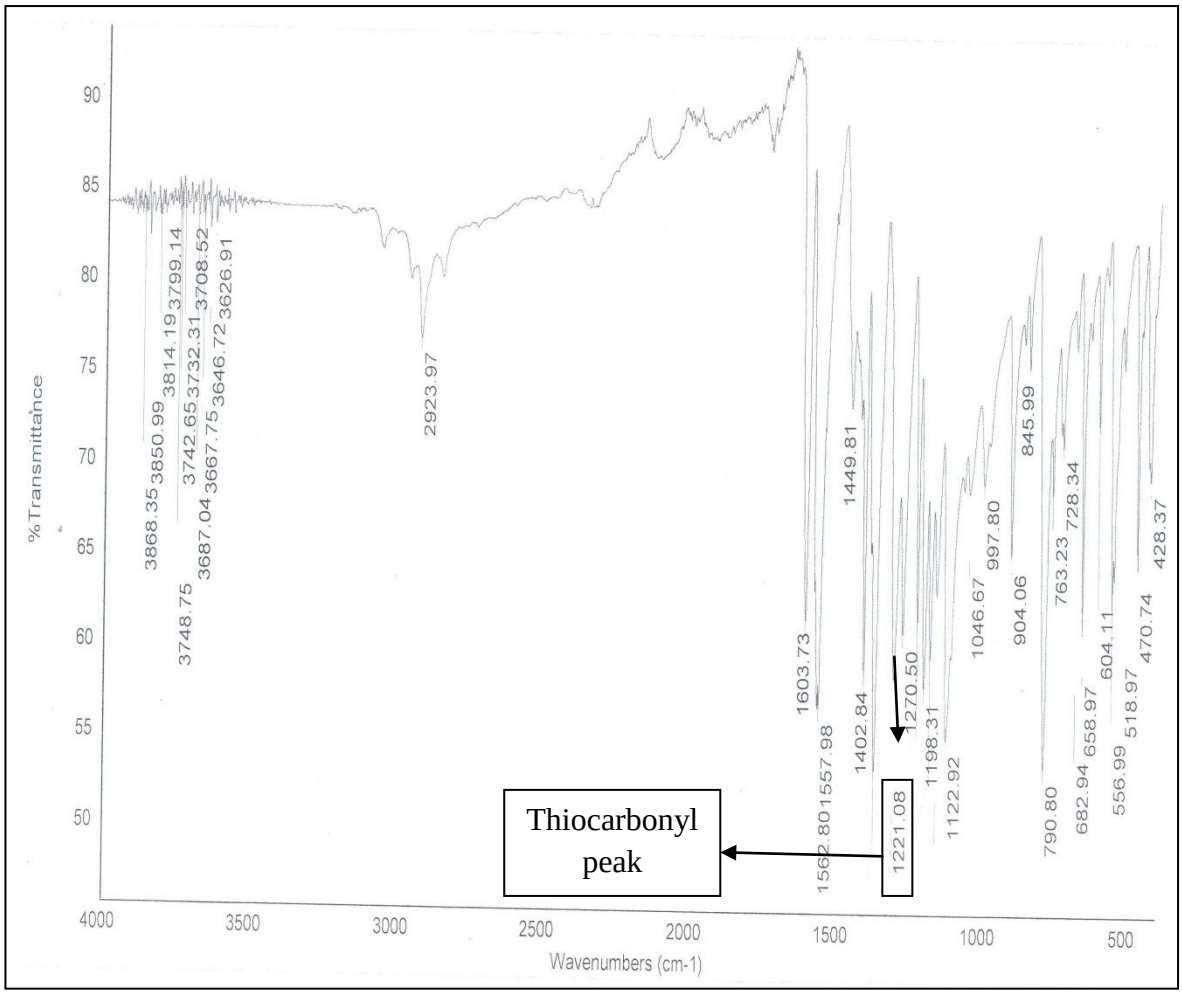


Figure 4.42. IR spectrum of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidine-4-thione.

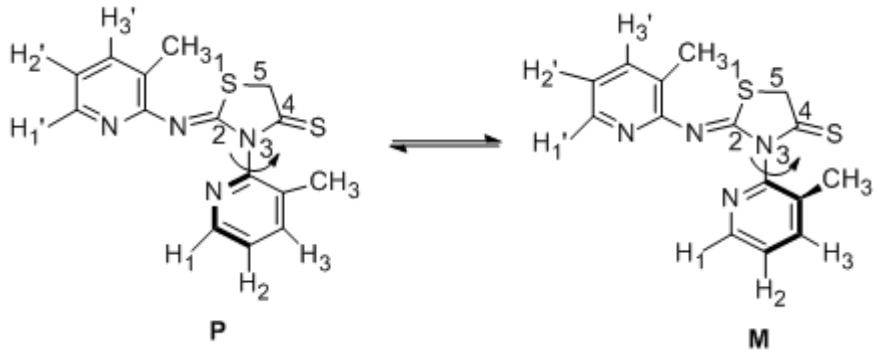


Figure 4.43. The restricted rotation around the N_3-aryl bond in 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidine-4-thione.

Like 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidine-4-one, this product also possesses a restricted rotation around the N_3-aryl single bond. However, this time the restricted rotation results from the steric interaction between the *ortho* substituent on the N_3-pyridine ring and, the exocylic sulphur atom and the imino nitrogen (Figure 4.43).

As a result of the restricted rotation, thermally interconvertible P and M enantiomers were formed and they were investigated by HPLC on Cellulose tris(3,5 dichlorophenylcarbamate)-Chiralpak IC column (Figue 4.44). For the analysis, n-Hexane/2-Propanol (70/30, flow rate: 0.6 ml/min) were used as mobile solvent mixture. Under these conditions retention times of the enantiomers were 20.4 min and 42.5 min and percentage of the enantiomers were as expected 50% to each.

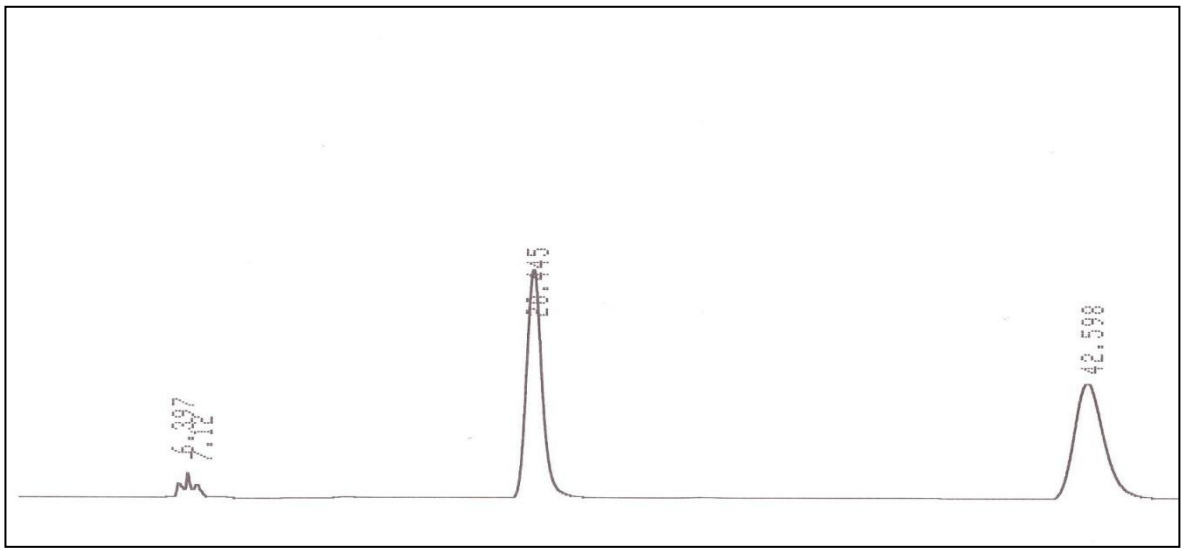


Figure 4.44. HPLC chramatogram of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino) thiazolidine-4-thione on Cellulose tris(3,5 dichlorophenylcarbamate)-Chiralpak IC column.

Since the two enantiomers were separable, determination of the rotational barrier to hindered rotation was done by thermally interconverting the micropreparatively separated one enantiomer to its counterpart. The same barrier calculation procedure of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one was used, except; the solution was kept in an oil bath at a constant temperature of 80 °C. The thermal

racemization process was followed by taking 40 µl of the separated sample at certain time intervals. This process was repeated until enough data (Table 4.6), which shows the change of the relative per cent composition of each enantiomer according to time, was recorded.

Table 4.6. Time vs relative percent composition of enantiomers of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino) thiazolidine-4-thione at 80 °C.

Time	**Enantiomer 1 (Percent ratio)**	**Enantiomer 2 (Percent ratio)**
0 s	82.59 %	17.41 %
1260 s	77.69 %	22.31 %
2760 s	74.00 %	26.00 %
4140 s	70.66 %	29.34 %
5580 s	67.96 %	32.04 %

The relative percent composition values were substituted into Equation 2.12 and a graph of the obtained results versus time (Figure 4.46) was plotted.

$$\ln ([M]-[M]_{eq}/[M]_0-[M]_{eq})=-2kt \qquad (2.12)$$

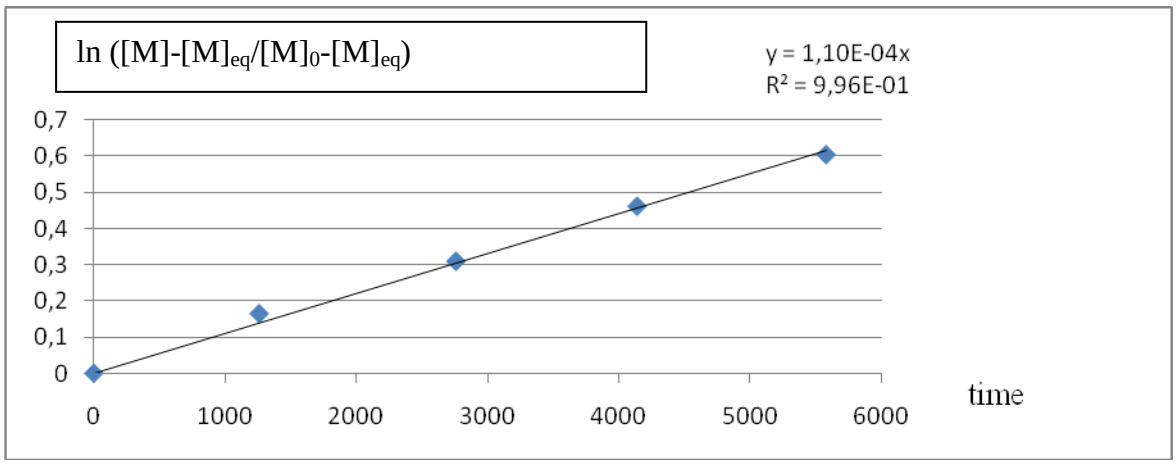


Figure 4.45. The plot of $\ln(([M]_0-[M]_{eq}/[M]-[M]_{eq}))$ versus time at 353 K for 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino) thiazolidine-4-thione.

From the slope of the graph ($y=1,1\times10^{-4}x$), the first order rate constant (k) was calculated and it was found to be $0,55\times10^{-4}$ s^{-1}. This value of the rate constant was substituted into Equation 2.13 and the energy barrier of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino) thiazolidine-4-thione was found to be 120.46 kJ/mole.

$$\Delta G^{\#}=RT\ln(k_b.T/k.h) \qquad (2.13)$$

In 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino) thiazolidin-4-one, the rotational barrier was found as 102.106 kJ/mole. So, replacing C-4 carbonyl oxygen of the compound with a sulphur atom increased the barrier by 18.3 kJ/mol.

The $-CH_2$ protons at C_5 position of the thiazolidinone ring of the compound becomes diastereotopic due to the restricted rotation and they are expected to give an AB splitting. Since the chemical shift difference ($\Delta\nu$) between the $-CH_2$ protons is very small in $CHCl_3$-d_1, the ^{1}H-NMR signal of the compound did not display an AB splitting in this solvent (Figure 4.46). On the other hand, the chemical shift difference between the two $-CH_2$ protons is large enough in benzene-d_6, and this situation allows these protons to give an AB splitting (Figures 4.47). For this solvents, the chemical shift values of the two $-CH_2$ protons were calculated according to Equations 2.2 and 2.3 and they were presented in Table 4.7.

Like the other 3-(aryl)-2-(arylimino)thiazolidin-4-ones, N_3-nitrogen of this compound also increases the electron density of pyridine ring on the imino group by a resonance. As a result of this resonance structure, pyridine ring protons on the imino group become more shielded than those of the other pyridine ring protons. So, aromatic protons of the compound can be observed seperately due to the shielding difference between the two pyridine rings. Chemical shift values of the protons in different solvents are given in Table 4.7.

According to the ^{13}C-NMR spectrum of the compound, thiocarbonyl and imino group carbons of the compound give signals at 199.7 and 149.9 ppm, respectively. The $-CH_2$ carbon gives a signal at 45.1 ppm and aromatic carbons are in the range between

158.4 and 119.5 ppm. The $–CH_3$ group on the N_3 pyridine ring and the other one on the imino pyridine ring display signals at 15.7 and 15.6, respectively (Figure 4.48).

Table 4.7. Chemical shift values of the protons of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino) thiazolidine-4-thione in different solvents.

Solvents	**$CHCl_3$-d_1**	**Benzene- d_6**
Protons on C-5 (ppm)	4.42	3.42 and 3.30
Aromatic protons (ppm)	8.49-6.86	8.06-6.12
-CH_3 protons (on the N_3 pyridine ring) (ppm)	2.17	1.66
CH_3 protons (on the imino pyridine ring) (ppm)	1.83	1.52

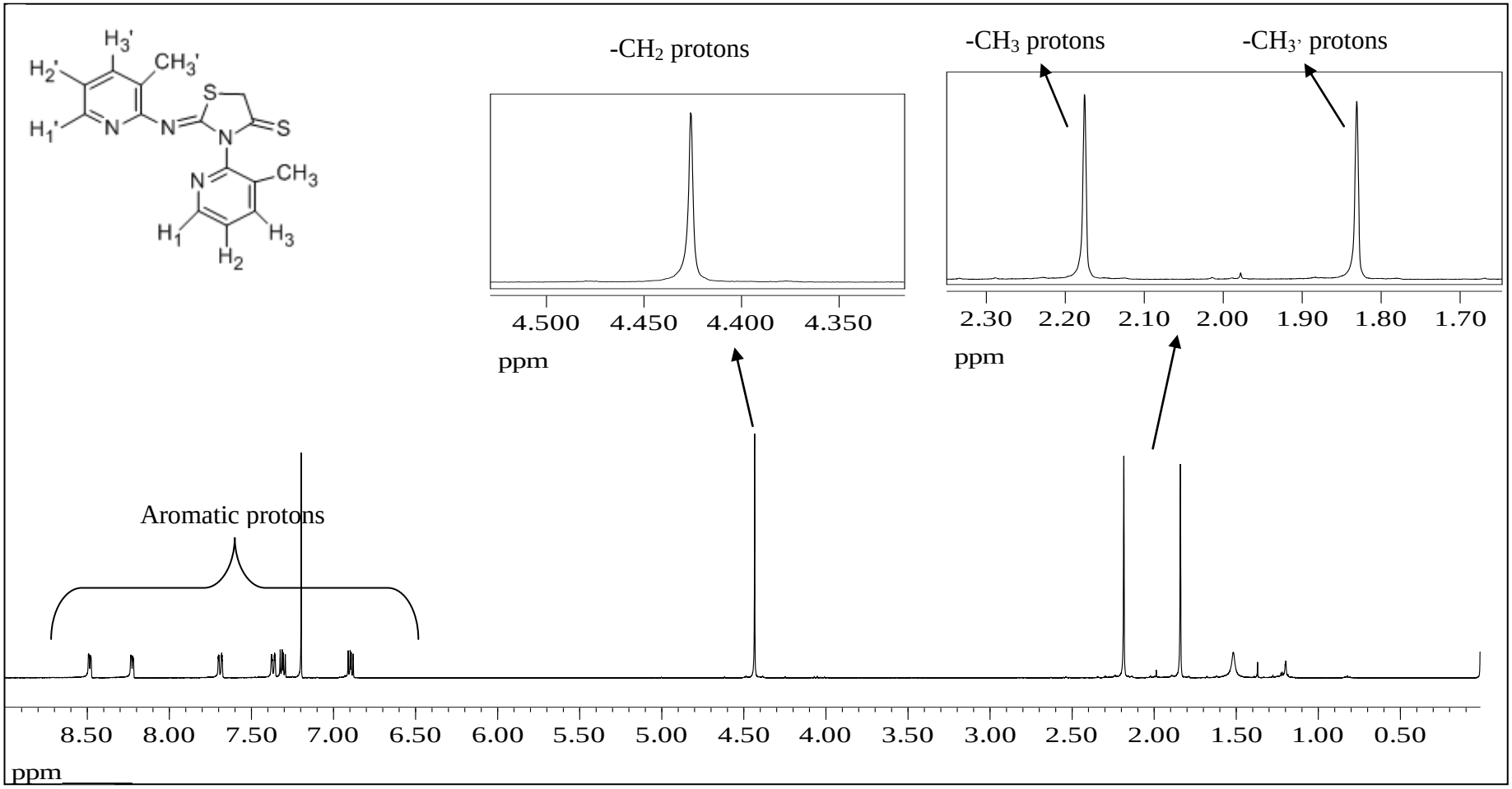


Figure 4.46. The 400 MHz ^{1}H-NMR spectrum of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidine-4-thione in $CHCl_3$-d_1.

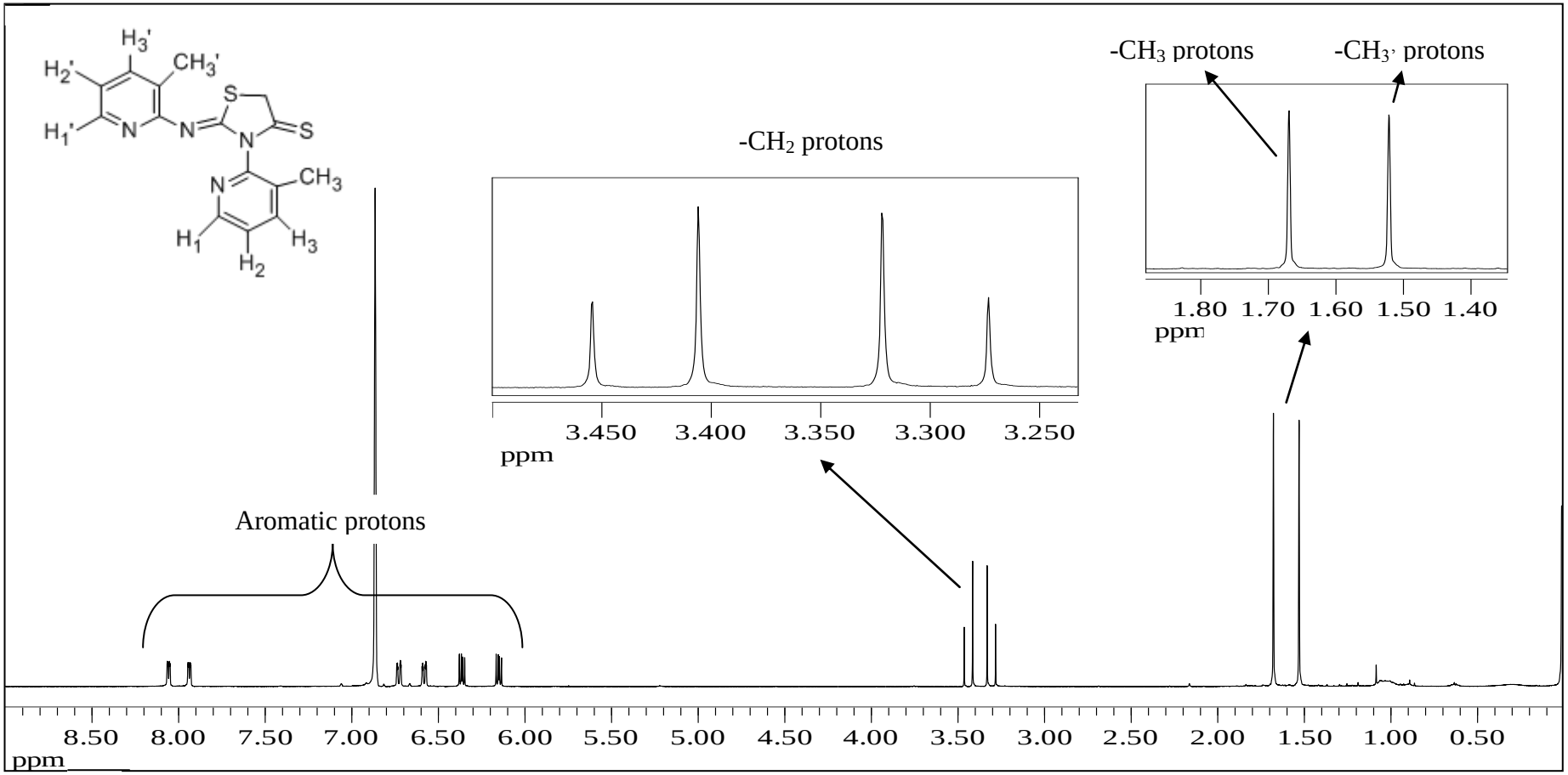


Figure 4.47. The 400 MHz ^{1}H-NMR spectrum of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidine-4-thione in benzene-d_6.

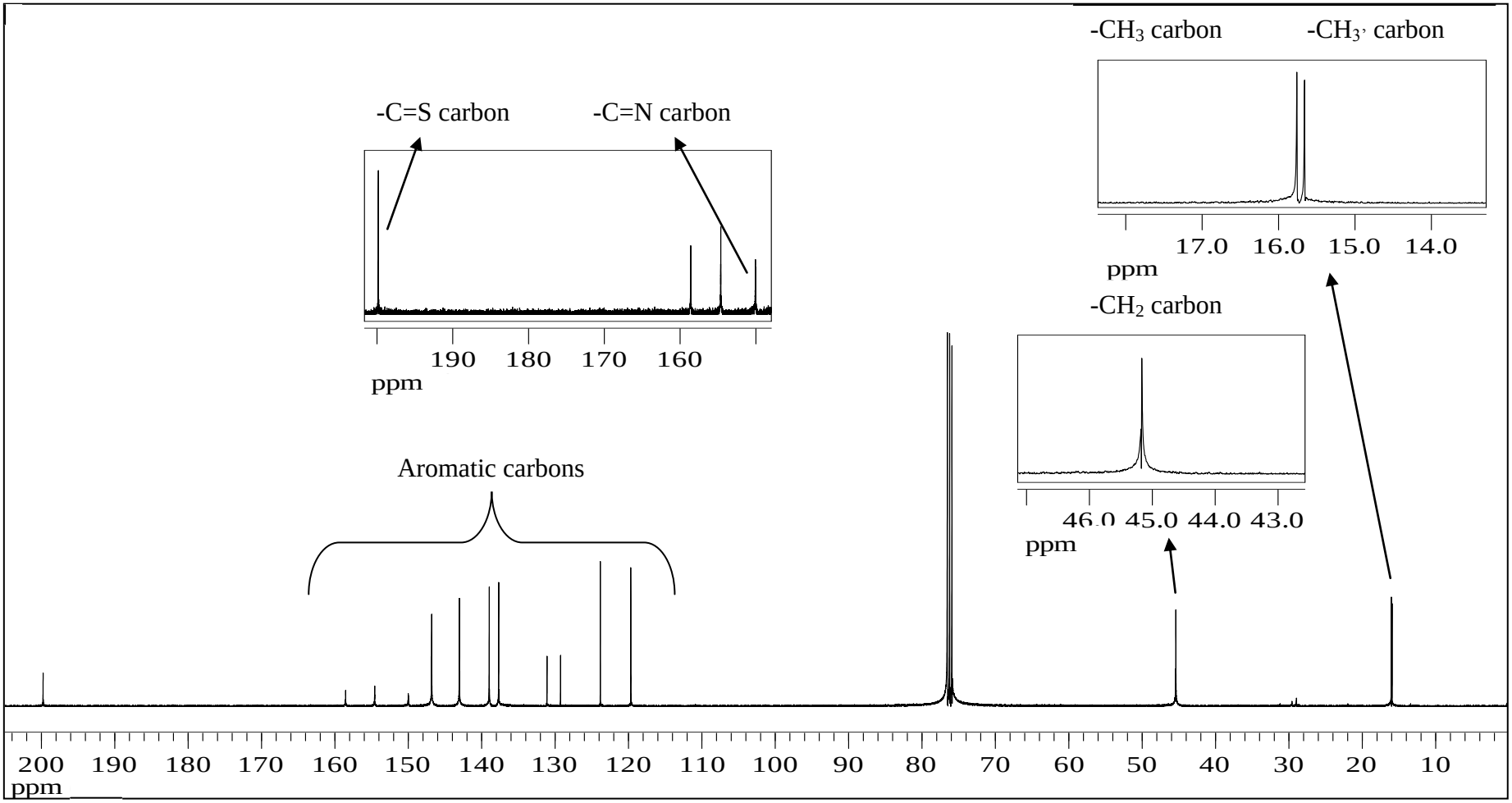


Figure 4.48. The ^{13}C-NMR spectrum of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidine-4-thione in $CHCl_3$-d_1.

4.6. 3-((R)-1-cyclohexylethyl)-2-((R)-1-cyclohexylethylimino)thiazolidin-4-one

Amidines contain an amino nitrogen atom which has a free electron pair conjugated with the π-electrons of the C=N double bond. They combine the properties of an azomethine-like -C=N double bond and an amide like C-N single bond with a partial double bond character. Since amidines are strong bases (pKa ranges from 5-12), various chiral amidines were synthesized as catalysts. The catalytic activities of the amidines are considerably higher than that of other catalysts used in the nitroalkane addition reactions [34].

So, this compound was synthesized as a chiral amidine base. The nitrogen of the imino group is expected to be basic as a result of the following resonance structure (Figure 4.49).

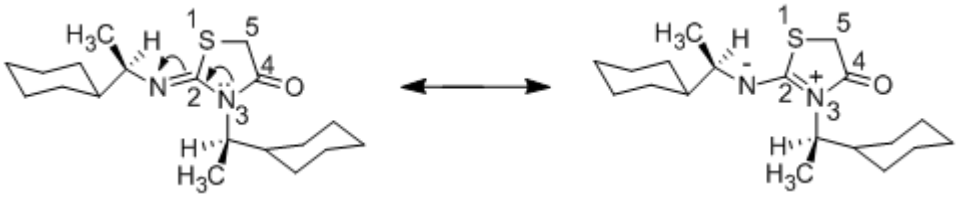


Figure 4.49. Resonance structure of the 3-((R)-1-cyclohexylethyl)-2-((R)-1-cyclohexylethylimino)thiazolidin-4-one.

^{1}H- NMR spectrum of the compound in $CHCl_3$-d_1 (Figure 4.50) shows the chemical shift difference between the two –CH protons at chiral centers. The –CH proton at the chiral center bonded to N_3-nitrogen is more deshielded than the other –CH proton due to the resonance structure. More deshielded –CH proton gives a signal at 4.13 ppm, whereas, less deshielded one displays a signal at 2.88 ppm. The $–CH_2$ protons of the compound at C_5 position give a signal at 3.67 ppm and, the two $-CH_3$ and cyclohexyl protons are in the range between 2.14 and 0.73 ppm (Figure 4.50).

According to the ^{13}C-NMR spectrum of the compound, carbonyl and imino group carbons of the compound give signals at 171.8 and 148.94 ppm, respectively. All other carbons of the compound are in the range between 63.5 and 15.4 ppm (Figure 4.51).

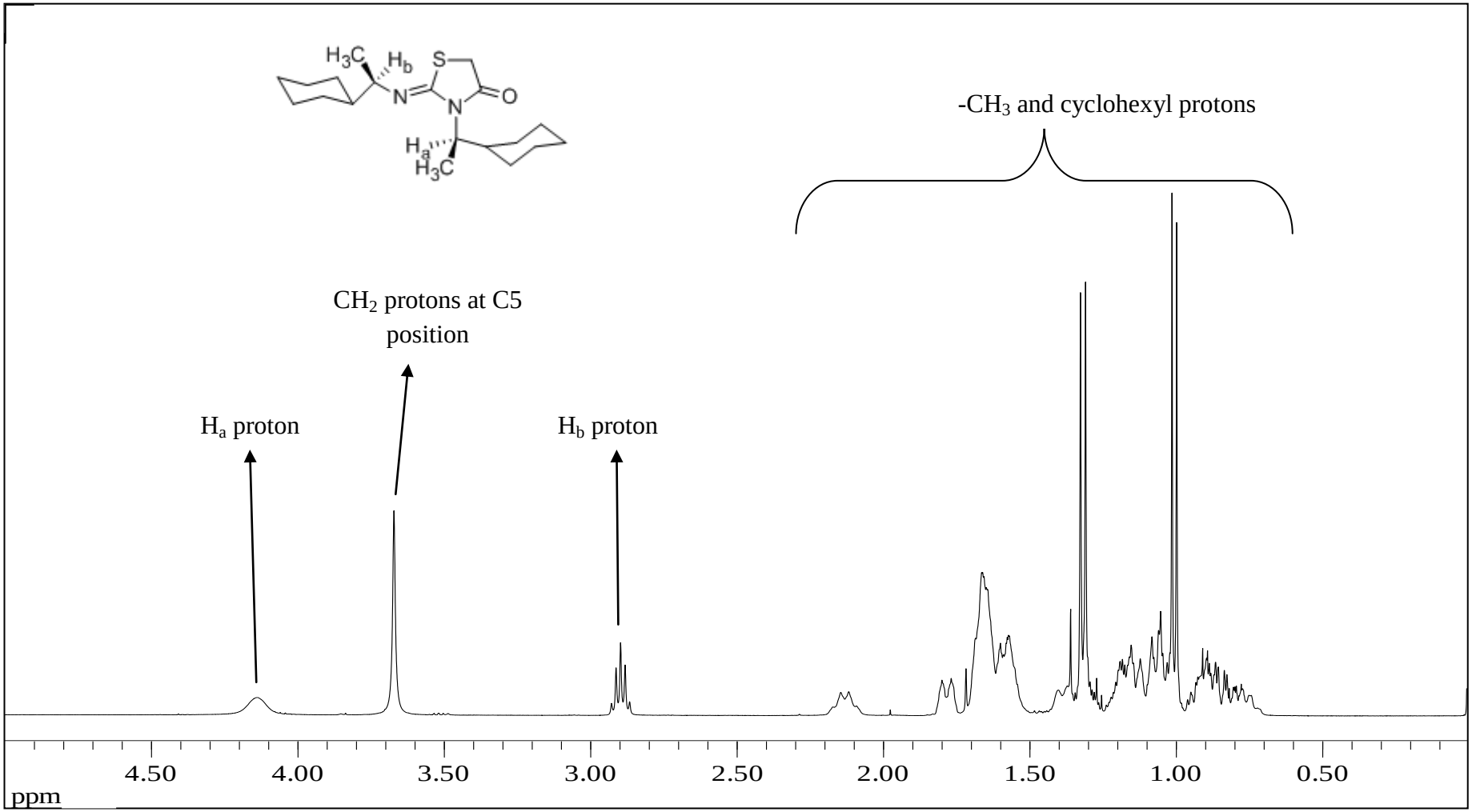


Figure 4.50. The 400 MHz ^{1}H-NMR spectrum of 3-((R)-1-cyclohexylethyl)-2-((R)-1-cyclohexylethylimino)thiazolidin-4-one in $CHCl_3$-d_1.

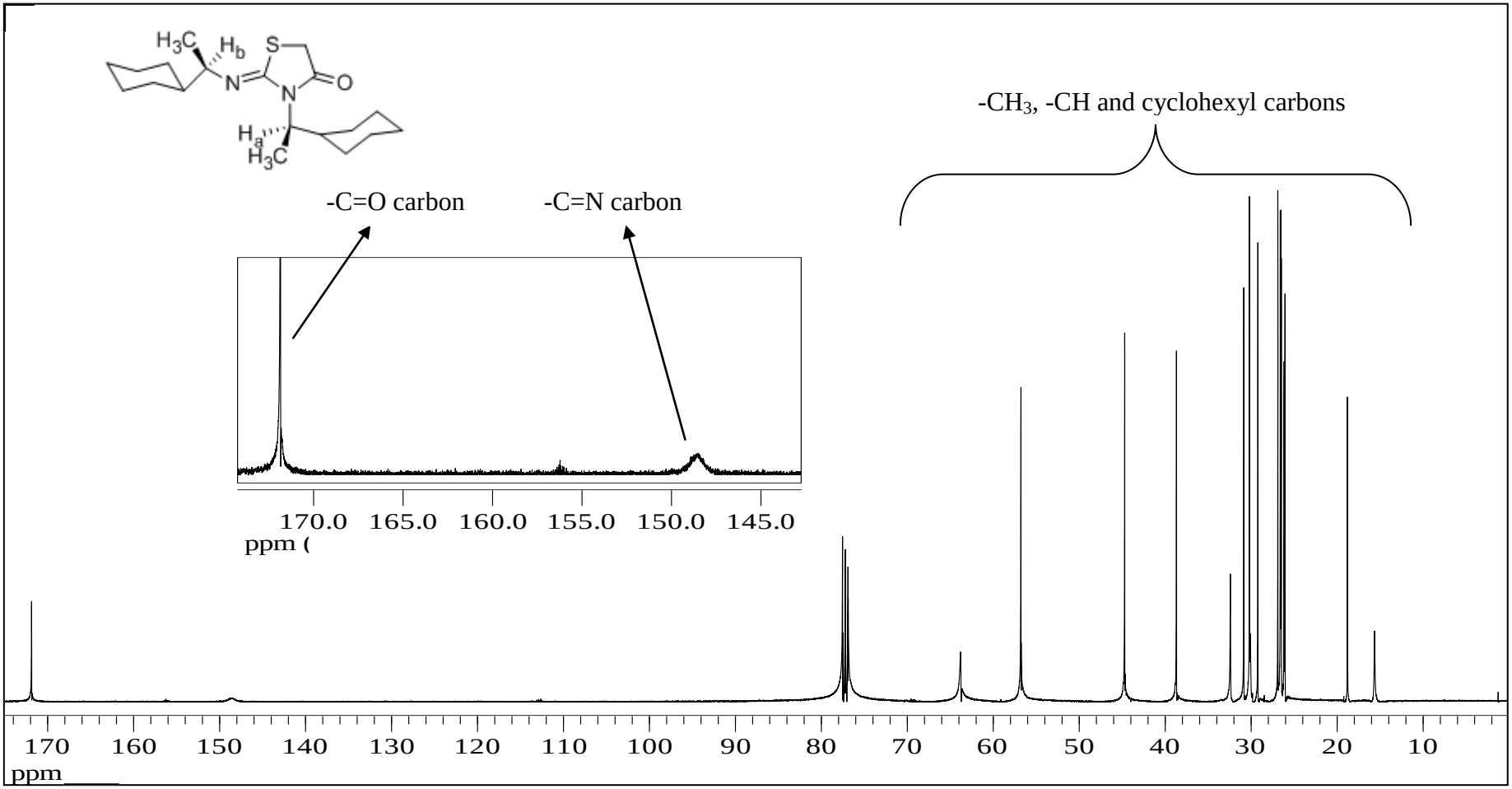


Figure 4.51. The ^{13}C-NMR spectrum of 3-((R)-1-cyclohexylethyl)-2-((R)-1-cyclohexylethylimino)thiazolidin-4-one in $CHCl_3$-d_1.

5. FUTURE WORK

An intramolecular H-bonding in the E,Z and Z,E conformers of 1,3-bis(3-methylpyridin-2-yl) thiourea was found to exist. As a result of this, a six membered ring forms. It is possible that the pyridine group on the N_b-nitrogen is not on the same plane with the formed six membered ring as a result of the hindered rotation about the N_b-C_2 bond caused by the steric interaction between the thiocarbonyl and the methyl group on the N_b-pyridine which would result in axial chirality (Figure 5.1). Low temperature (dynamic) NMR studies will be conducted to understand the possible axial chirality within this compound produced by a supramolecular interaction.

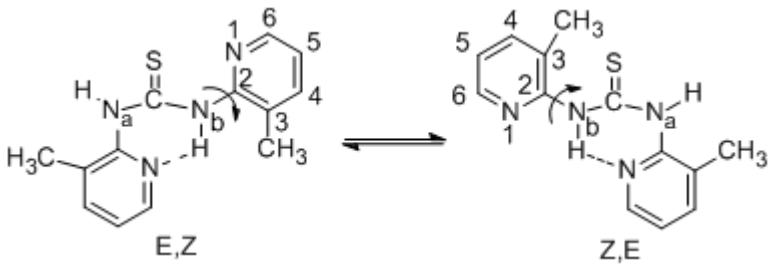


Figure 5.1. Possible restricted rotation around the N_b-aryl single bond in 1,3-bis(3-methylpyridin-2-yl) thiourea.

Another thiourea derivative, 1,3-bis((R)-1-cyclohexylethyl)thiourea, was synthesized to be used as a chiral catalyst in the addition of nitromethanes to aldehydes (Henry reaction). The catalytic activity of the compound will be tested in these reactions as a future work.

In comparison to other axially chiral compounds, very few axially chiral bidentate nitrogen ligands have been reported [17]. That is why, various axially chiral N,N'-bidentate nitrogen ligands were synthesized in this project. These ligands' chromatographic resolution will yield single enantiomers which will be potential N,N'-bidentate ligands in various asymmetric reactions. The catalytic activity of the synthesized 2-arylimino-3-aryl-

thiazolidine-4-ones will be tested especially in the reaction of enantioselective alkylation of aromatic aldehydes by diethylzinc.

In recent literature, particular interest has been focused on neutral organic bases with chelating proton acceptor funtionalities exhibiting enhanced basicity, known as “proton sponges” [35]. Synthesized 2-arylimino-3-aryl-thiazolidine-4-ones are will further be examined for their proton sponge activity (Figure 5.2).

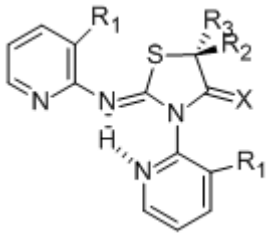


Figure 5.2. Possible proton sponge formation in 2-arylimino-3-aryl-thiazolidine-4-ones.

Moreover, 3-((R)-1-cyclohexylethyl)-2-((R)-1-cyclohexylethylimino)thiazolidin-4-one was synthesized as a chiral amidine base. Since the catalytic activities of the amidines are considerably higher than that of other catalysts used in Henry reactions [34], the catalytic activity of this compound will be tested as a chiral amidine base.

6. CONCLUSIONS

In this study, axially chiral enantiomeric and diastereomeric 2-arylimino-3-aryl-thiazolidine-4-one and 4-thiones have been synthesized, their stereostructures have been investigated, chiral separations of the enantiomers and diastereomers have been done chromatographically and the barriers to rotation have been determined.

The N,N'-diarylthioureas used as starting materials were found to have an intramolecular H-bonding resulting in the E,Z and Z,E conformers. Since the interconversion of the E,Z and Z,E conformers took place rapidly, these compounds displayed broad ^{1}H-NMR peaks at room temperature which sharpened at lower temperatures. The –NH proton of the compounds which participated in intramolecular H-bonding appeared more desielded than the other one.

Apart from the N,N'-diarylthioureas, 1,3-bis((R)-1-cyclohexylethyl) thiourea was also synthesized to be used as a chiral catalyst in Henry reaction.

In 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one, different HPLC peaks for P and M enantiomers were not observed due to the fast rotation around the N_3-aryl bond. Also, the ^{1}H-NMR signal of the $–CH_2$ protons of this compound appeared as a singlet due to fast rotation at room temperature in $CHCl_3$-d_1. An AB type splitting would have been observed if the rotation was slow. Even at -45 °C, the AB splitting could not be observed. This situation showed that the interconversion of the enantiomers of the compound is fast on the NMR timescale even at -45 °C.

On the other hand, the P and M enantiomers of 3-(3-methyl pyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one was observed separately by HPLC. Since the two enantiomers of the compound were separable, determination of the rotational barrier to hindered rotation was done by thermally interconverting the micropreparatively separated enantiomer to its counterpart. The energy barrier of this compound was found to be 102.106 kJ/mole. Also the restricted rotation around the N_3-aryl bond of the compound

was observed by an AB splitting pattern for the ^{1}H-NMR signal of the $-CH_2$ protons at C_5 position. Although the AB splitting of the $-CH_2$ protons could not be observed in $CHCl_3$-d_1, it was observed in other NMR solvents such benzene-d_6, TFA-d_1 and toluene-d_8. This situation showed that the chemical shift difference between the two $-CH_2$ protons in these solvents is large enough for the observation of AB spliting.

A 2D-NOESY experiment was performed to find out the stereochemistry of the C=N double bond of 3-(3-methyl pyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one. It was found that this compound has a Z configuration because 2D-NOESY crosspeaks could not be observed for the protons of its two pyridine rings.

3-(3-Methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one, has a central chirality at C_5 position. So, there are 4 possible isomers (PS, MS, PR and MR) of this compound and they were observed separately by HPLC. Since the isomers of the compound were separable, the forward ($\Delta G^{\#}_f$) and reverse ($\Delta G^{\#}_r$) energy barriers of the compound were calculated an they were found to be 99.88 kJ/mole and 99.58 kJ/mole, respectively. It was found that hydrogen atom of the compound at C_5 position gives two sets of quartets which belong to the two diastereomers of the compound. The two sets of quartets could not be observed separately in the ^{1}H-NMR spectrum of the compound in $CHCl_3$- d_1, on the other hand, the percent diastereomeric ratio was found to be 13% and 87% in benzene-d_6. Interestingly, the percent difference between the diastereomers of the compound decreased and approached to equilibrium rapidly in TFA-d_1 as a result of occuring hydrogen bonding which decreased the transition state energy of the compound for hindered rotation.

3-(3-Methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidine-4-thione also has thermally interconvertible P and M enantiomers. The energy barrier of this compound was found to be 120.46 kJ/mole. The ^{1}H-NMR signal of the $-CH_2$ protons at C_5 position of the compound although did not display an AB splitting in $CHCl_3$-d_1 due to the small chemical shift difference between the $-CH_2$ protons, an AB spectrum was obtained in C_6D_6.

It was found that replacing one C-5 proton with a methyl group decreased the rotational barrier by 2.2 kJ/mol. On the other hand, replacing C-4 carbonyl oxygen with a sulphur atom increased the barrier by 18.3 kJ/mol.

In all 2-arylimino-3-aryl-thiazolidine-4-ones, the N_3-nitrogen of the compounds increases the electron density of pyridine ring on the imino group by forming a resonance structure. The imino pyridine ring protons and carbons are thus become more shielded than those of the N_3 pyridine ring, rendering the observation of separate peaks in NMR.

Finally, 3-((R)-1-cyclohexylethyl)-2-((R)-1-cyclohexylethylimino)thiazolidin-4-one was synthesized as a chiral amidine base catalyst to be used in the asymmetric nitroalkane addition reactions. The nitrogen of the compound on the imino group is expected to be more basic than the corresponding amine.

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