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ABSTRACT

A systematic investigation has been carried out on the rhodium(I) catalyzed carbonylation of heterocyclic and acyclic compounds containing two heteroatoms at the 1,3-positions. The regioselectivities of carbon monoxide insertion are different in cyclic and acyclic compounds. When there is a choice between C-S and C-N bonds, in acyclic compounds, carbonylation of the C-N bond is more facile and the C-S bond is more easily carbonylated in acyclic compounds. When there is a possibility of ring or side chain carbonylation, it appears that the C-X bond of the side chain is more reactive.

Rhodium(I) was also used to catalyze the carbonylation reaction of the N-O bond of isoxazolidine derivatives. When Ir-complexes were used as catalysts, the carbonylation occured and was followed by hydrogen transfer affording tetrahydro-1,3-oxazines as the final products. It was also found that substituents on the isoxazolidines have a dramatic effect on the reactivity of these substrates.

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I would like to express my sincere gratitude to my thesis supervisor, Professor Howard Alper, for his invaluable and generous guidance and encouragement. His excellent supervision, understanding and putting up with me through this period is really much appreciated.

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Finally I would like to thank my family in Thailand for their continuous support.

LIST OF ABBREVIATIONS

Ac	Acetyl
Ad	Adamantyl
Ar	Aryl
9-BBN	(9-Borabicyclo[3,3,1]nonane)
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	N-Butoxycarbonyl
n-Bu	normal Butyl
t-Bu	tertiary Butyl
COD	1,5-Cyclooctadiene
COSY	Correlated Spectroscopy
Cy	Cyclohexyl
DEPT	Distortionless Enhancement by Polarization Transfer
dba	Dibenzylideneacetone
DIOP	2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
dppe	1,4-Bis(diphenylphosphino)ethane
dppp	1,4-Bis(diphenylphosphino)propane
Et	Ethyl
HMQC	Heteronuclear Multiple Quantum Coherence
Me	Methyl
NMR	Nuclear Magnetic Resonance
PEG-400	Polyethylene glycol molecular weight 400
Ph	Phenyl
i-Pr	iso-Propyl
IR	Infrared Spectroscopy

RT	Room Temperature
THF	Tetrahydrofuran
TMS	Tetramethylsilane
Tosyl, Ts	*p*-Toluenesulfonyl

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CHAPTER 1

TRANSITION METAL CATALYZED CARBONYLATION OF NITROGEN AND SULFUR CONTAINING MOLECULES

1.1. Introduction

The carbonylation reaction, i.e. the introduction of C=O into organic molecules, is a widely used method for the functionalization of various compounds. This reaction has attracted a great deal of attention among chemists dealing with transition-metal catalysis.[1-3] The first catalytic carbonylation reaction, viz. hydroformylation of ethylene with CO/H_2 in the presence of $HCo(CO)_4$ (eq. 1.1), was discovered over 50 years ago.[4]

$$CH_2{=}CH_2 + CO/H_2 \xrightarrow{HCo(CO)_4} CH_3CH_2CHO \qquad \text{eq 1.1}$$

The carbonylation reaction is carried out by using carbon monoxide gas neat or as a mixture with other reagents, for example, CO/H_2 (hydroformylation), $CO/HSiR_3$ (silylformylation), $CO/H_2/HSiR_3$ (silylhydroformylation), CO/ROH (hydrocarboxylation), etc. The scope of these and related carbonylation reactions is very wide. Some typical examples are summarized in **Tables 1.1-1.4**.[2]

Simple and functionally substituted alkenes, alkynes, dienes, allenes, enynes, alkyl, aryl and heteroaryl halides, N- and O-containing heterocycles and hydrocarbons have been carbonylated using transition metal catalysts. The data from **Tables 1.1-1.4** clearly show that the carbonylation reaction is a very useful, versatile and efficient method for the preparation of carbonyl

compounds. It is in fact so successful that the carbonylation reaction is currently used in industry for the preparation of many carbofunctional compounds.[2]

This chapter describes catalytic carbonylation reactions of N- and S-containing acyclic and heterocyclic compounds.

Table 1.1. Catalytic Carbonylation of Alkenes

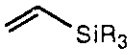
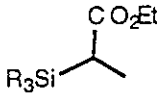
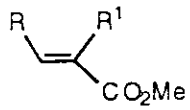
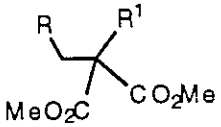
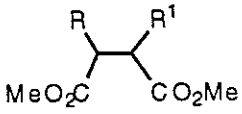
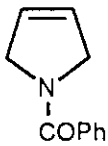
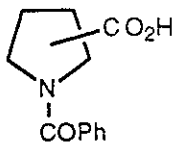
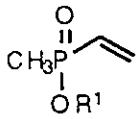
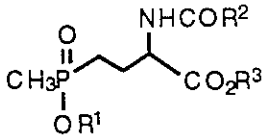
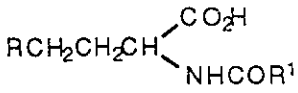
Substrate	Carbonylating agent	Catalyst	Product (major)	Reference
	CO / EtOH	L_2PdCl_2		5
		$Co_2(CO)_8$		
	CO / MeOH	L_2PdCl_2		6
		(DIOP)-$PdCl_2$		
	CO / H_2 H_2O, THF	$Co_2(CO)_8$		7
$H_2C{=}CH_2$	CO / MeOH	$Pd(OAc)_2$ / dppp		8
	CO / H_2 / R^2CONH_2 / R^3OH	$Co_2(CO)_8$		9
$RCH_2{=}CH_2$	CO / H_2 / R^1CONH_2	$Co_2(CO)_8$		10

Table 1.1. (continued)

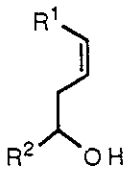
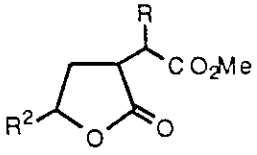
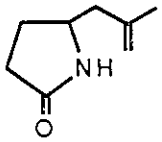
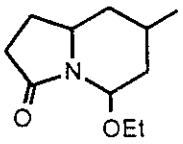
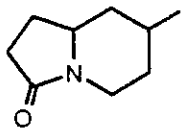
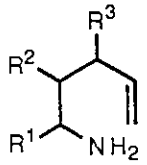
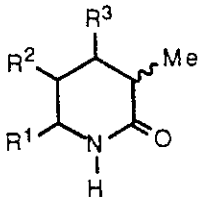
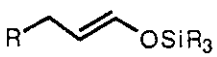
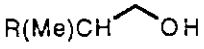
Substrate	Carbonylating agent	Catalyst	Product (major)	Reference
	CO / $MeC(OEt)_3$	$PdCl_2$ / $CuCl_2$		11
	CO / H_2 $CH(OEt)_3$	L_3RhCl		12
		$Co_2Rh_2(CO)_{12}$		
	CO / H_2	$Rh_2(OAc)_4$ / PPh_3		13
	CO / R_3SiH	$Co_2(CO)_8$		14
	CO / $NaBH_4$	$Rh(COD)BPh_4$		15

Table 1.2. Catalytic Carbonylation of Alkynes

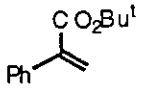
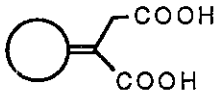
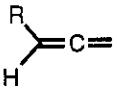
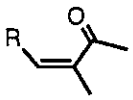
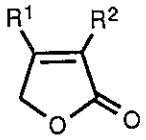
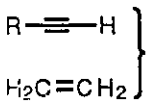
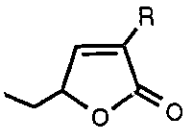
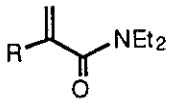
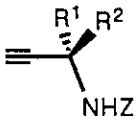
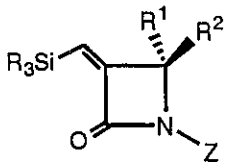
Substrate	Carbonylating agent	Catalyst	Product (major)	Reference
PhC≡CH	CO / t-BuOH	Pd_2dba_3 or $Pd(OAc)_2$		16
	CO	$Ni(CN)_2\ 4H_2O$		17
	CO / MeI	$Mn_2(CO)_{10}$		18
	CO / H_2O	$Rh_4(CO)_{12}$		19
	CO / i-PrOH	$Rh_4(CO)_{12}$ / PPh_3		20
	CO / Et_2NH MeI	$PdCl_2L_2$		21
	CO / R_3SiH / base	$Rh_4(CO)_{12}$		22

Table 1.2. (continued)

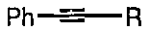
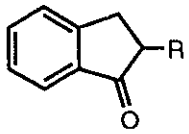
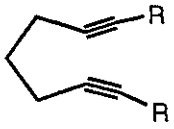
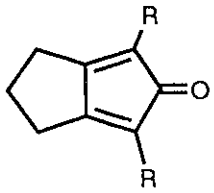
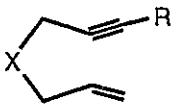
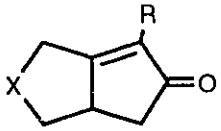
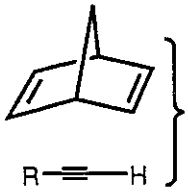
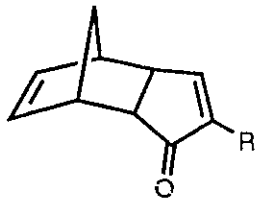
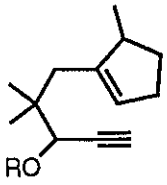
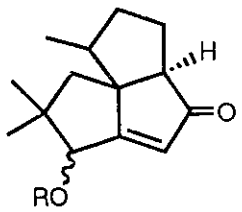
Substrate	Carbonylating agent	Catalyst	Product (major)	Reference
	CO/H_2O	$Co_2(CO)_8$		23
	CO	$Fe(CO)_5$		24
 X = C, O, N	CO	$Co_2(CO)_8$		24, 25, 26
	CO	$Co_2(CO)_8$		27
	$Co_2(CO)_8$	$Co_2(CO)_8$		28

Table 1.3. Catalytic Carbonylation of Halides and Triflates

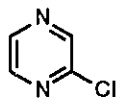
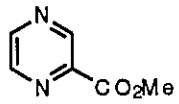
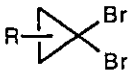
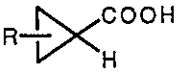
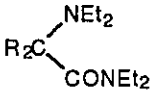
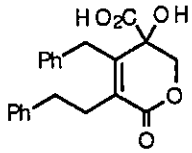
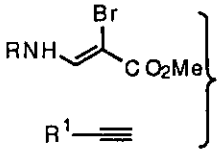
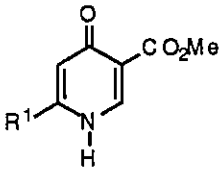
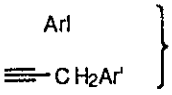
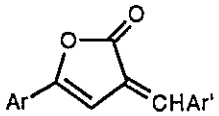
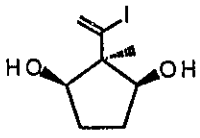
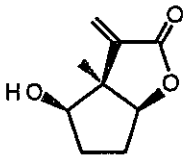
Substrate	Carbonylating agent	Catalyst	Product (major)	Reference
RX	CO / R^1OH or R^1CO_2H, $NaOR^1$	Pd(0), Co(0), L_2PdCl_2	RCO_2R^1	29, 30
	CO / MeOH	$Pd(OAc)_2$ / PPh_3		31
	CO / H_2 / KOH / PEG-400	$CoCl_2\,6H_2O$ $Ni(CN)_2\,H_2O$		32
R_2CX_2	CO / Et_2NH	$Co_2(CO)_8$		33
	CO / t-BuOH	$Sn[Co(CO)_4]_4$		34
	CO / MeOH	Pd(0)		35
	CO	$Pd(OAc)_2$		36
	CO / (R)-BINAP	$Pd(OAc)_2$	 50% ee	37

Table 1.3. (continued)

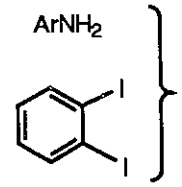
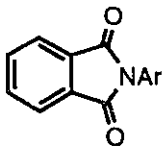
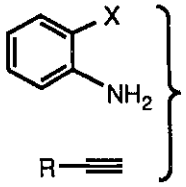
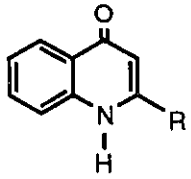
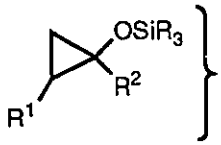
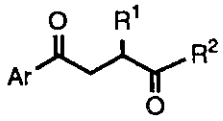
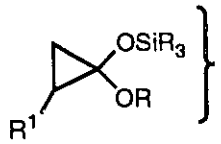
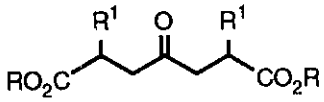
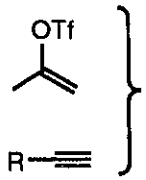
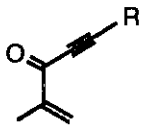
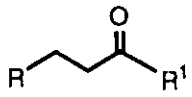
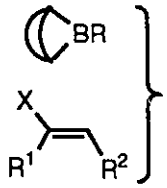
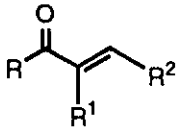
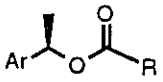
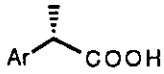
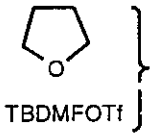
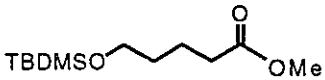
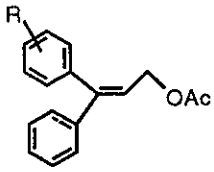
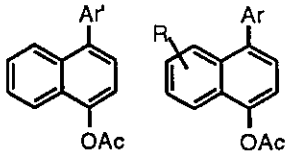
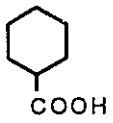
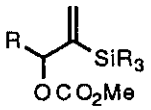
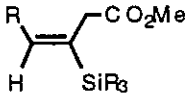
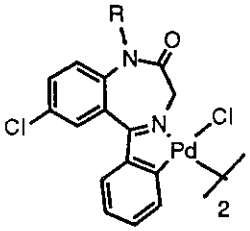
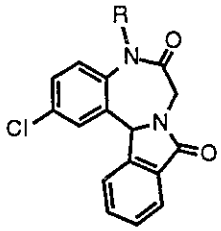
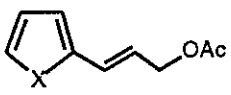
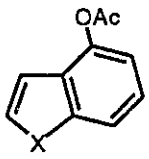
Substrate	Carbonylating agent	Catalyst	Product (major)	Reference
	CO	$PdCl_2$ / dppe		38
	CO	Pd(0)		39
	CO	L_4Pd		40
ArOTf 	CO	L_4Pd		
	CO	Pd(0)		41
	CO / 9 BBN / R^1I	L_4Pd		42
	CO	Pd(0)		43

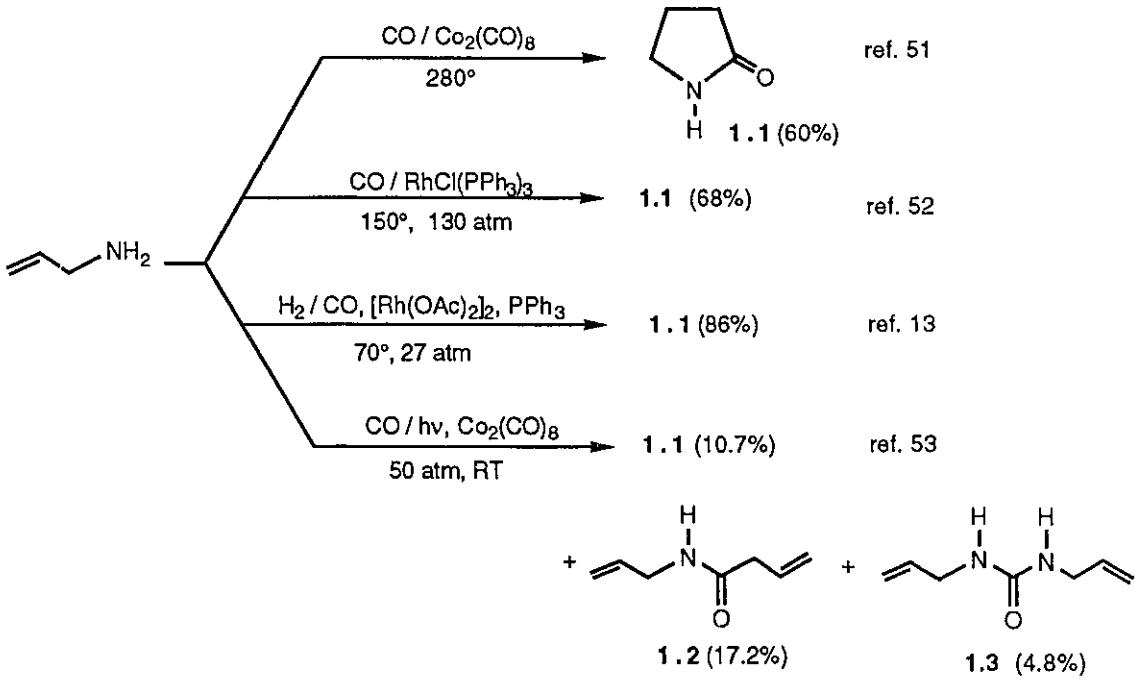
Table 1.4. Miscellaneous Carbonylations

Substrate	Carbonylating agent	Catalyst	Product	Reference
	CO / HCO_2^-	Pd(0)		44
 TBDMFOTf	CO / MeOH	$NaMn(CO)_5$		45
	CO / Ac_2O / NEt_3	$PdCl_2(PPh_3)_2$		46
	CO / CF_3COOH / $K_2S_2O_8$	$Pd(OAc)_2$ / $Cu(OAc)_2$		47
	CO	L_4Pd		48
	CO / ROH			49
 X = S, O, NAc	CO / Ac_2O	$PdCl_2L_2$		50

1.2. Carbonylation of Acyclic Amines

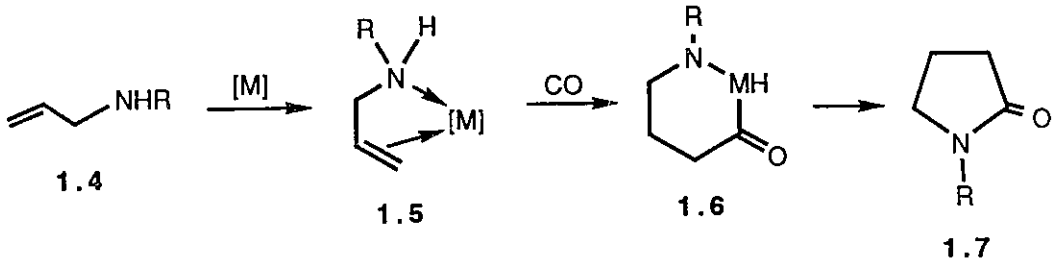
The carbonylation and/or hydroformylation of allylamine is catalyzed by rhodium, cobalt, palladium and other transition metals. Some examples are shown in **Scheme 1.1**. This reaction occurs via carbonylation of the C=C bond followed by intramolecular cyclization giving rise to pyrrolidinone (**1.1**).

Scheme 1.1



Rhodium catalysts produce the γ-lactam (**1.1**) in higher yields than cobalt carbonyl and under milder conditions.[13] **Scheme 1.2** shows a possible mechanism for this transformation.

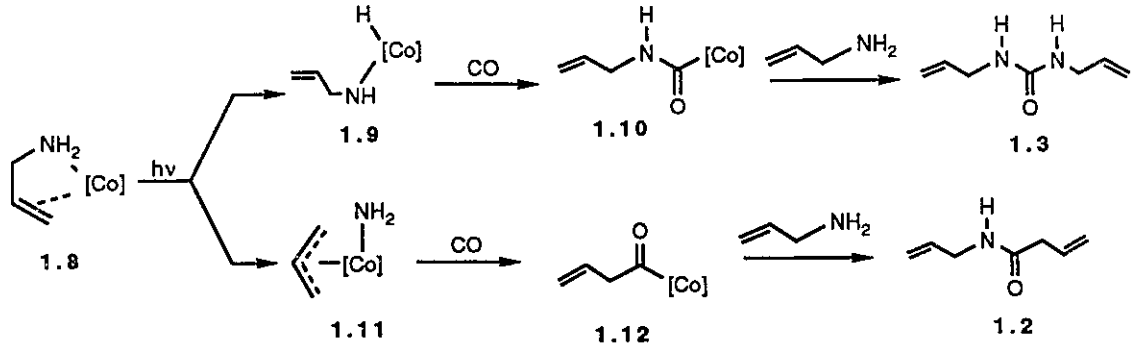
Scheme 1.2



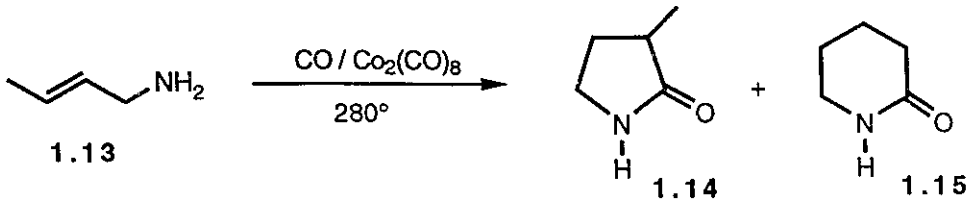
The best yield of γ-lactam (**1.1**) was obtained when the reaction was carried out under a CO/H_2 atmosphere.[13] The authors[13] concluded that the transfer of the amino hydrogen during the reaction does not occur as readily as has been proposed previously.[54] As a consequence, molecular hydrogen plays a significant role in the reaction.[13]

When the reaction is carried out under UV-irradiation using $Co_2(CO)_8$ as the catalyst, the formation of pyrrolidinone (**1.1**) is accompanied by amide (**1.2**) and urea (**1.3**). The latter products were suggested to arise via the pathways shown below (**Scheme 1.3**).[53]

Scheme 1.3

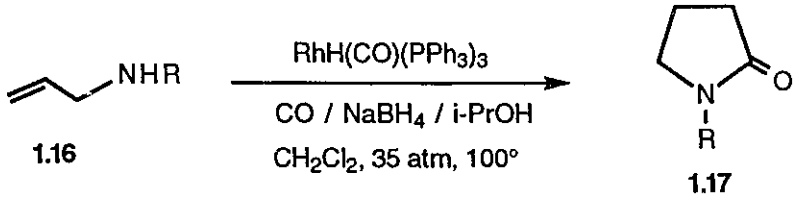


The carbonylation of crotylamine leads to two isomeric products, pyrrolidinone (**1.14**) and piperidinone (**1.15**) in a 9 : 1 ratio (40% overall yield). The piperidinone results from double bond isomerization of crotylamine under the drastic conditions required for the reaction.[51]



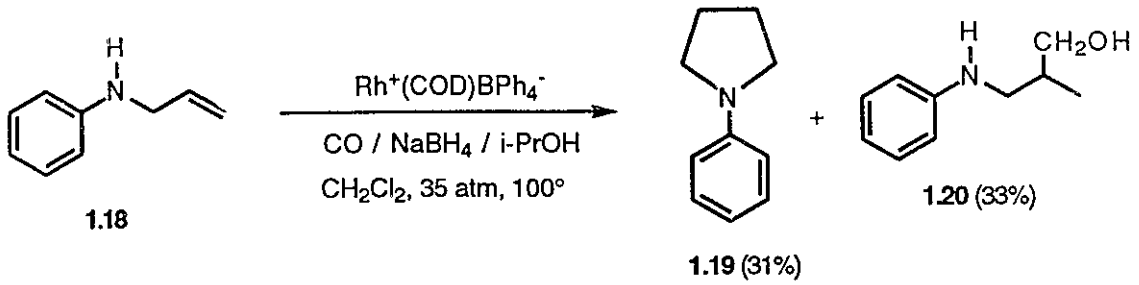
1.13 1.14 1.15

The rhodium(I)-catalyzed reductive carbonylation of N-alkyl-N-allylamines (**1.16**) affords N-substituted pyrrolidinones (**1.17**). The use of sodium borohydride as the hydrogen source permits the reaction to occur under relatively mild conditions.[55]



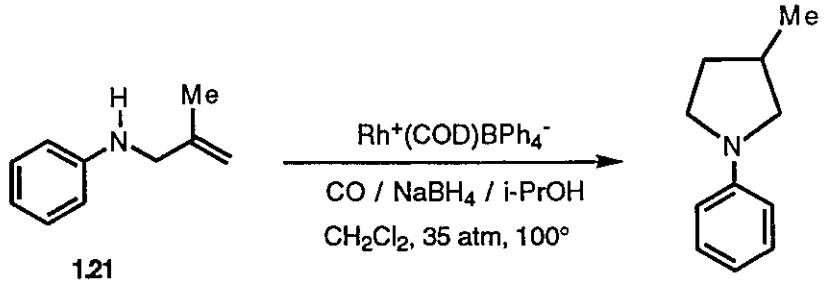
1.16 1.17

When a similar catalytic system was applied to secondary aromatic amines, such as allylaniline (**1.18**), two products, N-phenylpyrrolidine (**1.19**) and the amino alcohol **1.20** were isolated. When the reaction was carried out in the presence of 1,4-bis(diphenylphosphino)butane, only (**1.19**) was obtained in 68% yield.[55]



1.18 **1.19** (31%) **1.20** (33%)

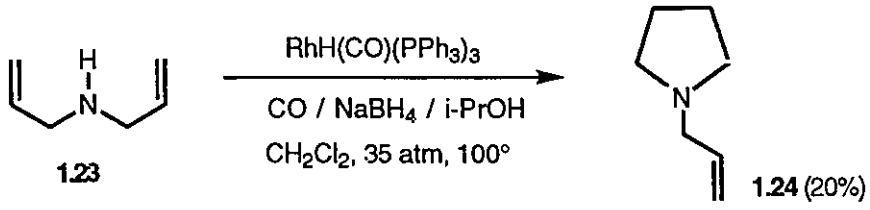
N-(2-Methylallyl)aniline (**1.21**) under identical conditions gave an N-phenylpyrrolidine derivative (**1.22**) in high yield.[55]



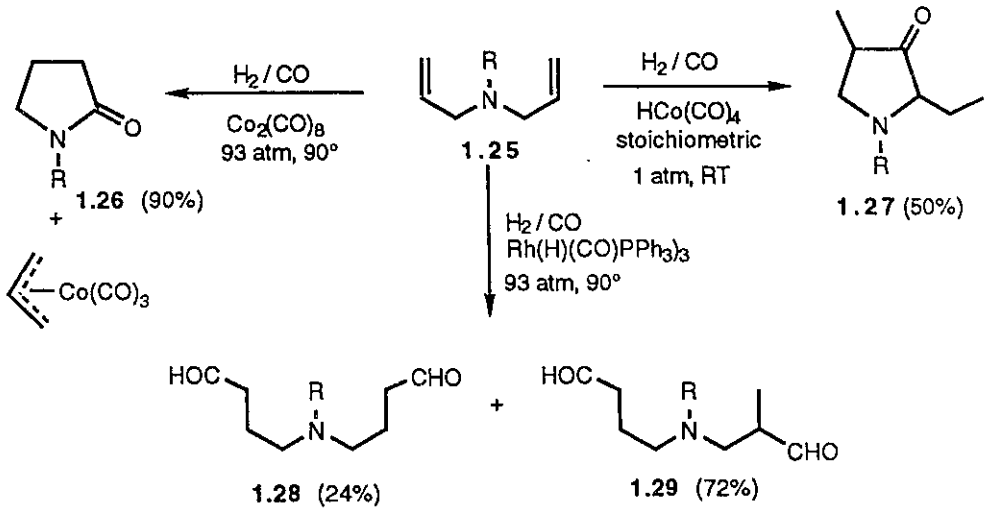
1.21 **1.22** (84%)

The authors explained the difference in reactivity of aliphatic and aromatic amines by their difference in basicity.[55]

The hydroformylation of N,N-bis(allyl)amine (**1.23** and **1.25**) can yield many different products depending on the catalyst and reaction conditions as shown below.[55, 56]

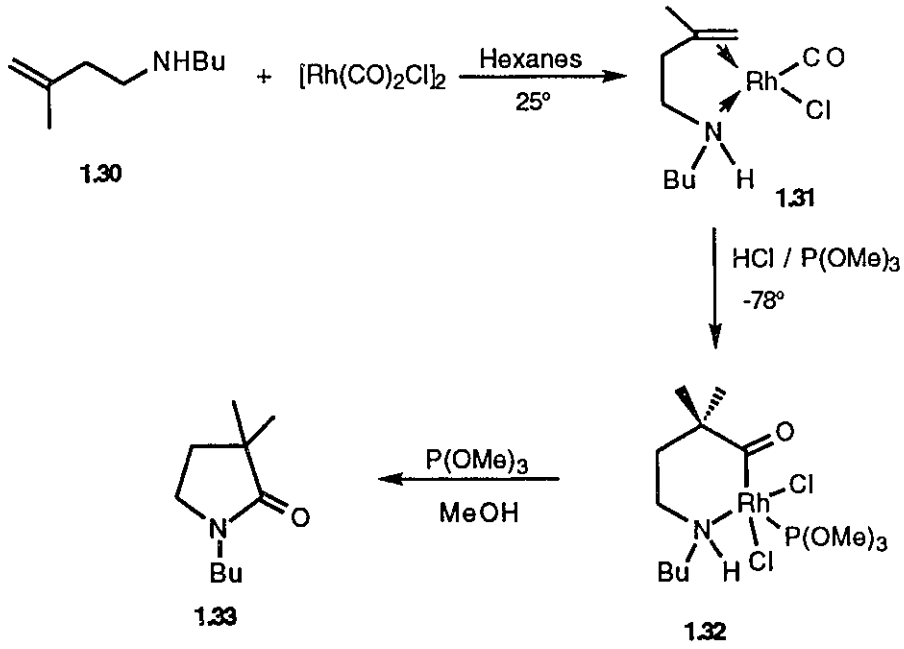


1.23 **1.24** (20%)

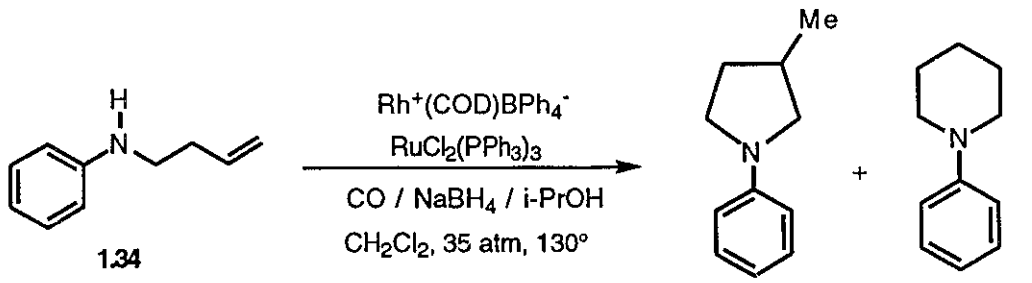


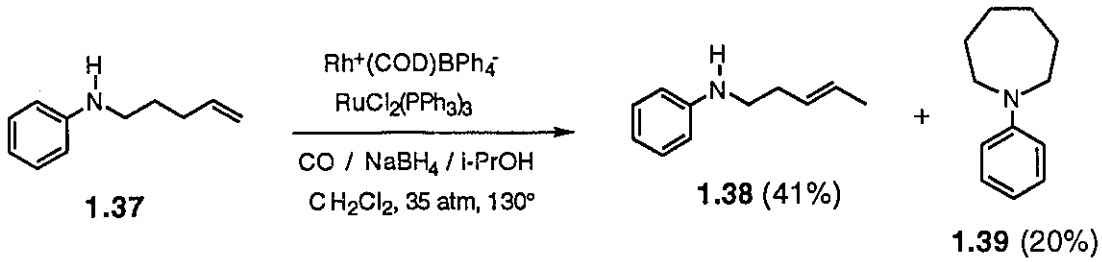
Krafft and Wilson have shown that the homoallylamine **(1.30)** reacts with rhodiumdicarbonyl chloride dimer to give **(1.31)** which undergoes reaction with HCl and trimethylphosphite to form complex **(1.32)**. The latter, in the presence of trimethylphosphite and methanol is converted to pyrrolidinone **(1.33)**. These transformations are shown in **Scheme 1.4**.[57-59]

Scheme 1.4

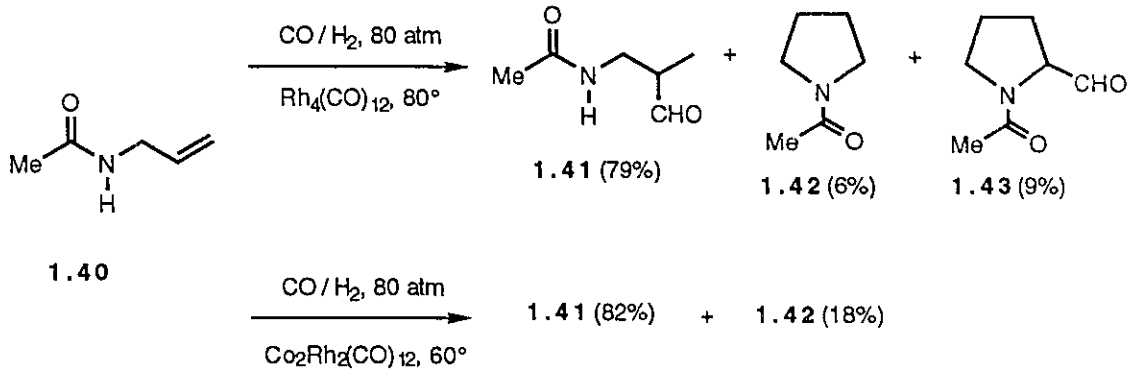


The rhodium(I)-catalyzed hydroformylation of homoallylic aromatic amines has also been studied. N-Butenylaniline **(1.34)** afforded N-substituted pyrrolidine **(1.35)** and piperidine **(1.36)** while N-pentenylaniline **(1.37)** undergoes isomerization **(1.38)** along with azepin **(1.39)** formation.[60]

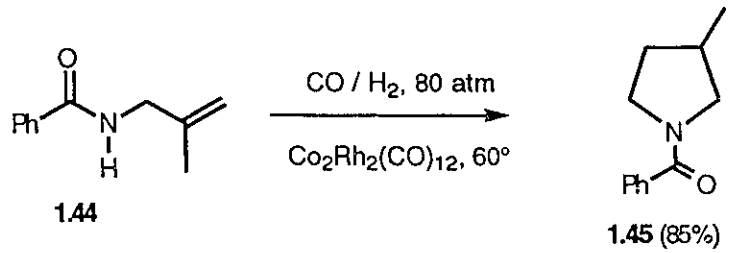




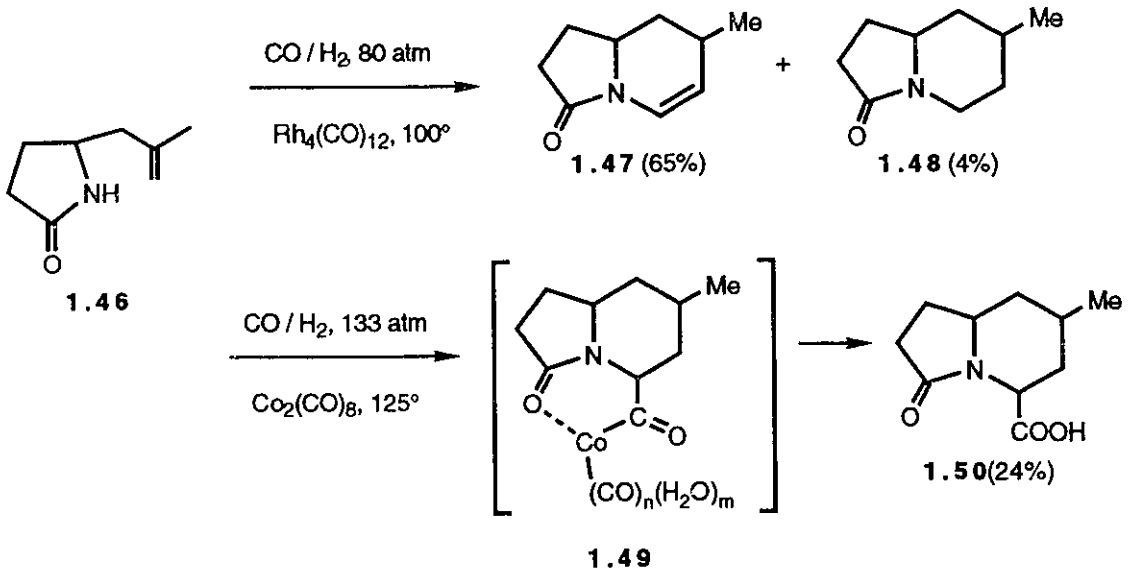
Less basic systems, such as N-allylamides, also undergo hydroformylation. N-acetyl-N-allylamine **(1.40)** readily reacts with CO/H_2 in the presence of rhodium or a mixed cobalt-rhodium catalyst, with the latter giving better selectivity.[61] The authors believe that the amide functionality leads to higher regioselectivity owing to chelation control. Consequently, the major product **(1.41)** is the branched aldehyde. The minor products (**1.42** and **1.43**) result from intramolecular traping and double carbonylation, respectively.



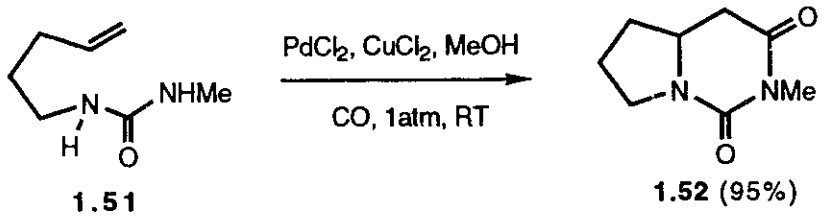
In the case of the closely related N-allyl-N-benzoylamine (**1.44**), the cyclocarbonylation product, N-benzoyl-3-methyl pyrrolidine (**1.45**), is formed selectively.[61]

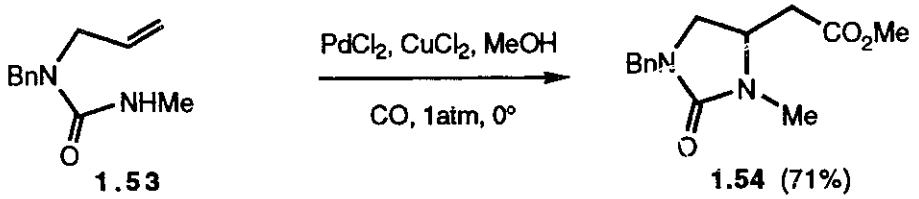


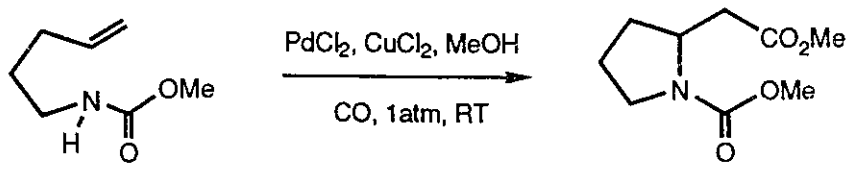
α-Homoallylic lactams such as (**1.46**) undergo carbonylation in the presence of rhodium or cobalt carbonyl to yield different bicyclic products. The carboxylic acid (**1.50**), obtained from the cobalt catalyzed carbonylation, may result by hydrolysis of a presumed acyl cobalt species (**1.49**).[12, 62]



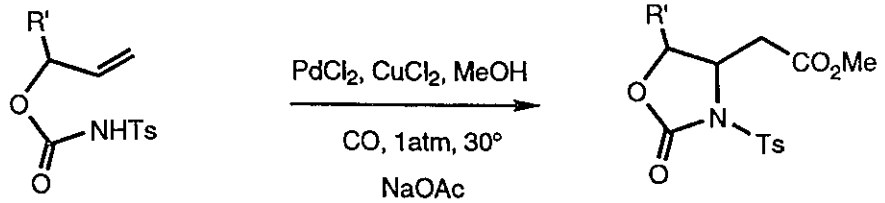
The intermolecular aminocarbonylation of N-alkenylureas (**1.51, 1.53**), N-alkenylcarbamate (**1.55**)[63] and O-allylcarbamate (**1.57**)[64] has been studied extensively by Tamaru and coworkers using catalytic palladium chloride in the presence of $CuCl_2$ as a reoxidant. In all cases, the corresponding heterocyclic products were obtained in good yield. It should be noted that the reaction involving endo-carbamate (**1.57**) occurs only for N-tosyl derivatives.[65]





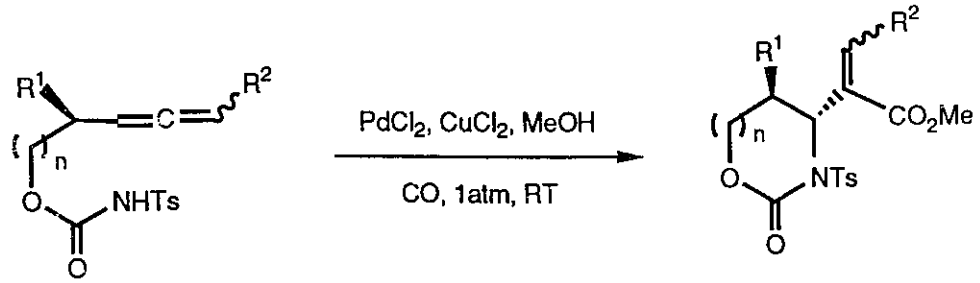


1.55 **1.56**(73%)



1.57 **1.58** (89%)

The above method was recently applied to allenes containing a carbamate function (**1.59**).[66] The room temperature aminocarbonylation of (**1.60**), unlike previous examples, proceeds to form both five- and six-membered ring heterocyclic products in moderate to good yields.



1.59

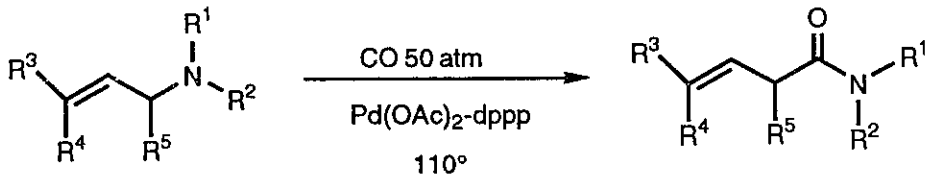
n = 0, 1

R^1, R^2 = H, Me

1.60 (41-99%)

Although there are many examples of the catalytic carbonylation of N-allylamine, there is only one result on the direct insertion of carbon monoxide into the C-N bond in an acyclic system. The carbonylation of N-

allylamines **(1.61)** in the presence of $Pd(OAc)_2$-dppp yields the corresponding amides **(1.62)** in moderate to good yields.[67]



1.61

R^1 = Me, Et, Bu
R^2 = Et, Bu, Ph, CH_2Ph
R^3 = H, Me, Pr, Ph
$R^4 = R^5$ = H, -$[CH_2]_3$

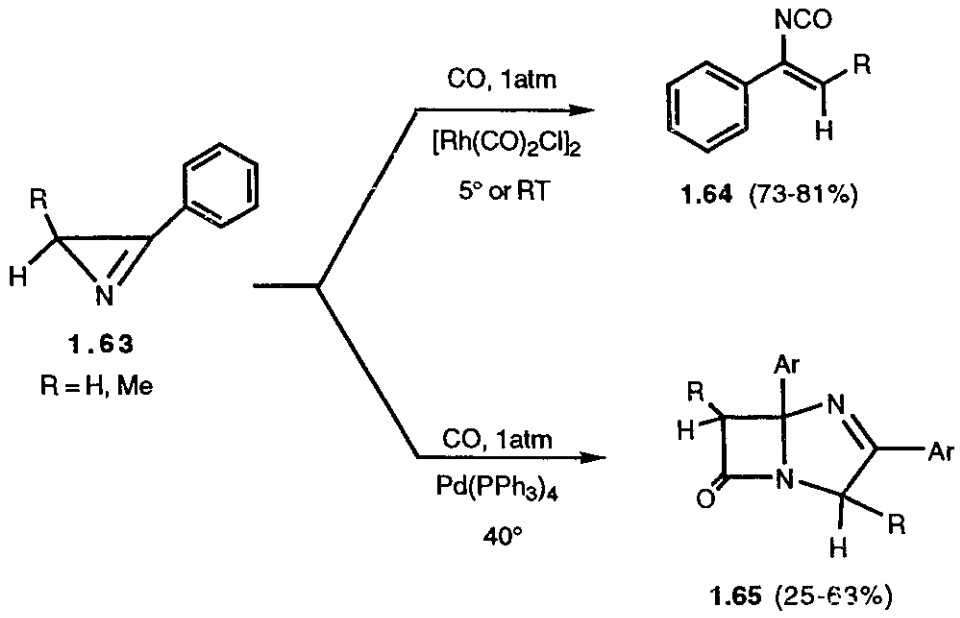
1.62(35-89%)

The formation of a π-allyl palladium complex is the apparent driving force for the reaction.

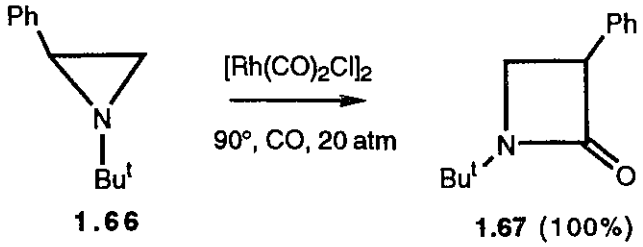
1.3. Carbonylation of Nitrogen-Containing Heterocycles

1.3.1. Aziridines, Diaziridines, Azetidines and Their Derivatives

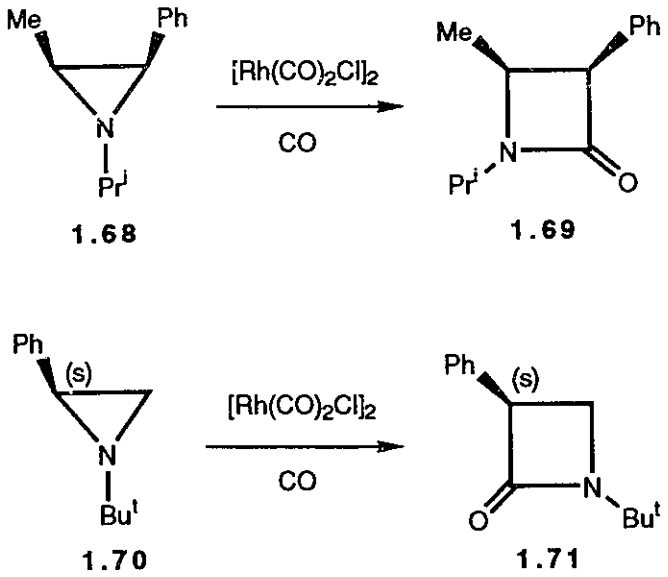
The carbonylation and ring expansion of heterocycles has been extensively studied in the last decade. The first example of carbonylation with ring expansion was described by Alper, Perera and Ahmed.[68] When azirines **(1.63)** were exposed to carbon monoxide in the presence of $Pd(PPh_3)_4$ under mild conditions, bicyclic β-lactams **(1.65)** were obtained in fair yields. An aza-π-allyl complex may be involved in the reaction. When using $[Rh(COD)Cl]_2$ as the catalyst, azirines **(1.63)** are converted to vinyl isocyanates **(1.64)** in good yields under very mild conditions.[69]



Monocyclic β-lactams can be obtained from aziridines by carbonylation using an appropriate catalyst. The first reported example involved chlorodicarbonyl rhodium(I) dimer as the catalyst.[70] The β-lactam **(1.67)** was prepared in quantitative yield.



In all cases, carbon monoxide inserts at the more substituted C-N bond. It has also been found that this reaction occurs with retention of configuration:[71]

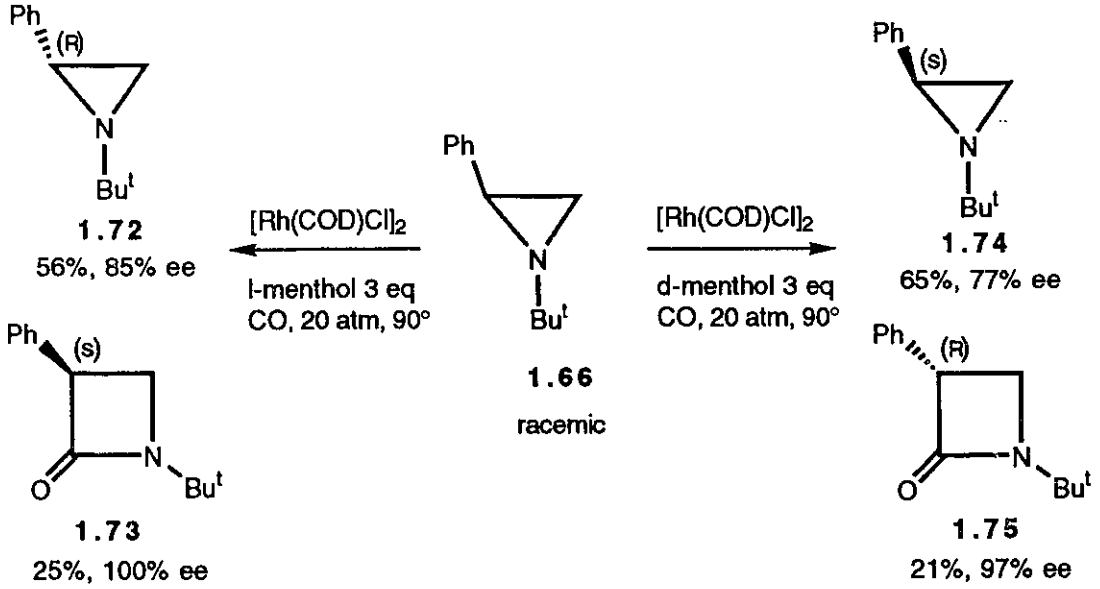


1.68 **1.69**

1.70 **1.71**

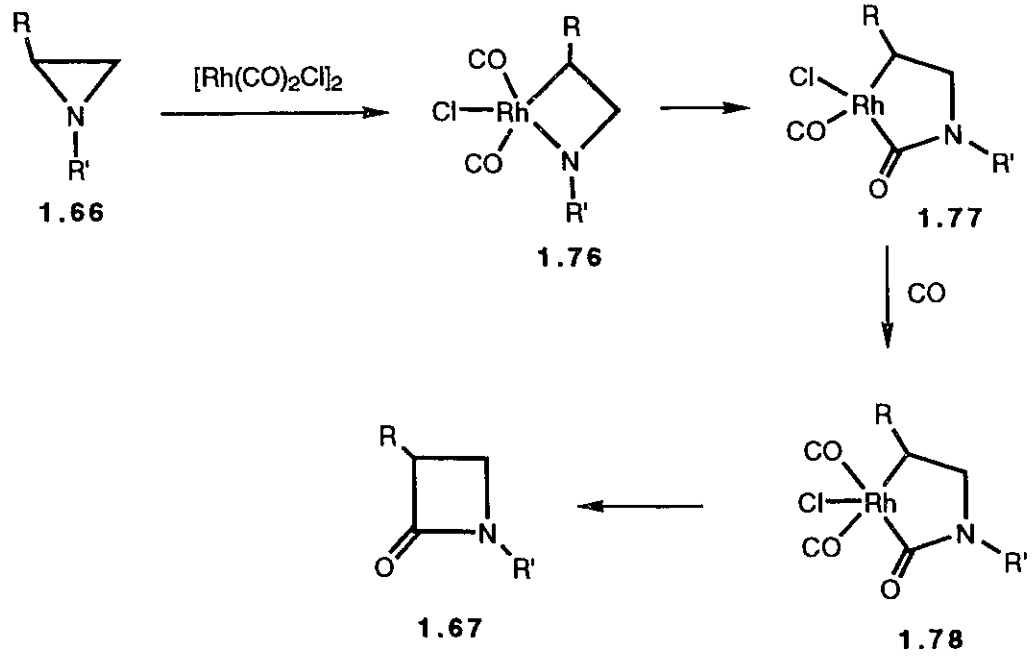
A remarkable feature of this reaction is that in the presence of menthol, a high degree of asymmetric induction is observed.[71] This represents not only the asymmetric synthesis of β-lactams, but also the preparation of enantiomerically enriched aziridines.

Scheme 1.5

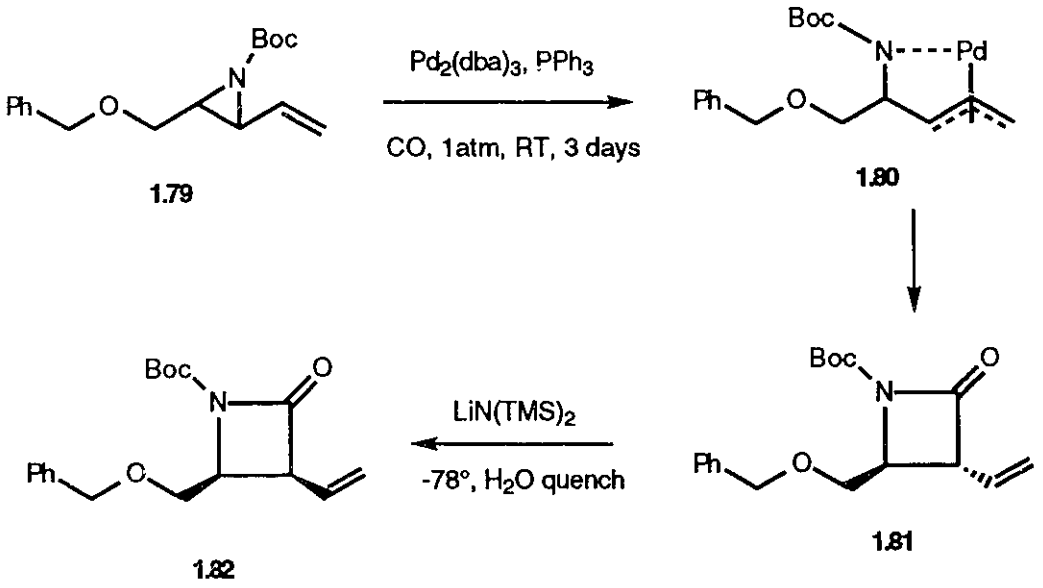


A possible mechanism for the catalytic carbonylation of aziridines has been proposed (**Scheme 1.6**).[71]

Scheme 1.6

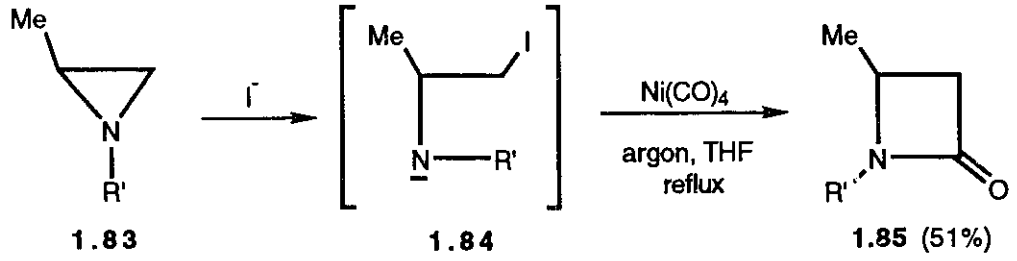


In 1991, Ohfune and coworkers[72] discovered that the carbonylation of a vinyl aziridine (**1.79**) afforded a β-lactam (**1.81**) using palladium(0) as the catalyst. In the authors' opinion, the vinylic moiety is essential for the reaction since this group is involved in the formation of an intermediate π-allyl complex (**1.80**). This reaction is highly stereoselective and affords trans-(**1.81**) in 51% yield. The latter can be easily isomerized to cis-(**1.82**) by a simple procedure.[72]



Aziridine carbonylation can also be achieved using an excess (10 equivalents) of nickel tetracarbonyl in the presence of iodide ion[73, 74] **(Scheme 1.7)**.

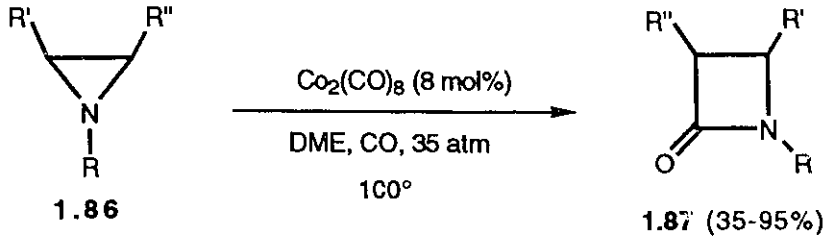
Scheme 1.7



Unlike the rhodium(I)-catalyzed carbonylation, carbon monoxide inserts here at the less substituted C-N bond.

Recently, Alper and Piotti discovered the carbonylation of alkyl substituted aziridines using dicobalt octacarbonyl and found that carbon

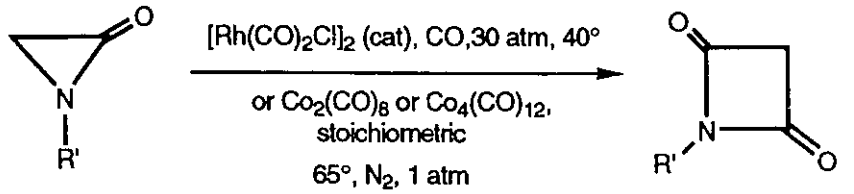
monoxide inserts exclusively into the less hindered C-N bond. The mechanism for this transformation is under examination.[75]



1.86 **1.87** (35-95%)

R = CH_2CH_2Ph, CH_2Ph, t-Bu
tosyl, C_6H_4OMe, COPh;
R' = Et, n-Bu, t-Bu;
R" = H, Me

The carbonylation-ring expansion reaction is also applicable to α-lactams (**1.88**) to yield 2,4-azetidinediones (**1.89**).[76]

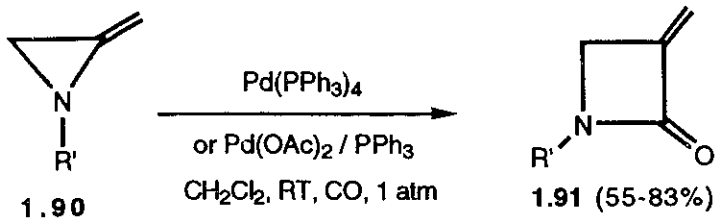


1.88 **1.89** (51-100%)

R, R' = t-Bu, 1-adamantyl

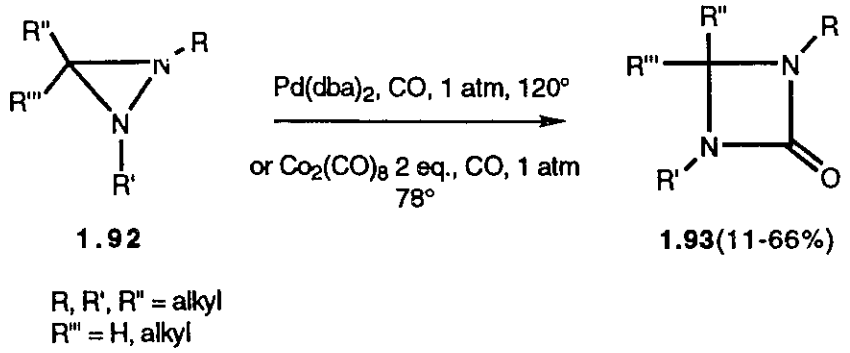
This reaction is carried out using rhodium(I) or cobalt carbonyl complexes, such as $[Rh(CO)_2Cl]_2$, $Co_2(CO)_8$ or $Co_4(CO)_{12}$.

The regiospecific carbonylation of methyleneaziridines (**1.90**) using palladium(0) affords α-methylene-β-lactams (**1.91**) in good yield.[77]



The reaction is regiospecific and occurs under mild conditions. The use of $Pd(PPh_3)_4$ gave the same results as $Pd(OAc)_2$, but Pd(0) complexes containing bidentate ligands such as bis(1,2-bisdiphenylphosphino)ethane or bis(dibenzylideneacetone) were not effective for the carbonylation.[77]

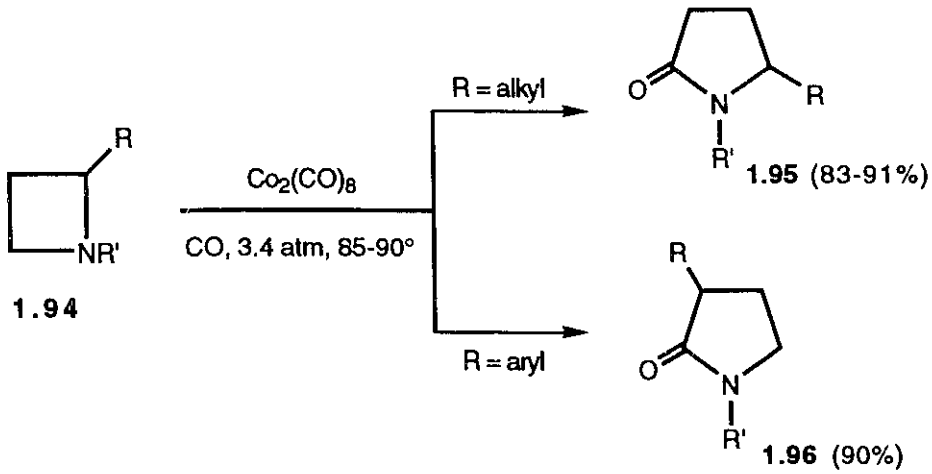
Three-membered ring heterocycles with two heteroatoms were also examined as substrates for the carbonylation reactions. It was found that carbon monoxide inserts exclusively into the N-N bond of diaziridines **(1.92)** giving rise to 1,3-diazetidine-2-ones **(1.93)**.[78]



This reaction was accomplished with catalytic quantities of a palladium(0) complex or a stoichiometric amount of dicobalt octacarbonyl. Even though the transformation is the same, the mechanism and the applicable substrates are different for the palladium and cobalt complexes. Palladium

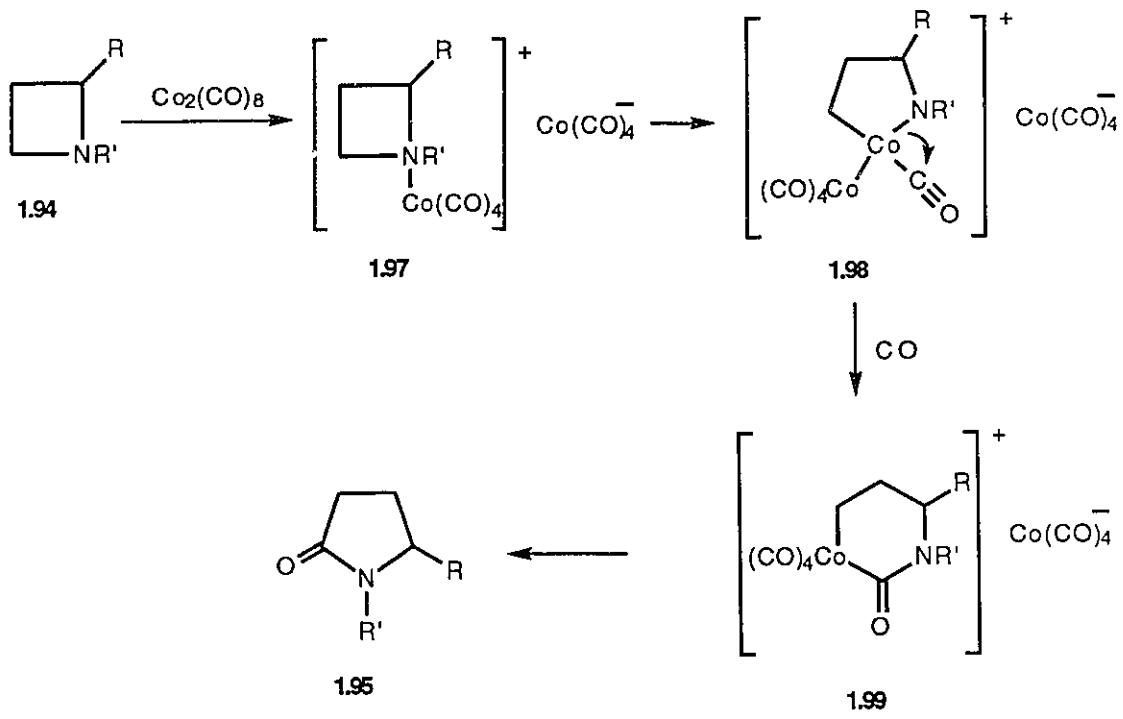
complexes do not catalyze the carbonylation of 3,3-disubstituted diaziridines while cobalt carbonyl is ineffective for monosubstituted diaziridines.

In the presence of catalytic amounts of dicobalt octacarbonyl, azetidines (**1.94**) undergo carbonylation under moderate pressures to yield pyrrolidinones in good yields.[79] The ring expansion occurs with good regioselectivity. For example, 2-arylazetidines lead to 3-arylpyrrolidinones (**1.95**) while 2-alkylazetidines form 5-alkylpyrrolidinones (**1.96**).

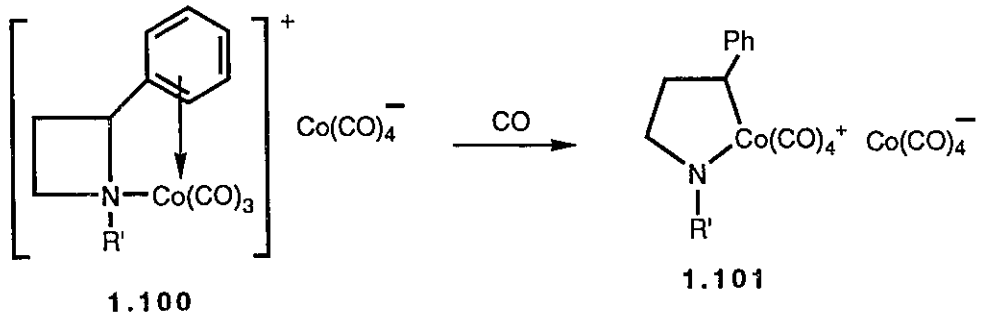


The mechanism proposed to account for these results is shown in **Scheme 1.8**.

Scheme 1.8

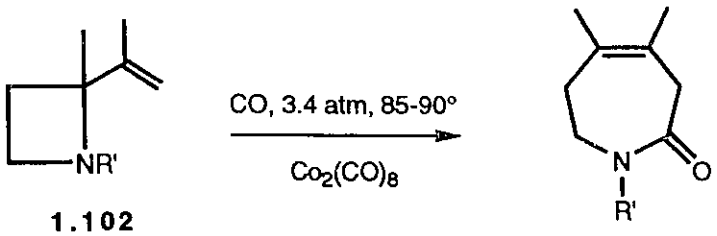


The opposite regiochemistry observed in the arylazetidine series is proposed to result from coordination of the aromatic ring to the cobalt.



In the case of 2-alkylazetidines, the alkyl group cannot coordinate to cobalt and therefore carbon monoxide insertion occurs into the less substituted C-N bond.

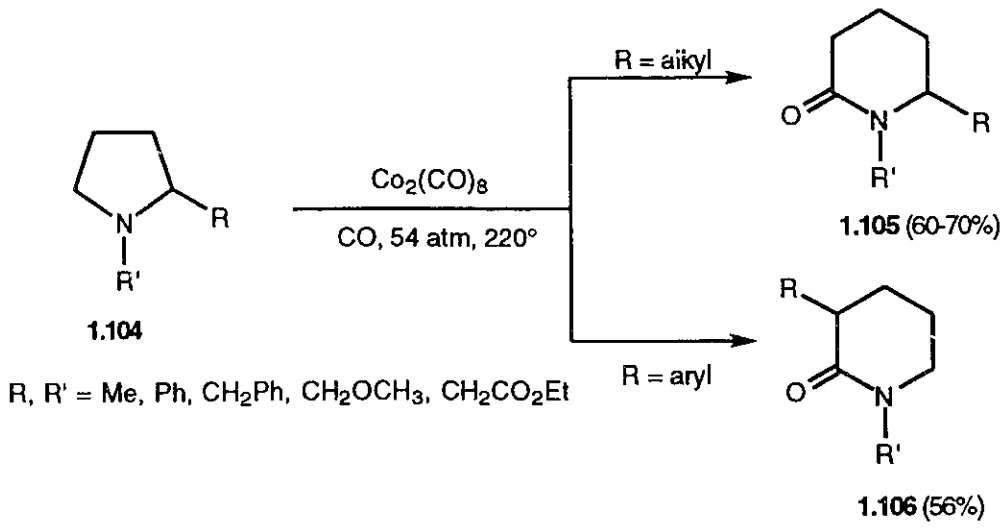
The same authors also found that when a 2-vinylazetidine (**1.102**) was subjected to reaction with carbon monoxide, the vinyl side chain was incorporated into the ring to yield azepinone derivatives (**1.103**).[79]



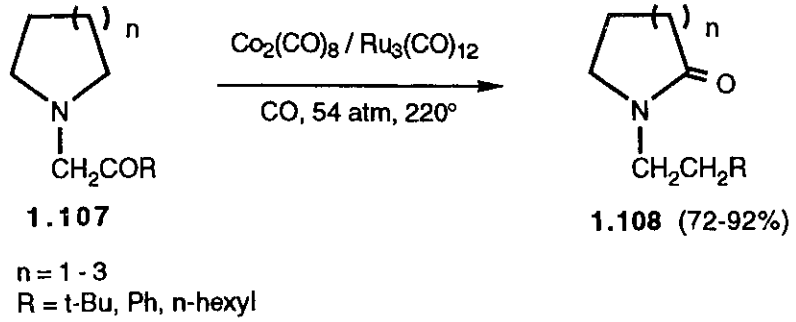
1.102 **1.103**

1.3.2. Pyrrolidines and Piperidines

The cobalt carbonyl catalyzed carbonylation of pyrrolidines to piperidinones was discovered recently by Alper and Wang.[80] The reaction conditions were quite drastic due to the lack of strain in the starting material. The regioselectivity of the carbon monoxide insertion is the same as that observed for azetidine systems. If there is an aryl substituent at the ring carbon next to nitrogen, it leads to the insertion of carbon monoxide into the more substituted C-N bond and is opposite to that for the 2-alkyl substituted analog. The proposed mechanism is similar to that invoked for azetidines (see **Scheme 1.8**).[80]



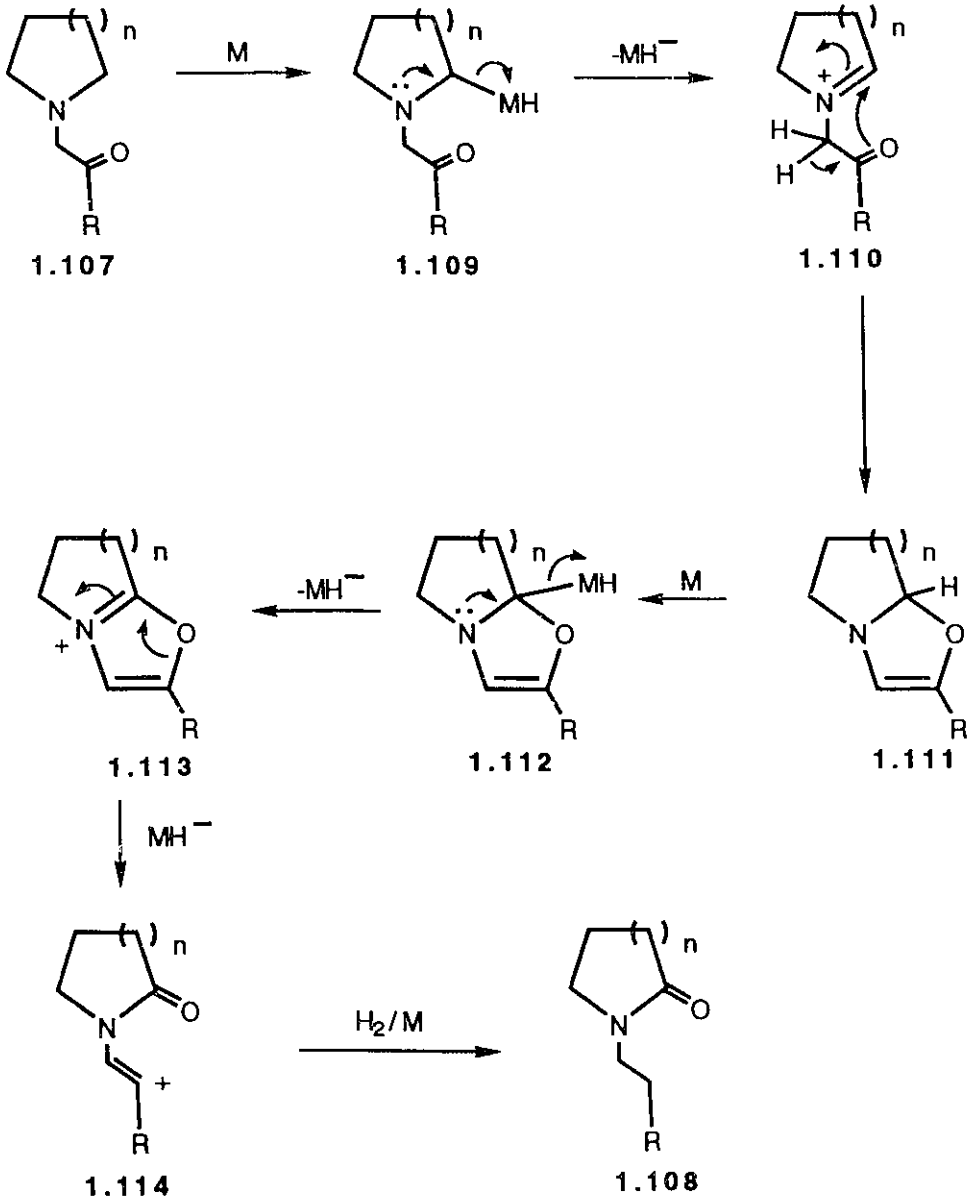
When the starting material **(1.107)** contains a methylene ketone side-chain at nitrogen, a remarkable rearrangement occurs giving rise to the pyrrolidinones **(1.108)** in good yield. This reaction also takes place for six-, seven- and eight-membered ring systems.



The proposed mechanism for this transformation is shown in **Scheme 1.9** The ^{13}C labelling experiment using ^{13}CO revealed that no ^{13}C was incorporated into the final product. The role of CO is probably to stabilize one or more key reaction intermediates since there was only 5% yield of product when the reaction was run under nitrogen. Furthermore, when the starting material contains ^{13}C at the carbonyl carbon of the side chain, the labelled

carbon was converted to the methylene carbon unit in the product. This result provides evidence for the positional exchange of the oxygen and two hydrogen atoms.[80]

Scheme 1.9

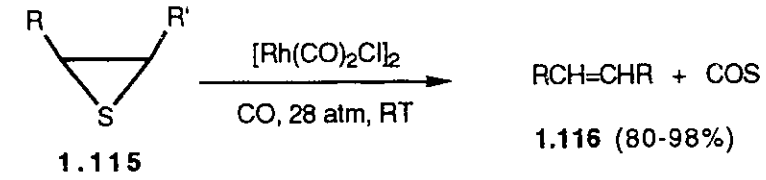


In conclusion it should be noted that there are no reports on the carbonylation and ring expansion of six-membered or larger ring systems.

1.4. Carbonylation of Sulfur-Containing Heterocycles

1.4.1. Thiiranes

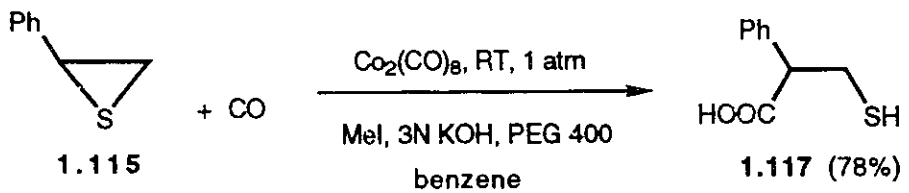
The rhodium(I)-catalyzed reaction of thiiranes with carbon monoxide was examined by Alper and Calet in 1986.[81] Unlike aziridines, thiiranes (**1.115**) do not give the corresponding β-thiolactones. In all cases the desulfurized products, alkenes (**1.116**), are obtained in high yield. It is conceivable that a thiolactone is formed in the reaction and experiences expulsion of COS.



1.115

R, R' = Ph, -$(CH_2)_4$- , n-Bu

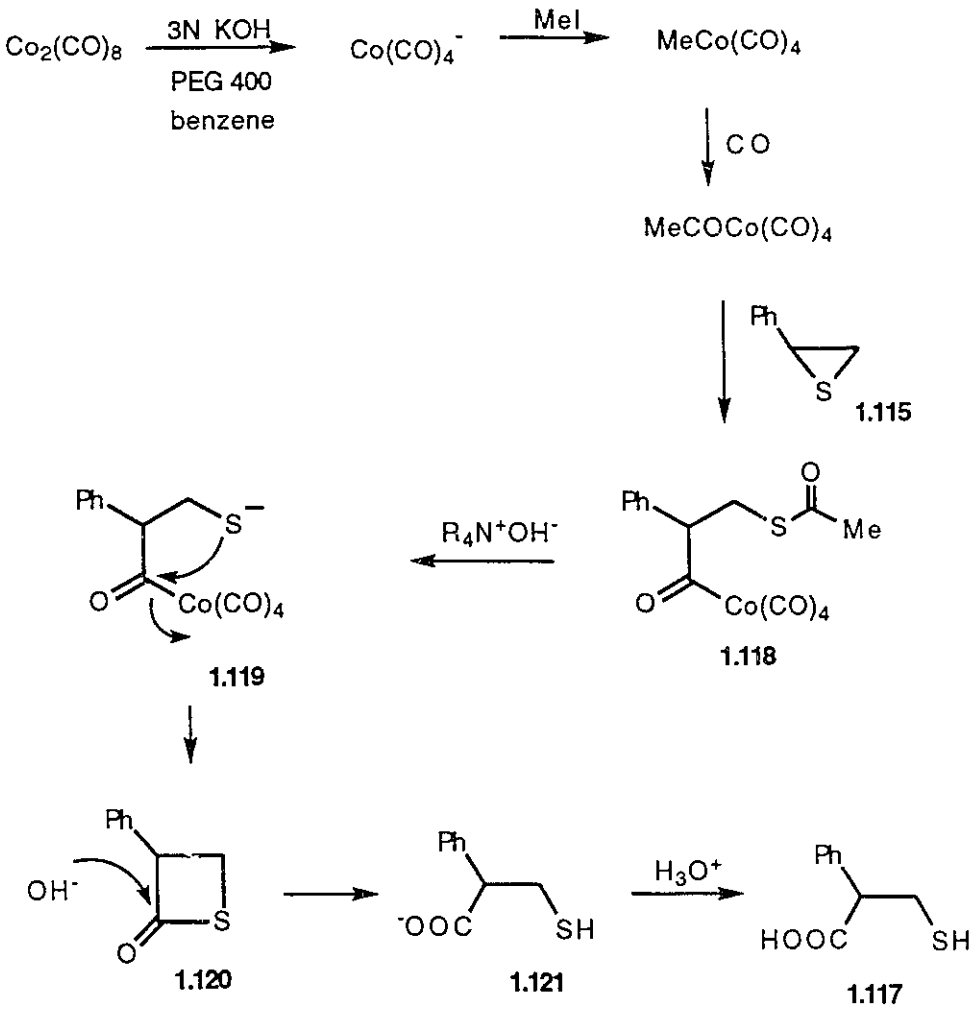
Dicobalt octacarbonyl and phase-transfer-catalyzed carbonylation of 2-arylthiiranes (**1.115**) has also been carried out. The reaction occurs under very mild conditions and affords β-mercaptoacids (**1.117**) in good yield.[82]



1.115

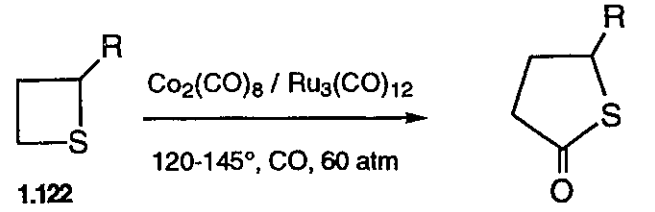
Scheme 1.10 shows the proposed mechanism for this reaction, possibly involving a thiolactone intermediate.

Scheme 1.10



1.4.2. Thietanes

Thietanes **(1.122)** undergo carbonylation with ring expansion to give γ-thiolactones in high yield by using the mixed catalytic system of $Co_2(CO)_8$ / $Ru_3(CO)_{12}$ (1:1).[83]

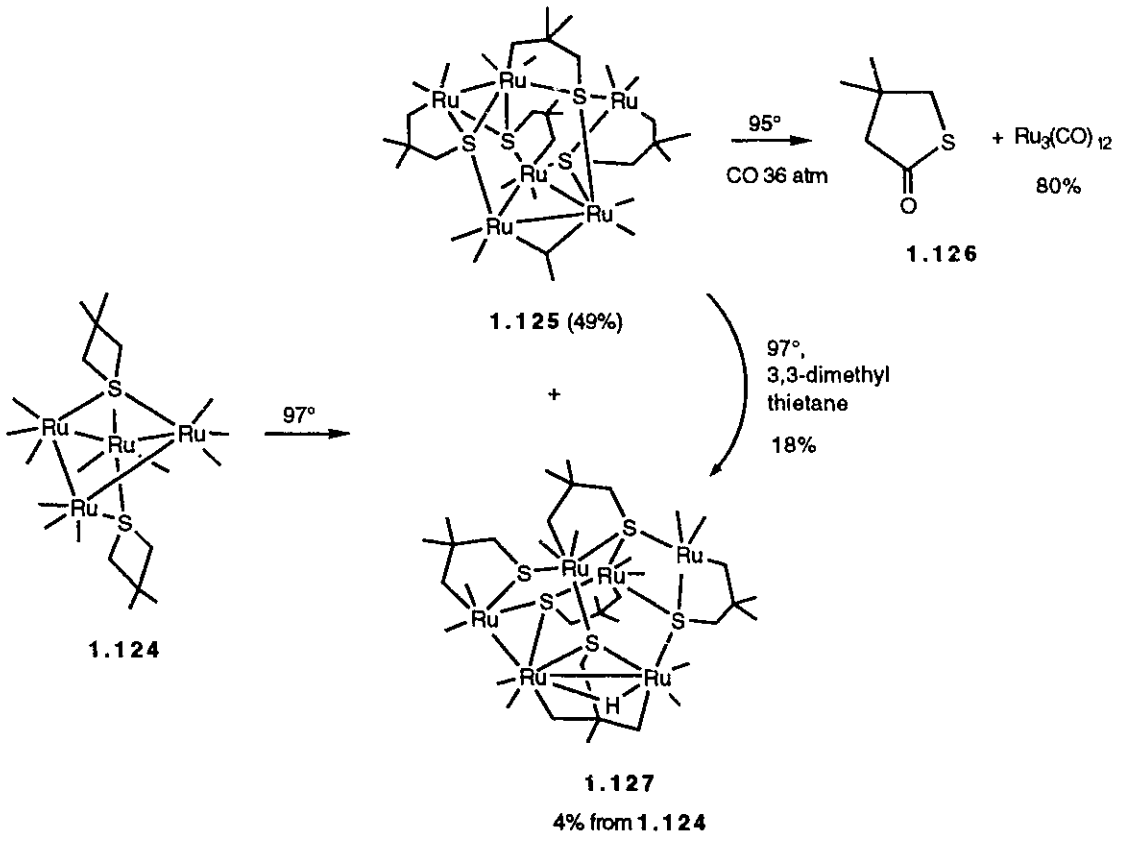


1.122
R =alkyl

1.123 (87-100%)

When the reactions were run using only $Co_2(CO)_8$ or $Ru_3(CO)_{12}$ the yields were much lower (R = H, [Co] / [Ru] = 100% yield, [Co] = 29%, [Ru] = 61%). The roles of the two metals are obscure. Note that a thietane ruthenium cluster complex **(1.124)** was recently shown to give complex **(1.125)** upon heating. The latter affords γ-thiolactone when treated with carbon monoxide. Similar intermediates may be responsible for the carbonylation of thietanes **(1.122)**.[84]

Scheme 1.11



1.5. Conclusion

The analysis of literature data on the carbonylation of acyclic amines and N- and S-containing heterocycles shows that these reactions provide convenient, efficient and one-step methods for the preparation of a variety of carbofunctionalized derivatives. Carbonylation reactions are catalyzed mostly by metal carbonyls ($Co_2(CO)_8$, $Ru_3(CO)_{12}$), Pd(II) as well as Rh(I) complexes. Rhodium complexes usually catalyze carbonylation under milder conditions. There are no data in the literature on the carbonylation of both acyclic and cyclic molecules containing two different heteroatoms, in

particular, nitrogen and sulfur. Their transformations under carbonylation conditions may result in the synthesis of valuable products containing an α–carbonyl group as well as heteroatoms. Such compounds are also of interest as intermediates in the synthesis of biologically active derivatives. That is why we investigated the reactions of a variety of both acyclic and cyclic N,S-containing compounds and some related systems with carbon monoxide. Since rhodium catalysts proved to be more active than others, the carbonylation reactions were principally studied using the commercially available complex, $[Rh(COD)Cl]_2$.

CHAPTER 2

RHODIUM CATALYZED REACTIONS OF THIAZOLIDINES AND RELATED FIVE-MEMBERED RING HETEROCYCLES WITH CARBON MONOXIDE

2.1. Introduction

Transition metal catalyzed reactions of heterocyclic compounds with carbon monoxide provides direct access to a large variety of organic compounds including lactams, lactones and thiolactones.[1-3] While the transition metal catalyzed carbonylation and ring expansion of three and four membered ring heterocycles has been shown to be reasonably facile, there have been only a few reports of the carbonylation of five membered ring heterocyclic compounds (see Chapter 1).

Although the carbonylation of heterocycles containing one heteroatom (N, O, or S) has been investigated in considerable detail, there are no examples of the carbonylation and ring expansion of a heterocycle containing two different heteroatoms. While the first example of metal catalyzed insertion of CO into a pyrrolidine to produce a δ-lactam was reported recently,[80] the question is how the replacement of CH_2-group in the pyrrolidine ring by a second heteroatom affects the reactivity of the heterocycle. Another question which arises is the degree of site selectivity for carbon monoxide insertion into rings containing two heteroatoms. In particular, the regioselectivity of the ring expansion reaction (insertion into carbon-nitrogen vs carbon-sulfur bonds of an N,S-containing heterocycle) is a matter of considerable interest. To this end, we have prepared and examined

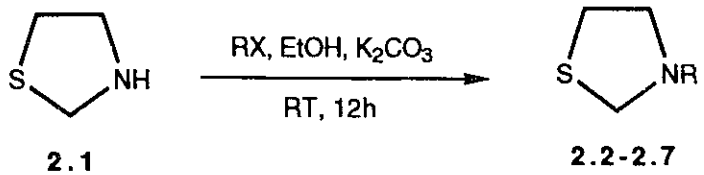
the carbonylation of N-substituted thiazolidines. For comparison purposes, a number of oxazolidines and imidazolidines have been synthesized and subjected to the carbonylation reaction.[85]

2.2. Results and Discussion

2.2.1. Synthesis of Starting Materials

2.2.1.1. Synthesis of N-Substituted Thiazolidines

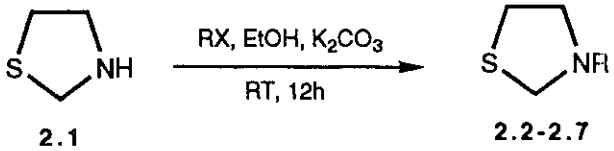
Four groups of thiazolidines have been prepared in this study. The first group consists of six derivatives **(2.2-2.7)**, substituted only at position 3. All N-substituted thiazolidines **(2.2-2.7)** were obtained by reacting commercially available thiazolidine **(2.1)** with different alkylating agents. The halides (ethyl bromoacetate, bromoacetophenone and n-butyl iodide) used were commercially available. 2-Phenoxyethyl bromoacetate and 1-adamantylmethyl bromoacetate were prepared by reaction of $PhOCH_2CH_2ONa$ or $1\text{-}AdCH_2ONa$, respectively, with bromoacetyl bromide in dry benzene. Methyl 2-iodopropanoate was obtained from the corresponding bromide by its reaction with NaI under liquid-liquid PTC conditions. Alkylation reactions of **(2.1)** were carried out using a 10 mol% excess of the halide, ethanol as the solvent and potassium carbonate (1.2 mol. equivalent) as the base at room temperature for 12 h.



2.1 **2.2-2.7**

The results of the synthesis of starting thiazolidines are summarized in **Table 2.1**.

Table 2.1. Alkylation of Thiazolidines



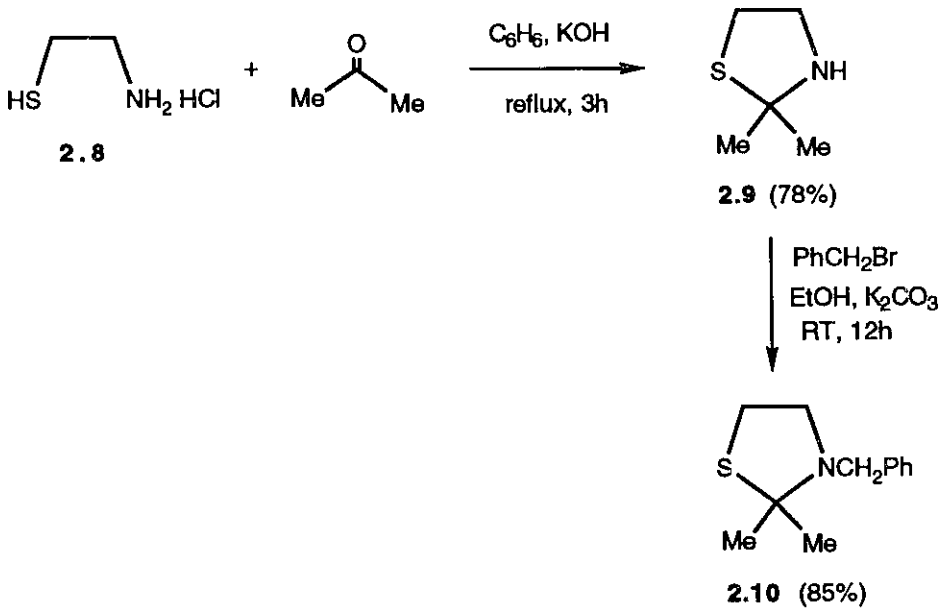
2.1 **2.2-2.7**

Alkylating agent	Product	Isolated yield, %
$BrCH_2CO_2Et$	**2.2**	78
$BrCH_2COPh$	**2.3**	82
$BrCH_2CO_2CH_2CH_2OPh$	**2.4**	64
$BrCH_2CO_2CH_2O$-1-Ad	**2.5**	68
$ICH_2CH_2CO_2Me$	**2.6**	64
$I\text{-}CH_2CH_2CH_2CH_3$	**2.7**	73

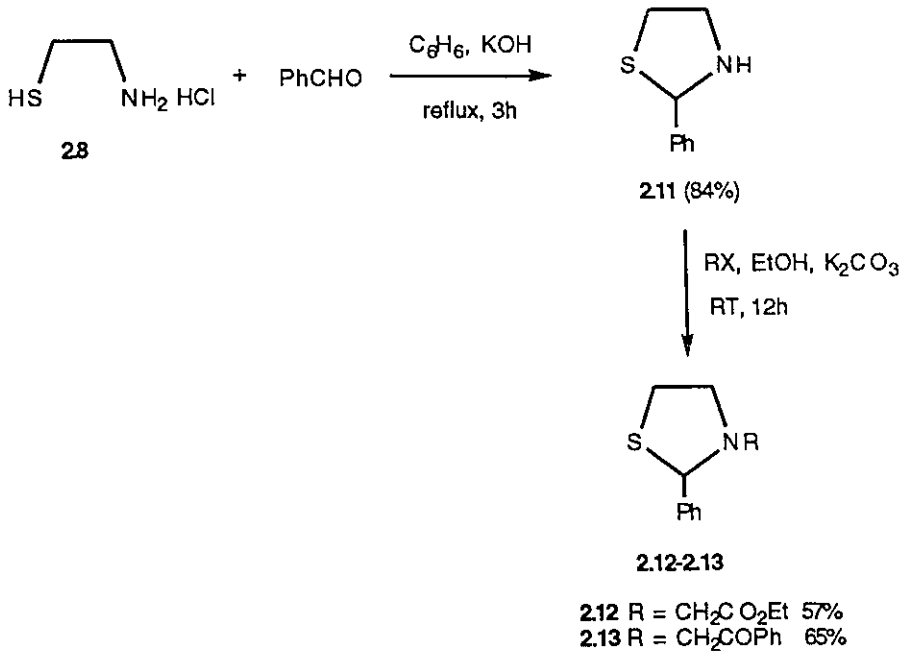
Compounds **(2.2-2.7)** were previously unknown, and were isolated from the reaction mixtures by column chromatography on silica gel using ethyl acetate / hexanes (20 / 80) as the eluant. The products were identified by ^1H and ^{13}C NMR spectra, MS and IR spectra (see Experimental Section 6.6).

Representative ^{1}H and ^{13}C NMR spectra of compound **(2.3)** are shown in **Fig. 2.1**.

The second type of thiazolidine is represented by 1-benzyl-2,2-dimethyl thiazolidine **(2.10)**. It was prepared by reaction of 2-aminoethanethiol hydrochloride **(2.8)** with acetone in the presence of potassium hydroxide followed by alkylation of 2,2-dimethylthiazolidine **(2.9)** with benzyl bromide. Both **(2.9)** and **(2.10)** were isolated by column chromatography in 78 and 85 % yield, respectively Their spectral data are given in the Experimental Section (see Section 6.6.7, 6.6.8).

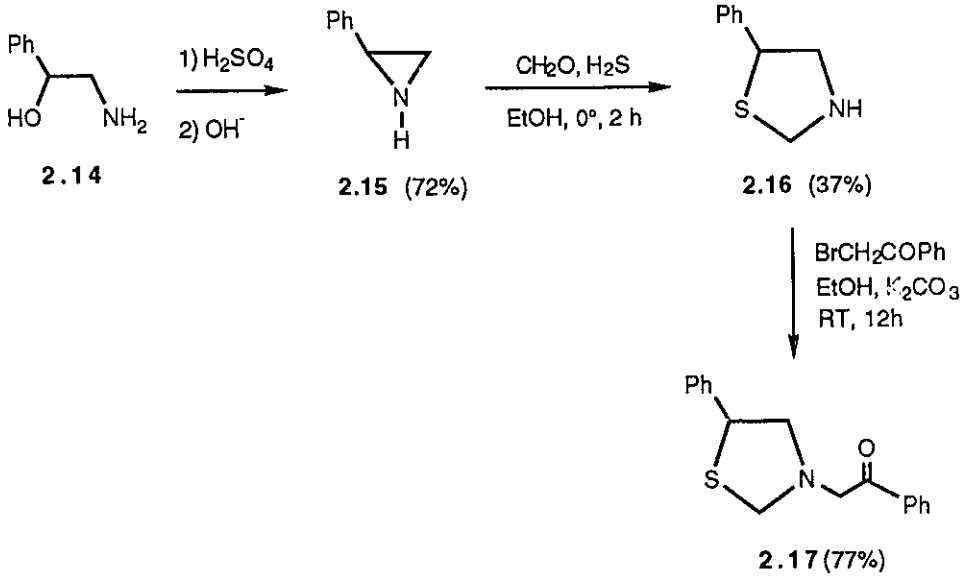


Two representatives of the third group of thiazolidines, viz. 1-ethoxycarbonylmethyl- and 1-(benzoylmethyl)thiazolidine **(2.12** and **2.13)** were prepared by alkylation of 2-phenylthiazolidine **(2.11)**[86] with ethyl bromoacetate and bromoacetophenone, respectively.



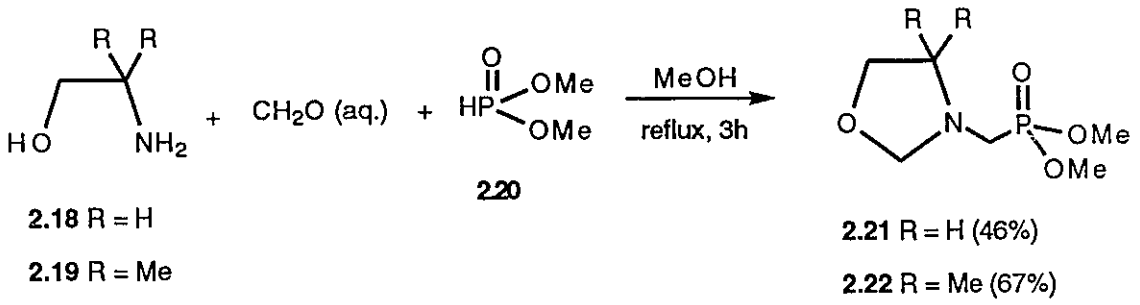
Both **(2.12)** and **(2.13)** are new compounds identified by ^{1}H and ^{13}C NMR, MS and IR spectra (see Experimental Section 6.6.9).

Finally, 1-benzoylmethyl-4-phenyl thiazolidine **(2.17)** was prepared from 4-phenylthiazolidine **(2.16)**[87,88] and bromoacetophenone in 77% yield. See Experimental Section 6.6.10 for the spectral data of **(2.17)**.



2.2.1.2. Synthesis of N-Substituted Oxazolidines

Three different types of N-substituted oxazolidines were prepared using three distinct procedures. First, compounds **2.21** and **2.22** were synthesized in fair yield by condensing aminoalcohol (**2.18**), formaldehyde (40% aqueous solution) and dimethyl phosphite in refluxing methanol as described previously for phenylglycinol.[89] Using aminoalcohol (**2.23**), CH_2O and diphenyl phosphite (**2.24**), the corresponding oxazolidine derivative (**2.25**) was also prepared in 37% yield.



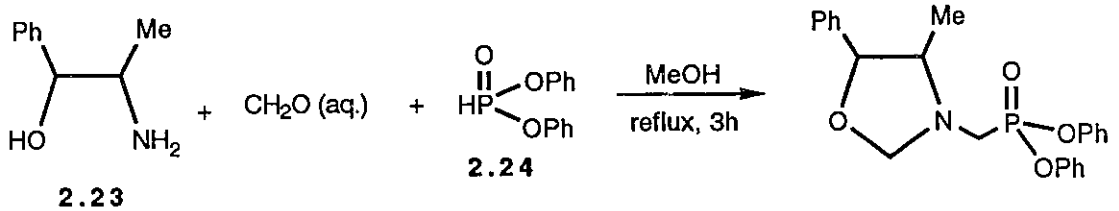
2.18 R = H

2.19 R = Me

2.20

2.21 R = H (46%)

2.22 R = Me (67%)

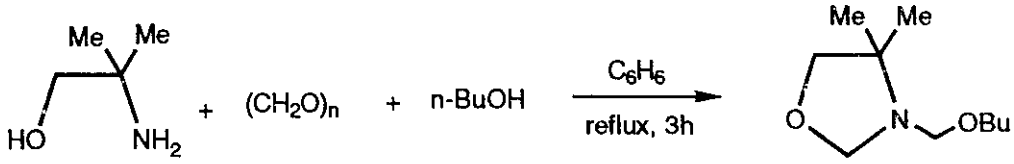


2.23

2.24

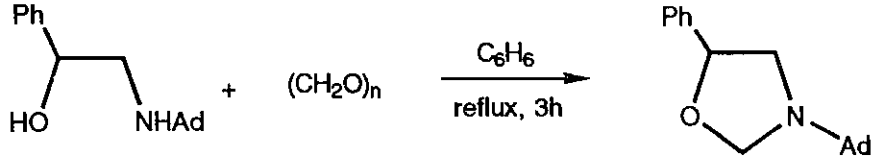
2.25 (37%)

Secondly, N-butoxymethyl-4,4-dimethyloxazolidine (**2.26**) was obtained in high yield by reacting aminoalcohol (**2.19**), paraformaldehyde and n-butanol in refluxing benzene as described previously by Johnson and Kerkman.[90]



2.19 **2.26** (92%)

Finally, N-(1-adamantyl)oxazolidine **(2.28)** was obtained in good yield by the reaction of N-(1-adamantyl) substituted aminoalcohol **(2.27)**[91] with paraformaldehyde.

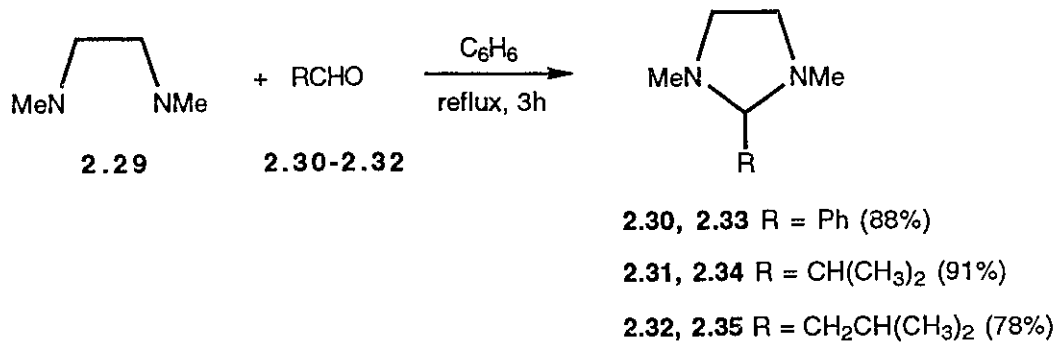


2.27 **2.28** (78%)

Compounds (**2.16-2.18, 2.20**) were purified by column chromatography and characterized by ^{1}H and ^{13}C NMR spectra (see Experimental Section 6.7).

2.2.1.3. Synthesis of 1,3-Dimethyl-2-Substituted Imidazolidines

Three representatives **(2.33-2.35)** of the title compounds were prepared in high yield by the condensation of N,N'-dimethylethylenediamine with benzaldehyde[92], isobutyraldehyde[93] and isovaleraldehyde, respectively.



2.29 **2.30-2.32**

2.30, 2.33 R = Ph (88%)

2.31, 2.34 R = $CH(CH_3)_2$ (91%)

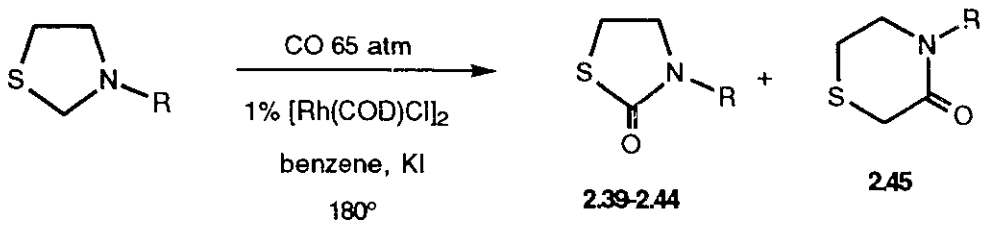
2.32, 2.35 R = $CH_2CH(CH_3)_2$ (78%)

2.2.2. Reaction of N-Substituted Thiazolidines and Related Compounds with Carbon Monoxide Catalyzed by $[Rh(COD)Cl]_2$.

The carbonylation of a series of N-substituted thiazolidine derivatives (**2.2-2.7**) was carried out in dry benzene, at 65 atm of carbon monoxide and 180°C for 48 h (96 h for **2.7**) using $[Rh(COD)Cl]_2$ as the catalyst precursor and potassium iodide as the promotor.[94] Under these conditions, complete conversion of starting materials occured and the corresponding thiazolidinones (**2.39-2.44**) were obtained as the only products in good to excellent yields. The results are presented in **Table 2.2**. Only 1% $[Rh(COD)Cl]_2$ is needed to catalyze the carbonylation, as well as one equivalent of KI per rhodium atom. Lower product yields resulted in the absence of the iodide promoter (as in **2.2** and **2.3**) and in some cases (e.g. **2.4**, **2.5**) the reaction is completely inhibited. More importantly, in the case of (**2.2**), a key intermediate in the thiazolidinone synthesis (**2.45**) can be isolated when KI is not present (*vide infra*).

Some thiazolidinones are of commercial value, e.g. (**2.44**) possesses fungicidal activity.[95] Surprisingly, cobalt carbonyl or a 3:1 mixture of $Co_2(CO)_8$: $Ru_3(CO)_{12}$, a useful catalyst for the ring expansion of pyrrolidines to piperidinones,[80] is almost ineffective in the case of thiazolidines. It is also

interesting, that under conditions where the corresponding pyrrolidines underwent the carbonyl transposition reaction, the starting thiazolidines were recovered unchanged (e.g. **2.2**, **2.3**).



2.2, 2.39, 2.45 R = CH_2CO_2Et

2.3, 2.40 R = CH_2COPh

2.4, 2.41 R = $CH_2CO_2CH_2CH_2OPh$

2.5, 2.42 R = $CH_2CO_2CH_2$-1-Adamantyl

2.6, 2.43 R = $CH_2CH_2CO_2Me$

2.7, 2.44 R = $(CH_2)_3CH_3$

Table 2.2. Rhodium(I) Catalyzed Carbonylation of Thiazolidines[a]

Reactant	Reaction Time h	Product	% yield[b]
2.2	48	**2.39**	80 (58)[c,d]
2.3	48	**2.40**	82 (65)[c]
2.4	48	**2.41**	70
2.5	48	**2.42**	68
2.6	48	**2.43**	(56)[c]
2.7	96	**2.44**	88

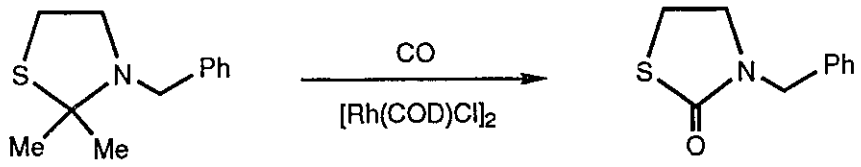
[a] reaction conditions : 5 mmole of **(2.2-2.7)**, 1 mol% $[Rh(COD)Cl]_2$, 10 ml of benzene, 65 atm CO, 180°C

[b] yield of purified product

[c] the yield in parenthesis was obtained by running the reaction in the absence of KI

[d] total yield of 58% without KI : 30% **(2.39)**, 28% **(2.45)**

When 3-benzyl-2,2-dimethylthiazolidine **(2.46)** was carbonylated under the same conditions as **(2.2-2.7)**, again the only product was thiazolidinone **(2.47)**. However, in this case the yield was substantially lower (30-32%).



2.46 **2.47**

All carbonylated derivatives **(2.39-2.45, 2.47)** were isolated by column chromatography on silica gel. The structures of **(2.39-2.45, 2.47)** were assigned on the basis of spectral data (see Experimental Section 6.10.1). The ^1H NMR spectra show that the singlet for the methylene protons inbetween the sulfur and nitrogen atoms disappears, and the two triplets due to CH_2S and CH_2N in the thiazolidine ring are shifted downfield by approximately 1 ppm. The ^{13}C NMR spectra display a signal for the thiazolidinone carbonyl carbon at δ 172.70-173.05 ppm. Representative ^1H and ^{13}C NMR spectra are shown in **Fig 2.1.** Molecular ion peaks consistent with structure **(2.40)** are observed in the mass spectra. The structure of **(2.40)** was also confirmed by X-ray crystallography **(Fig 2.2)**. For Tables of crystal data and a stereoview of the packing diagram, see Appendices.

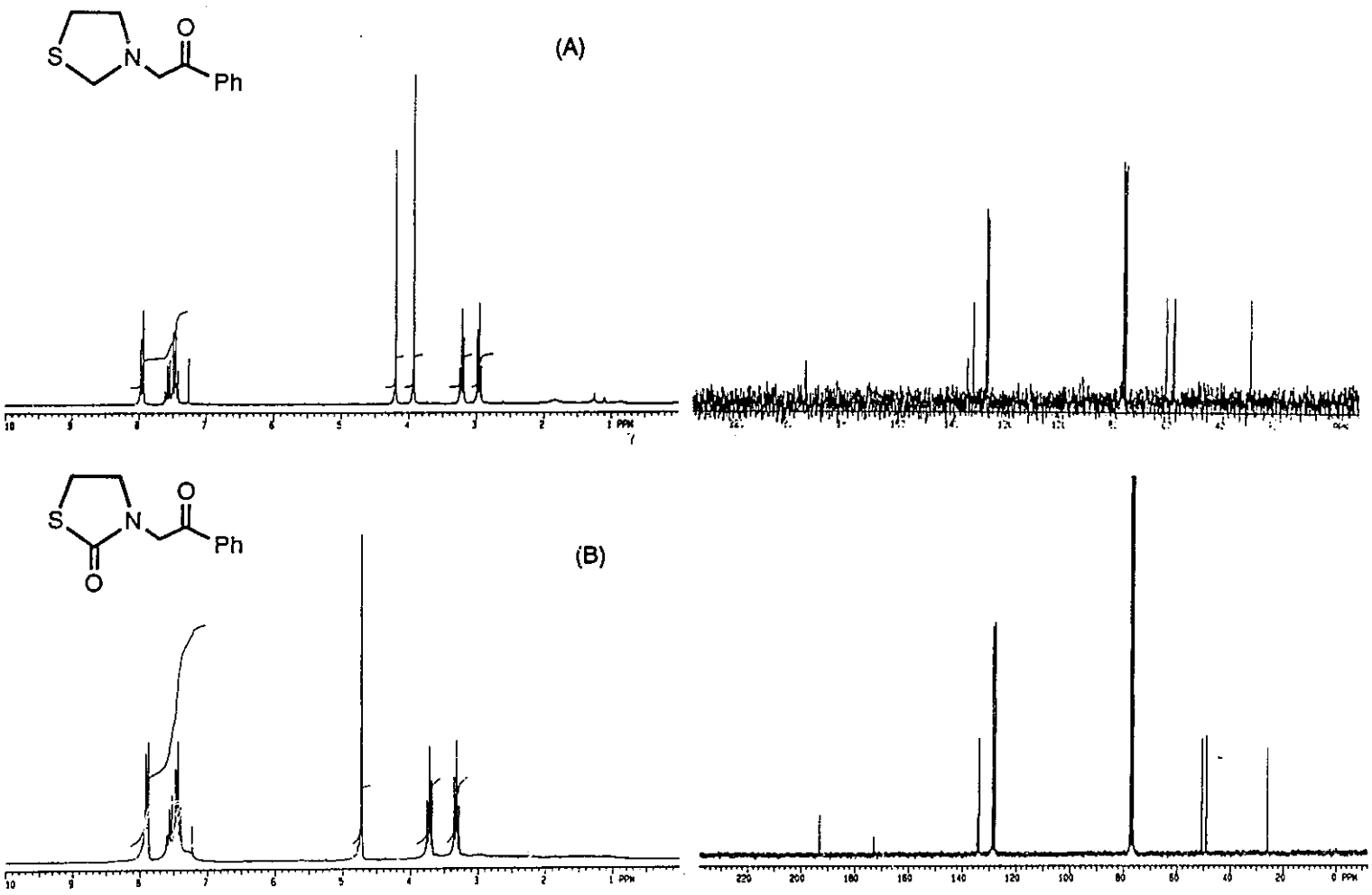


Fig. 2.1. ^{1}H and ^{13}C NMR Spectra of 1-(benzoylmethyl)thiazolidine **(2.3)** (A) and 1-(benzoylmethyl)thiazolidin-2-one **(2.40)** (B)

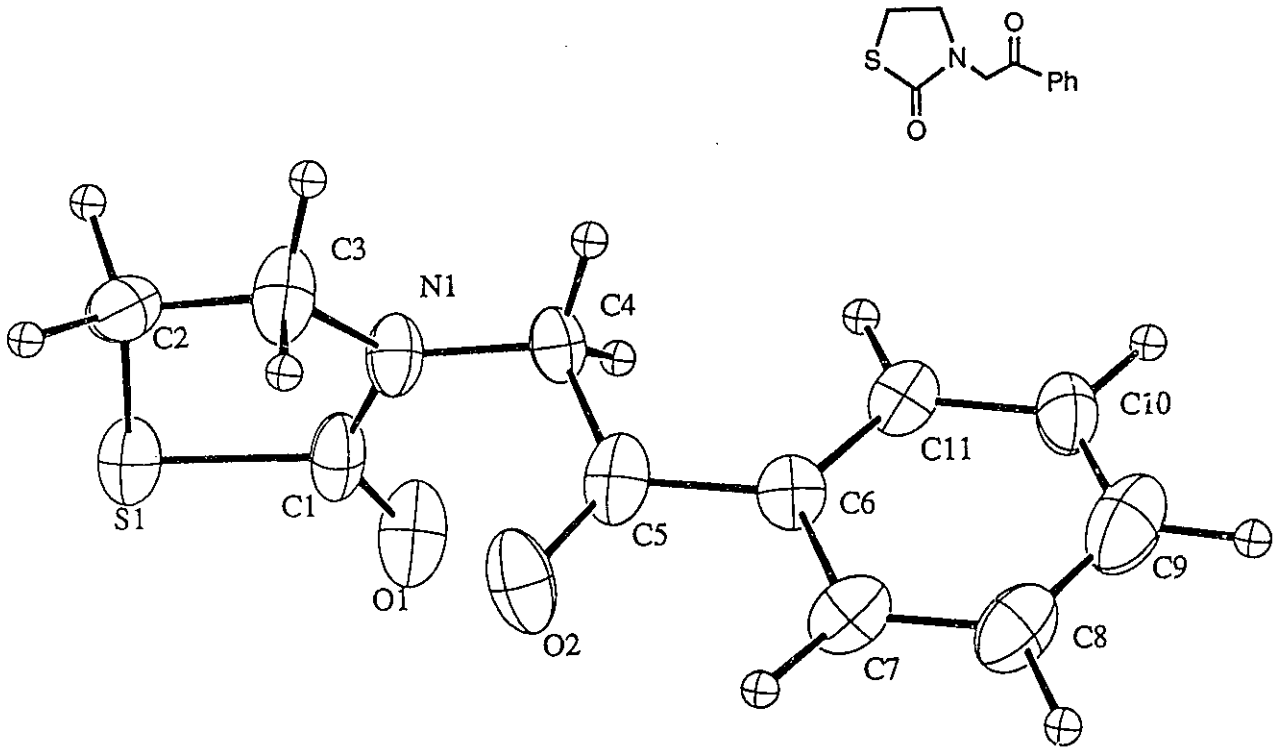


Fig. 2.2. ORTEP Diagram of 1-(benzoylmethyl)thiazolidin-2-one **(2.40)**

The conversion of thiazolidines to thiazolidinones appears, on first consideration, to be an oxidation of a methylene to a carbonyl group. While pursuing information about the mechanism of this formal oxidation we made some intriguing and quite unexpected observations. Most importantly, the anticipated ring expansion of the 1,3-thiazolidine to a thiazinone *does* occur. Specifically, when **(2.2)** was treated with carbon monoxide and $[Rh(COD)Cl]_2$ in the absence of potassium iodide, the 6-membered ring heterocycle **(2.45)** was isolated in 28% yield together with 30% of **(2.39)**. The structure of **(2.45)** was identified by spectral data. The ^1H NMR spectrum **(Fig 2.3)** shows that the triplet signal for the protons of the ring methylene group adjacent to nitrogen is shifted downfield by 0.6 ppm and the singlet for the methylene side chain is also shifted by 0.2 ppm. The ^{13}C NMR spectra displays an amide carbonyl at δ 168.83 ppm. The mass spectrum gave a signal at m/e 203 which is consistent with the mass of the molecular ion. The structure was also confirmed by elemental analysis. The isolation of **(2.45)** from the reaction mixture demonstrates that the ring expansion is regiospecific, with exclusive carbon monoxide insertion into the nitrogen-C2 bond of **(2.2)**, and no insertion into the other ring carbon-nitrogen bond or into either carbon-sulfur bond. After isolating **(2.39)** and **(2.45)** in the absence of KI, the question arose as to whether **(2.45)** was involved in the conversion of **(2.2)** to **(2.39)**. When **(2.45)** was subjected to the standard reaction conditions ($[Rh(COD)Cl]_2$, KI, CO, C_6H_6, 65 atm) **(2.39)** was obtained in quantitative yield **(Fig 2.3)**. Note that repetition of the experiment in the absence of KI afforded **(2.39)** in only 19% yield.

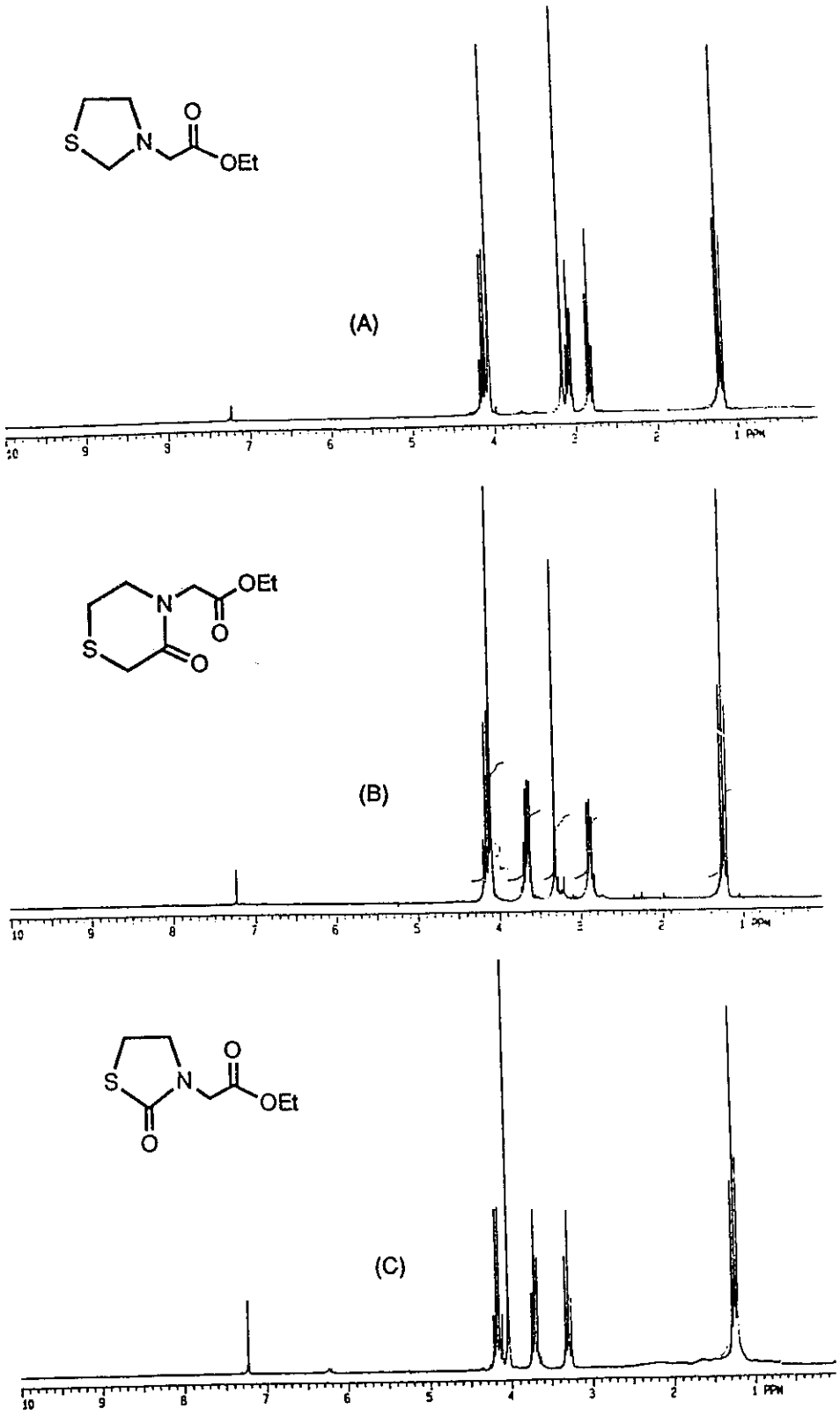
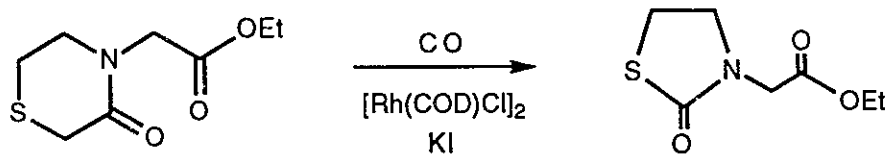


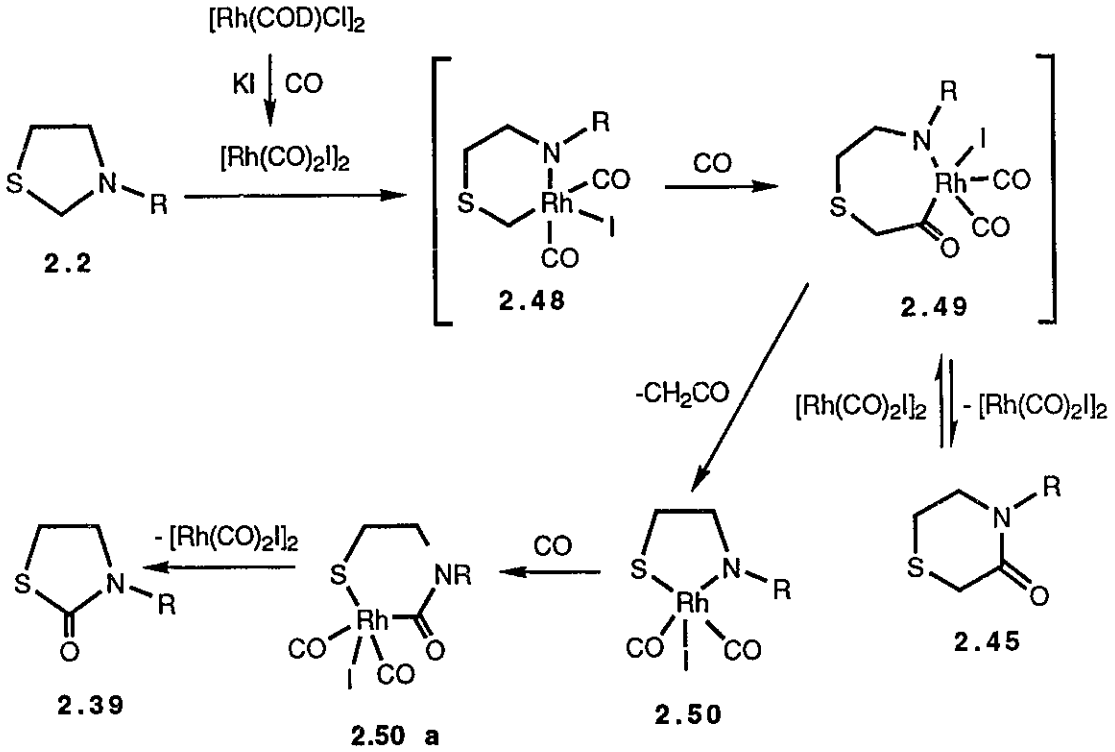
Fig. 2.3. ^{1}H NMR Spectra of 3-(ethoxycarbonylmethyl)thiazolidine **(2.2)** (A), 3-(ethoxycarbonylmethyl)thiazin-3-one **(2.45)** (B), 3-(ethoxycarbonylmethyl)thiazolidin-2-one **(2.39)** (C)



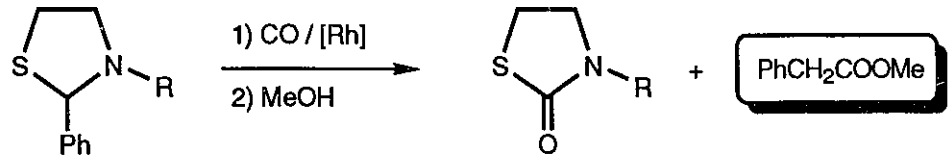
2.45 **2.39** (100%)

In addition, simply heating **(2.45)** in the absence of the rhodium catalyst gave only starting material and some decomposition. Given these results, it is clear that rhodium(I) not only catalyzes the ring *expansion*, but also the subsequent ring *contraction*. This sequence of events **(Scheme 2.1)** requires an unusual ketene elimination to give **(2.50)** and *in situ* carbonylation of **(2.50)** to **(2.39)**.

Scheme 2.1



In order to determine whether or not ketene was produced, the rhodium (I) catalyzed reaction of 2-phenyl substituted thiazolidine **(2.52)** was carried out and the reaction mixture was worked up with methanol. As in the case of unsubstituted thiazolidines this reaction afforded not only thiazolidinone **(2.40)** in 83% yield but also methyl phenylacetate. The latter is derived from the addition of methanol to phenyl ketene. Methyl phenylacetate is also produced in the reaction of substrate **(2.51)** along with thiazolidinone **(2.39)** (72% yield).



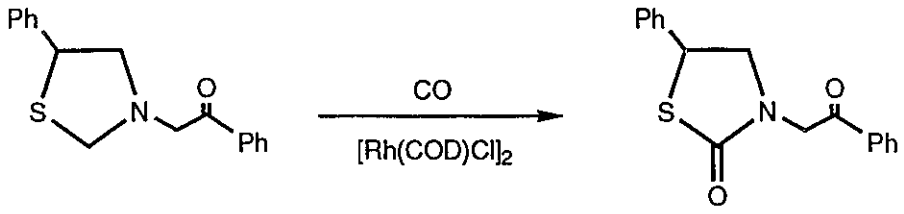
2.51, R = CH_2CO_2Et
2.52, R = CH_2COPh

2.39 (72%)
2.40 (83%)

The lower yield of methyl phenylacetate is likely due to the instability of the ketene under the reaction conditions. Note that an infrared spectrum of the reaction mixture prior to workup with methanol showed an absorption band due to ketene stretching at 2163 cm^{-1}.[96]

These results, especially the isolation of **(2.45)** from the reaction mixture, demonstrate the regiospecificity of carbonyl insertion into the nitrogen-C2 bond. In an attempt to direct CO insertion into the C-S bond, in accord with previous results,[97] the 5-phenyl substituted thiazolidine **(2.53)** containing a benzylic C-S bond was prepared and subjected to the standard carbonylation reaction conditions. Note that in acyclic systems containing an aliphatic or benzylic amine and a benzylic sulfide, carbonylation occurs exclusively at the C-S bond (see Chapter 3, Section 3.2.2). However, substrate **(2.53)** surprisingly behaves similar to other N-substituted thiazolidines

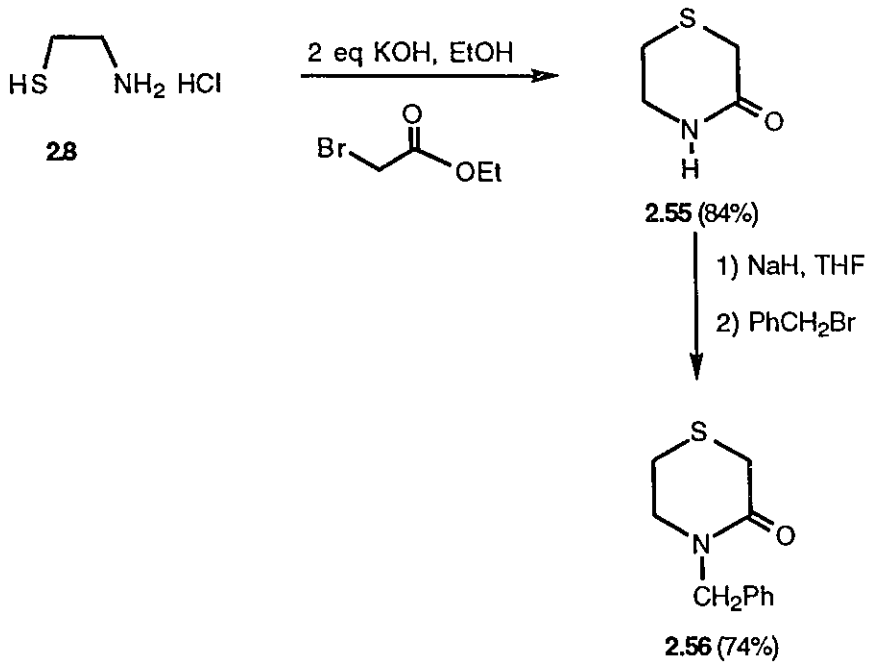
affording 5-phenyl-3-benzoylmethylthiazolidinone (**2.54**) in 72% yield. The regiochemistry of the carbon monoxide insertion is therefore completely opposite in cyclic and acyclic systems, with the presence of a phenyl group at the 5-position of a thiazolidine ring having no influence on the course of the reaction.



2.53 **2.54** (72%)

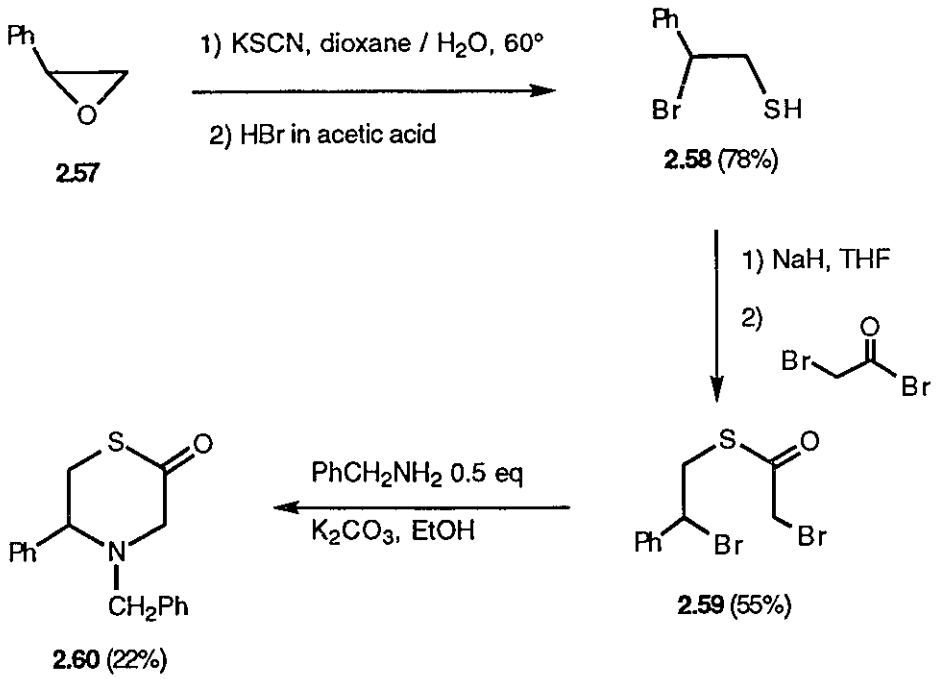
In order to prove that the carbonylation reaction proceeded by CO insertion into the C-N, not the C-S bond, both 1,4-thiazin-3-one (**2.56**) and 1,4-thiazin-2-one (**2.60**) were synthesized by alternative methods (**Scheme 2.2** and **2.3**). Compound (**2.56**) was prepared in 55% overall yield by reacting 2-aminoethanethiol hydrochloride with ethyl bromoacetate in the presence of ethanolic KOH followed by alkylation of 1,4-thiazin-3-one (**2.55**) with benzyl bromide.

Scheme 2.2

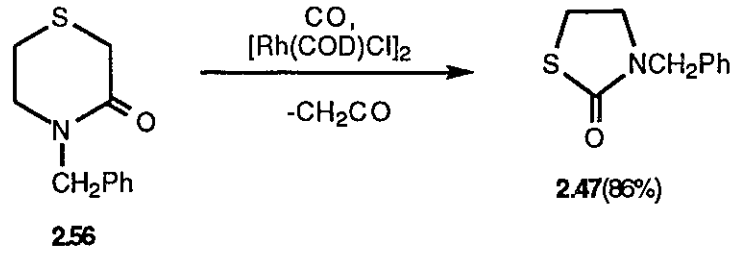


Compound **(2.60)** was prepared as follows. Reaction of 2-phenyloxirane **(2.57)** with potassium thiocyanate in aqueous dioxane gave the corresponding thiirane.[98] The latter, without isolation, was ring opened with hydrobromic acid in acetic acid to give 2-bromo-2-phenylethanethiol **(2.58)**. The acylation of **(2.58)** with bromoacetylbromide afforded the dibromide **(2.59)**. Finally, the reaction of **(2.59)** with benzylamine gave the desired heterocycle **(2.60)**.

Scheme 2.3



Under the standard carbonylation conditions (Rh(I) catalyst, KI, CO (65 atm), C_6H_6), compound **(2.56)** was converted cleanly to **(2.47)** in 86% yield. Compound **(2.60)** did not react with CO under identical conditions and the starting material was recovered unchanged. The formation of **(2.47)** from **(2.56)** is in accord with the conversion of **(2.45)** to **(2.39)**.

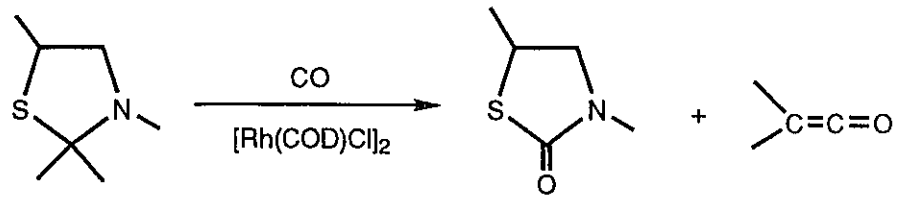


The results obtained in the rhodium-catalyzed carbonylation of thiazolidines prompted us to study similar reactions involving other five-

membered ring heterocycles with two heteroatoms (for their synthesis, see Section **2.2.1.1-2.2.1.4**). Unfortunately, oxazolidines (**2.21, 2.22, 2.25, 2.26**) and imidazolidines (**2.33-2.35**) unlike their N,S-containing counterparts, do not undergo any carbonylation under the same conditions (both using Rh(I) and Co / Ru carbonyls).

2.3. Conclusion

Various thiazolidines have been prepared and converted to thiazolidinones in good to excellent yields by rhodium(I) catalyzed carbonylation, with ketenes as the accompanying products.



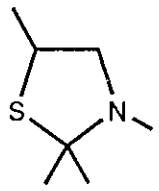
The overall process is indeed novel, and involves the insertion of two molecules of carbon monoxide, two ring expansion steps as well as a ring contraction, and a regiospecific carbonyl insertion into one of the two ring carbon-nitrogen bonds. This new catalytic reaction appears to be characteristic of various 1,3-N,S-containing five-membered ring heterocycles.

CHAPTER 3

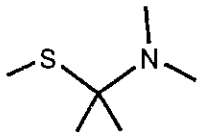
RHODIUM CATALYZED CARBONYLATION OF N,S-ACETALS*

3.1. Introduction

The study of reactions of thiazolidines (**3.1**) with carbon monoxide in the presence of $[Rh(COD)Cl]_2$ revealed novel and unusual transformations of these heterocycles containing sulfur and nitrogen atoms in the 1,3-positions (Chapter 2). It is clearly very interesting to examine similar reactions involving N,S-acetals (**3.2**), acyclic analogs of thiazolidines, and to compare their behaviour under the catalytic carbonylation conditions.



3.1



3.2

The achievement of the carbonylation of acyclic, unstrained compounds itself is a challenging problem in organic chemistry. This rare process has been reported by Murahashi and co-workers[67] for the palladium(0) catalyzed carbonylation of allylamines to the corresponding amides. (see Section 1.2 - conversion of **1.61** → **1.62**)

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* The systematic name of this class of compounds is 1-alkylthioamines;[99] the IUPAC name is N,N-alkyl / aryl -N-(alkyl / arylthiomethyl)amine[100]

We were intrigued by the possibility of realizing carbonyl insertion in an acyclic system for which there is no stabilization by a π-allyl metal complex, although π-benzyl complex formation is conceivable. N,S-Acetals[99] appear to be excellent candidates for such an investigation as insertion could, in principle, occur into any of the carbon-sulfur or carbon-nitrogen bonds.

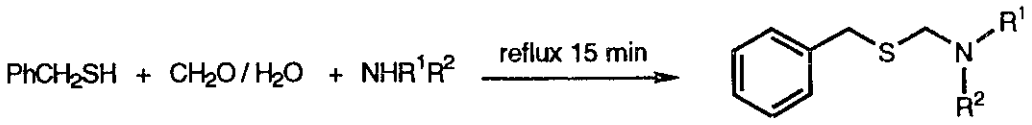
In this chapter we describe the results of this investigation. In addition, the carbonylation of O,N-aminals, S,O-thioacetals and N,N-aminals structurally related to N,S-acetals (**3.2**), have also been studied.

3.2. Results and Discussion

3.2.1. Synthesis of Starting Materials

3.2.1.1. Synthesis of N,S-Acetals

Seven representative N,S-acetals (**3.3-3.9**) were prepared using Grillot's method.[100] According to this procedure, a stoichiometric mixture of benzylmercaptan and secondary amine in an excess amount of 40% aqueous formaldehyde was heated at reflux for 15 min.



3.3-3.9

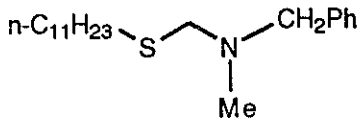
Products (**3.3-3.9**) were obtained in good yield and were isolated from reaction mixtures by vacuum distillation. The results of the synthesis of N,S-acetals are summarized in **Table 3.1**.

Table 3.1. Synthesis of N,S-Acetals (**3.3-3.9**)

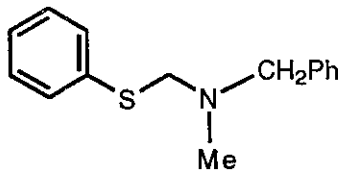
R^1	R^2	Product	% yield
Ethyl	Ethyl	**3.3**	92
i-Butyl	i-Butyl	**3.4**	98
Cyclohexyl	Cyclohexyl	**3.5**	73
Methyl	Cyclohexyl	**3.6**	80
Allyl	Cyclohexyl	**3.7**	80
Methyl	Benzyl	**3.8**	84
Allyl	Allyl	**3.9**	70

Compounds (**3.3-3.9**) were identified by ^1H and ^{13}C NMR and mass spectroscopy (see Experimental Section 6.14). Representative ^1H and ^{13}C NMR spectra of the previously unknown N,S-acetal (**3.4**) are shown in **Fig 3.1**.

In order to clarify the role of the substituents at the heteroatoms, alkylthio- and (phenylthio)methyl amines (**3.10** and **3.11**) were obtained by the same method using n-undecylmercaptan and thiophenol, respectively.

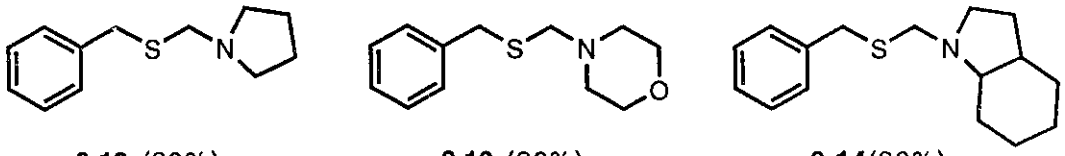


3.10 (74%)



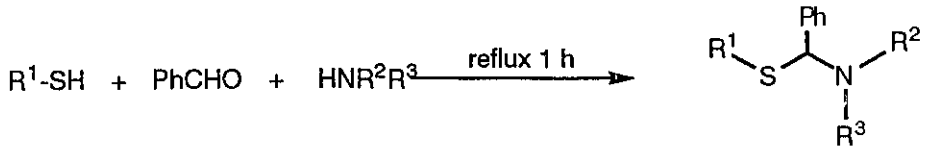
3.11 (68%)

Also, N,S-acetals **(3.12-3.14)** were synthesized in fair yield using the cyclic secondary amines, pyrrolidine, morpholine and perhydroindoline, respectively.



3.12 (80%) **3.13** (82%) **3.14**(80%)

Finally, N,S-acetals **(3.15-3.18)** containing a benzylidene group between sulfur and nitrogen were prepared from the thiol, benzaldehyde and a secondary amine **(Table 3.2)**.



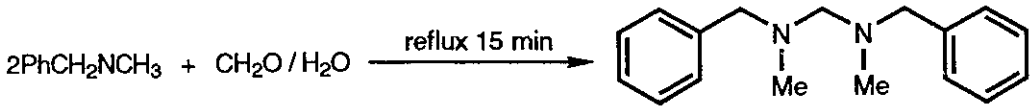
3.15-3.18

Table 3.2. Synthesis of N,S-Acetals **(3.15-3.18)**

R^1	R^2	R^3	Product	% yield
Benzyl	Ethyl	Ethyl	**3.15**	89
Benzyl	Methyl	Benzyl	**3.16**	68
Benzyl	$-CH_2CH_2OCH_2CH_2-$		**3.17**	78
n-Undecyl	Methyl	Benzyl	**3.18**	82

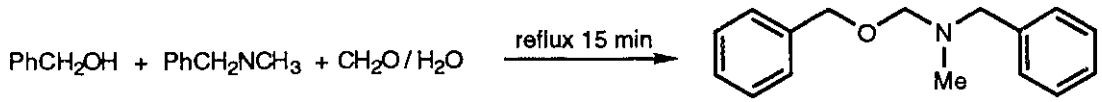
3.2.1.2. Synthesis of Structurally Related Acyclic 1,3- and 1,4-Heteroatom-Containing Molecules

Three acyclic compounds containing various heteroatoms in the 1,3-position of the chain were synthesized in order to study their reactivity in the carbonylation reaction and to compare them with N,S-acetals. Bis(N-benzyl-N-methyl)methylenediamine **(3.19)** was prepared in high yield by reacting N-benzyl-N-methylamine with formaldehyde at reflux for 15 min.



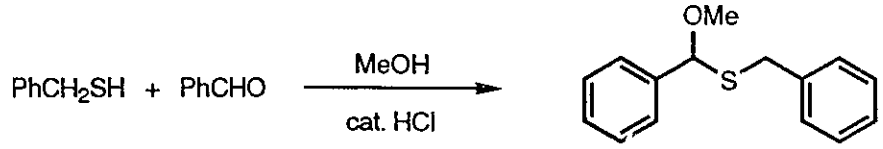
3.19 (84%)

Similarly, using benzyl alcohol, formaldehyde and N-benzyloxy-methylamine, N-benzyl-N-benzyloxymethyl-N-methylamine **(3.20)** was obtained in good yield.



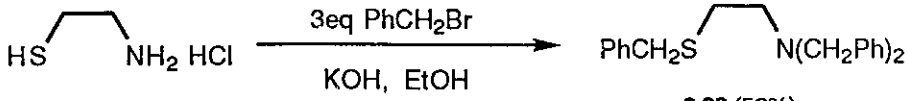
3.20 (72%)

Monothioacetal **(3.21)** was prepared in fair yield by reaction of benzylmercaptan with benzaldehyde in methanol in the presence of catalytic amounts of HCl.[101]



3.21 (67%)

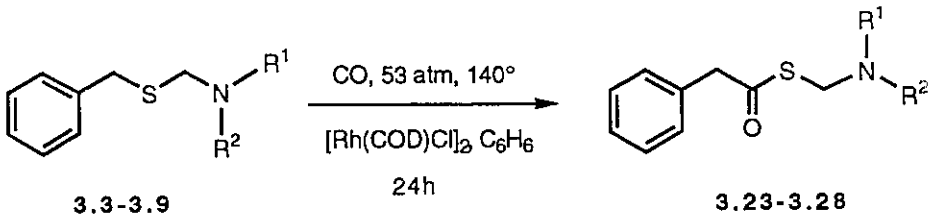
N,N-Dibenzyl-N-(benzylthio)ethylamine (**3.22**), in which sulfur and nitrogen bear a 1,4-relationship, was synthesized by alkylating 2-aminoethanethiol hydrochloride with benzyl bromide using ethanolic KOH as a base.



3.22 (56%)

3.2.2. Carbonylation of Acyclic N,S-Acetals and Their Analogues Catalyzed by $[Rh(COD)Cl]_2$

The carbonylation of N,S-acetals (**3.3-3.9**) was carried out in dry benzene at 53 atm of carbon monoxide and 140° for 24 h in the presence of 1 mol% $[Rh(COD)Cl]_2$. In all cases, except a diallyl-containing N,S-acetal, aminomethylthiol esters (**3.23-3.28**) were obtained as the only products in 68-92% isolated yields (**Table 3.3**).



3.3-3.9 3.23-3.28

3.3, 3.23 $R^1 = R^2 = Et$

3.4, 3.24 $R^1 = R^2 = i\text{-}Bu$

3.5, 3.25 $R^1 = R^2 =$ cyclohexyl

3.6, 3.26 $R^1 =$ Me, $R^2 =$ cyclohexyl

3.7, 3.27 $R^1 =$ allyl, $R^2 =$ cyclohexyl

3.8, 3.28 $R^1 =$ Me, $R^2 =$ Bn

3.9 $R^1 = R^2 =$ allyl

Table 3.3. Rhodium Catalyzed Carbonylation of N,S-Acetals **(3.3-3.9)**[a]

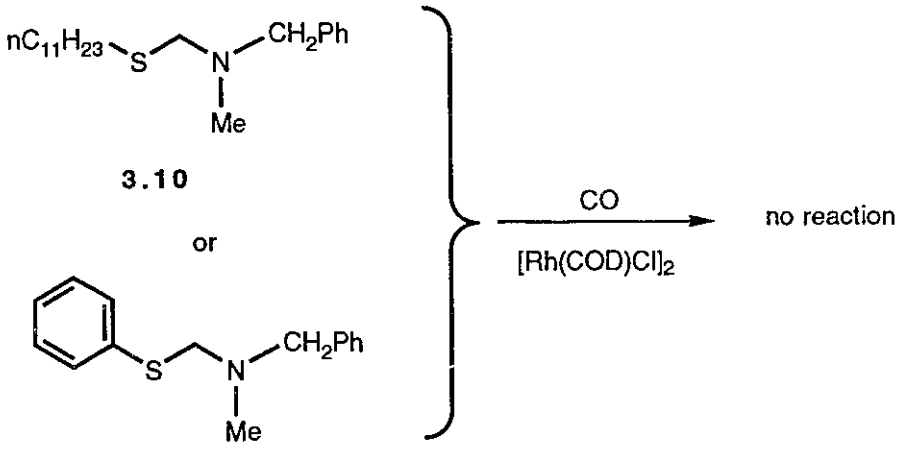
Reactant	R^1	R^2	Product	% Isolated yield
3.3	Et	Et	**3.23**	74
3.4	i-Bu	i-Bu	**3.24**	82
3.5	Cy	Cy	**3.25**	92
3.6	Me	Cy	**3.26**	81
3.7	Allyl	Cy	**3.27**	68
3.8	Me	Bn	**3.28**	81
3.9	Allyl	Allyl	b	–

[a]reaction conditions : 5 mmol of **(3.3-3.9)**, 1% mole $[Rh(COD)Cl]_2$, 10 ml of benzene, 53 atm CO, 140°, 24 h

[b]a complex mixture of unidentified products was formed

The structure of the products **(3.23-3.28)** was assigned on the basis of spectral data (see Experimental Section 6.19). The ^{1}H NMR spectra show that after the reaction, the protons at the benzylic position next to sulfur resonated upfield by approximately 0.5 ppm compared to the starting materials **(3.3-3.8)**. The ^{13}C NMR spectra show a carbonyl carbon at 200.91-207.22 ppm due to C(O)S. Molecular ion peaks consistent with structure **(3.23-3.28)** were observed in the mass spectra. Representative ^{1}H and ^{13}C NMR spectra of thiol ester **(3.4)** are shown in **Fig 3.1**.

Under identical conditions, (alkylthiomethyl)amine **(3.10)** and (phenylthiomethyl)amine **(3.11)** do not undergo carbonylation, with only starting materials and decomposition products observed in these cases. Therefore, a benzyl group attached to sulfur is required in order to effect the carbon monoxide insertion. No carbon monoxide insertion into the C-N bond was found, even when the amine is benzylated as in $PhCH_2SCH_2N(Me)CH_2Ph$ **(3.8)**.



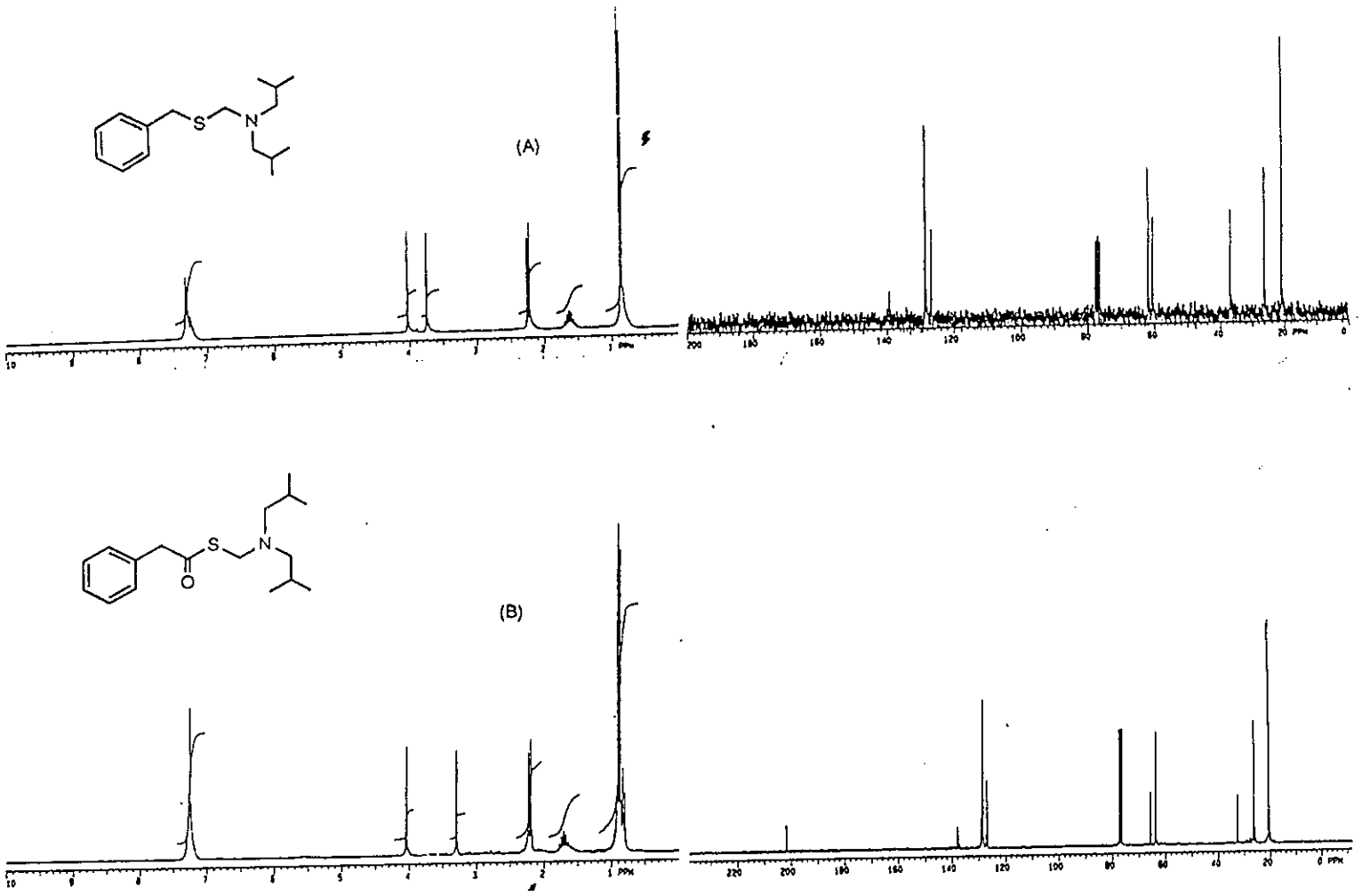
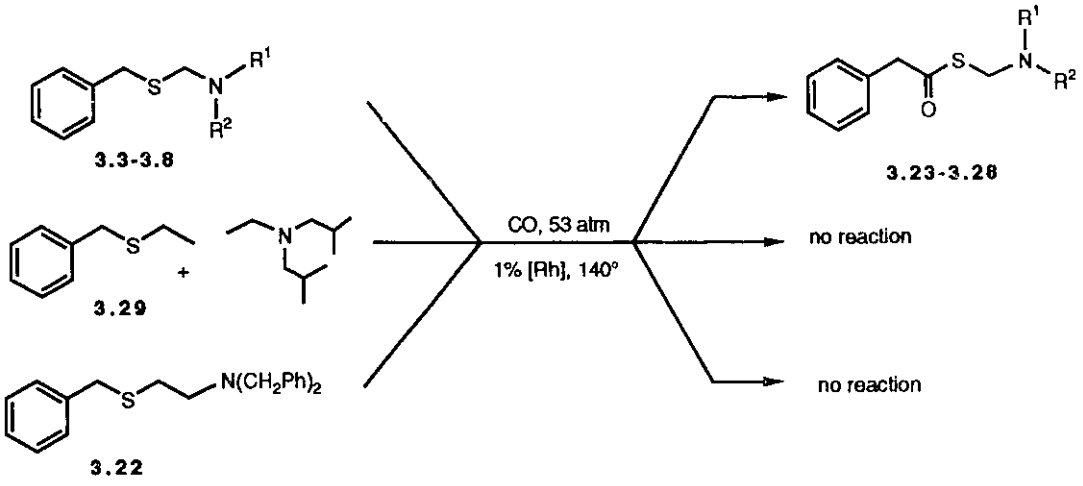


Fig 3.1. ^{1}H and ^{13}C NMR of N-(Benzylthio)methyl-N,N-diisobutylamine **(3.4)** (A) and (Diisobutylamino)methyl 2-phenylethanethiolate **(3.24)** (B)

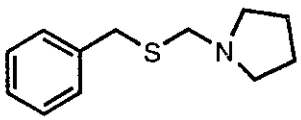
The regiospecific carbon monoxide insertion into the C-S bond in this series is quite unusual. To our knowledge, in cyclic systems the ease of carbonylation is of the order of C-N > C-S > C-O.[79,83] In addition, carbon monoxide inserts exclusively into the C-N bond rather than the C-S bond of a thiazolidine (see Chapter 2, Section 2.2.2).

Although no carbonylation of the C-N bond is observed, the presence of this functionality is crucial to the success of insertion of CO into the C-S bond. For instance, benzyl ethyl sulfide, $PhCH_2SCH_2CH_3$ **(3.29)** is recovered unchanged under the conditions described for the N,S-acetal carbonylation, even with added diisopropylethylamine. Furthermore, not only is it necessary to have nitrogen in the molecule, it must be in a 1,3 relationship with respect to sulfur. Benzylthioamine **(3.22)** having two methylene groups between nitrogen and sulfur, is completely inert under the described conditions.

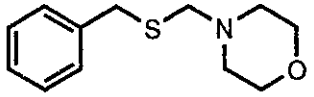


Since the 1,3-N,S functionality is necessary for catalysis, it is likely that the substrate is binding to rhodium in a bidentate manner. Surprisingly, when the nitrogen atom is part of a heterocyclic ring **(3.12-3.14)**, there was no

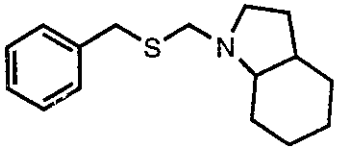
reaction under the standard conditions, with decomposition at higher temperature (e.g. 170°). The reason for this reactivity difference is unclear.



3.12

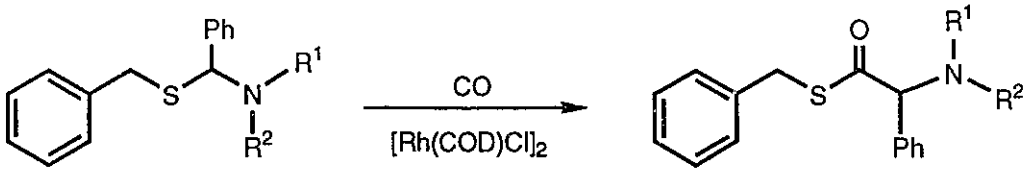


3.13



3.14

In order to investigate the regiospecificity of the carbonylation reaction we studied the carbonylation of compounds **(3.15-3.17)** where both carbons which are bound to sulfur are benzylic in nature. Treatment of these substrates, with carbon monoxide and the rhodium(I) catalyst, under standard conditions, led to the exclusive insertion of carbon monoxide into the C-S bond adjacent to nitrogen (46-83% yield) **(Table 3.4)**. Contrary to the results described above, carbonylation also proceeded in good yield when the nitrogen atom was part of a heterocyclic ring (i.e. **3.17** → **3.32**). Representative NMR spectra of the N,S-acetal **(3.15)** and the product from the reaction **(3.30)** are shown in **Fig 3.2**.

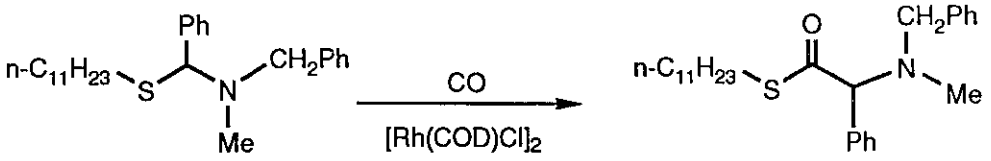


3.15-3.17 3.30-3.32

Table 3.4. Rhodium Catalyzed Carbonylation of N,S-Acetals (**3.15-3.17**)

Reactant	R^1	R^2	Product	% Isolated yield
3.15	Et	Et	**3.30**	83
3.16	Me	Bn	**3.31**	46
3.17	$-CH_2CH_2OCH_2CH_2-$		**3.32**	80

A rational for this striking difference is presented below (**Scheme 3.1**). It is conceivable that the other benzylic unit, furthest from nitrogen, may not be required for reaction to occur. Indeed, compound (**3.18**), in which an n-undecyl group is substituted for a benzyl substituent, experienced carbonyl insertion to form the expected product (**3.33**) in 55% isolated yield.



3.18 **3.33** (55%)

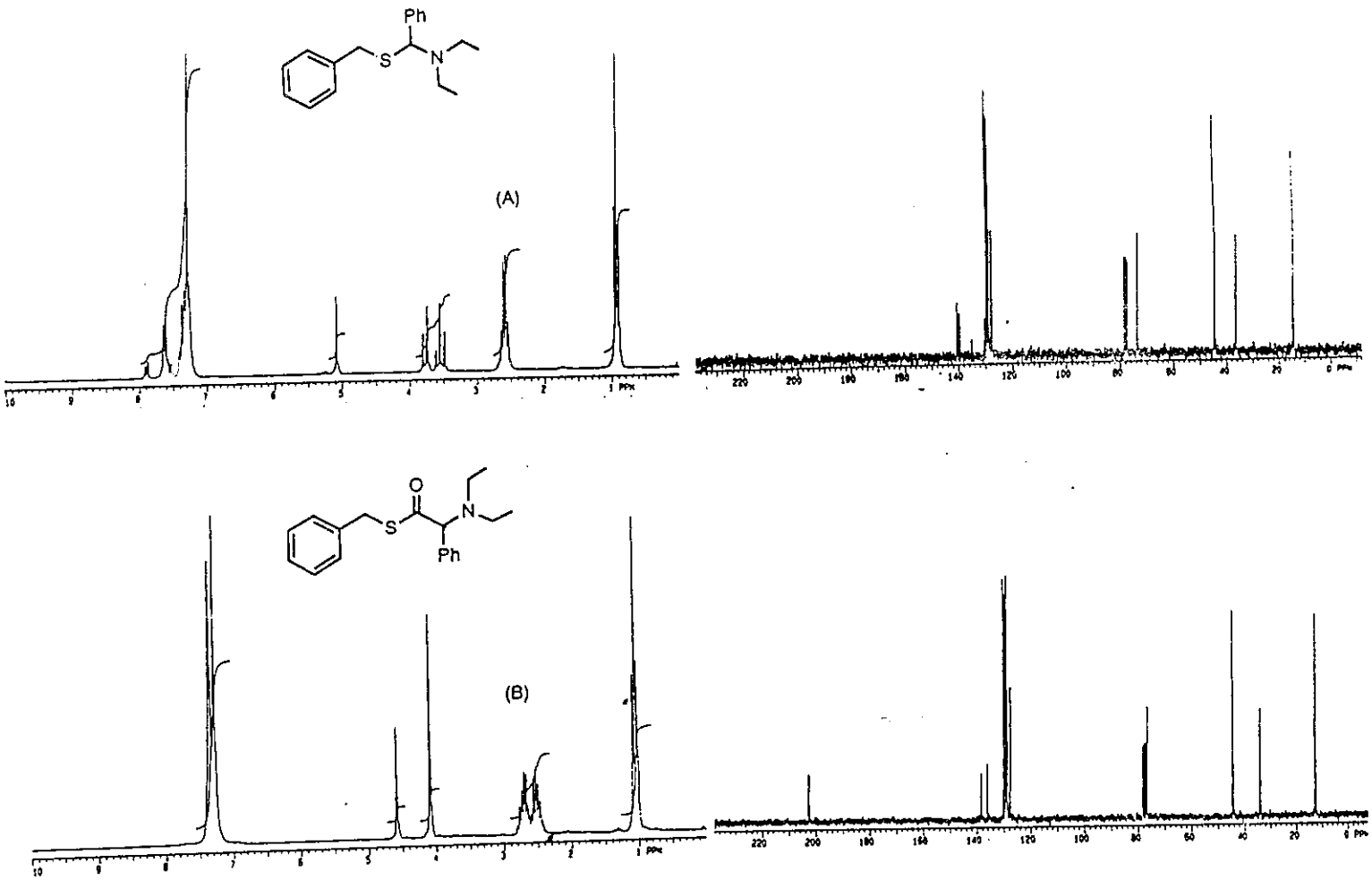
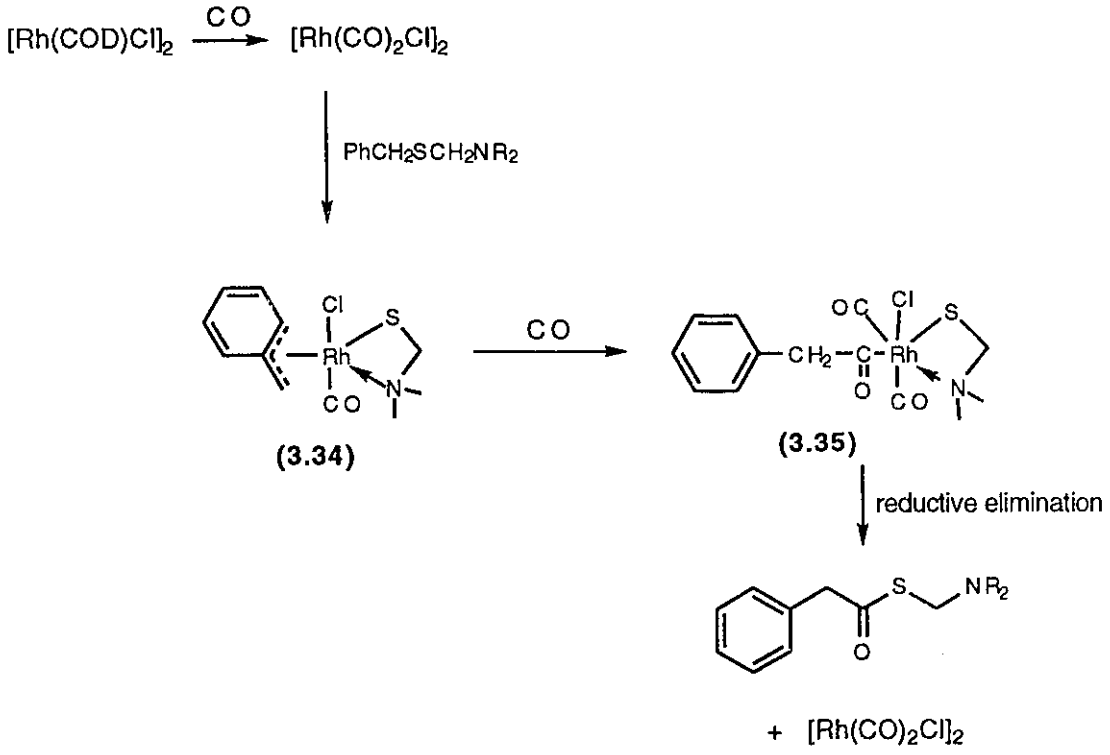


Fig 3.2. ^{1}H and ^{13}C NMR of N-(Benzylthio)(phenyl)methyl-N,N-diethylamine **(3.15)** (A) and Benzyl 2-(N,N-diethylamino)-2-phenylethanethiolate **(3.30)** (B)

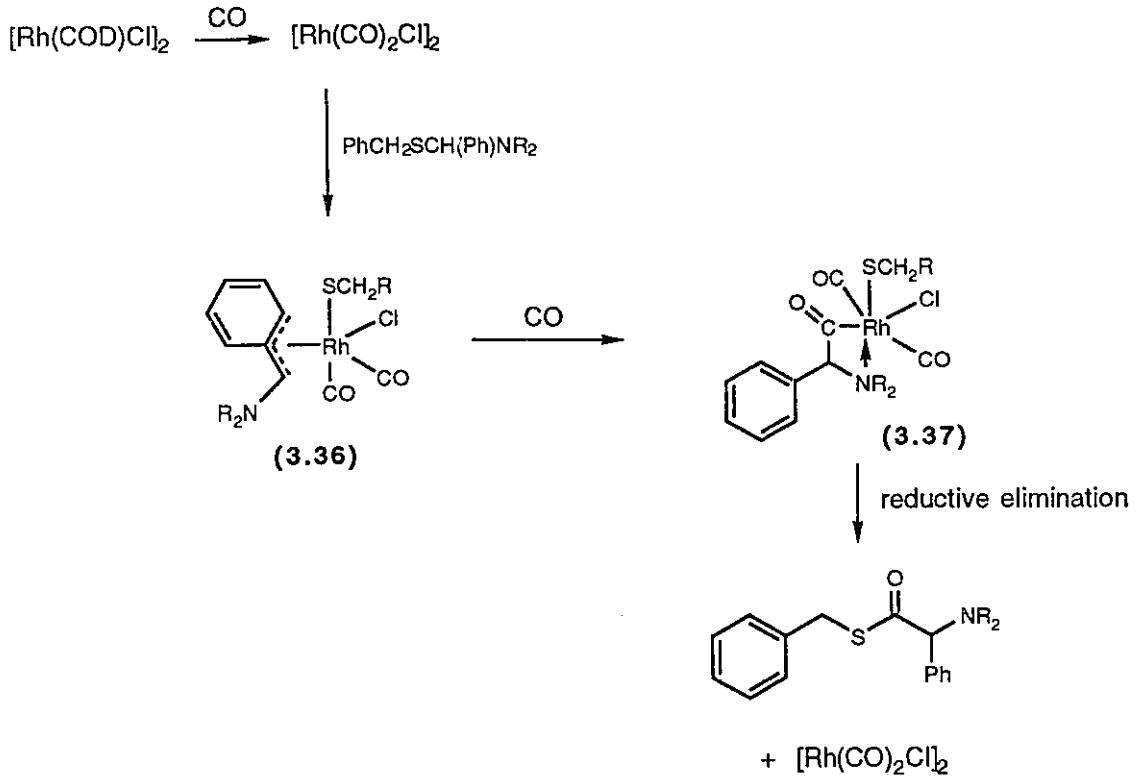
Let us consider possible mechanisms for these transformations. In all cases the initial step is conversion of the catalyst to $[Rh(CO)_2Cl]_2$.[102] In the conversion of **(3.3-3.8)** to **(3.23-3.28)**, cleavage of the benzylic carbon sulfur bond of the starting material would generate a π-benzyl complex **(3.34)**[102a] which, in the presence of carbon monoxide, affords the σ-benzyl rhodium complex **(3.35)** **(Scheme 3.1)**. Metal induced cleavage of the carbon-sulfur bond has been observed in other systems including heterocycles.[103] When the nitrogen is part of a heterocyclic ring **(3.12-3.14)** the disposition of the lone pair with respect to the other groups and rhodium in **(3.34)** and **(3.35)** may be such as to destabilize these complexes. The final step is the reductive elimination to form the product **(3.23-3.28)** and regenerate the catalyst.

Scheme 3.1

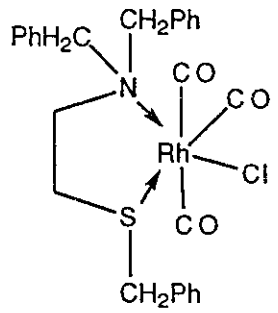


In **Scheme 3.2** is presented a pathway for the formation of **(3.30-3.33)** from **(3.15-3.18)**. In this case, selective cleavage of the carbon-sulfur bond of $SCH(Ph)NR_2$ occurs to form a π-benzyl complex **(3.36)**[102a], since the phenyl group could be the reason that these compounds cannot form the intermediate like **(3.34)**. Ligand migration of **(3.36)** to **(3.37)**, and reductive elimination affords **(3.30-3.33)** and regenerates the catalyst.

Scheme 3.2



The lack of reactivity of compound **(3.22)**, which has S and N at the 1,4-positions, is probably due to the formation of stable intermediate **(3.38)**.

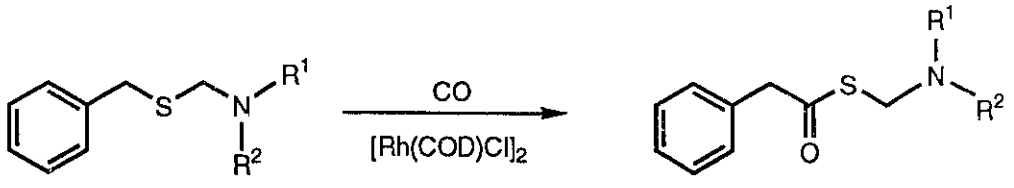


(3.38)

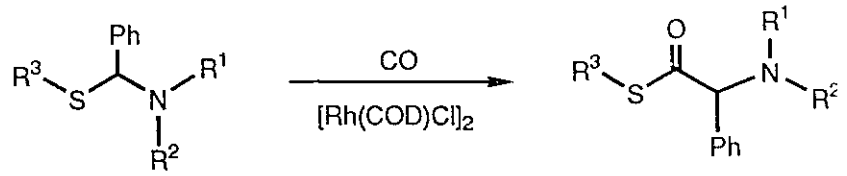
The carbonylation reactions of bis(N-benzyl-N-methyl)methylenediamine **(3.19)**, N-benzyl-N-benzyloxymethyl-N-methylamine **(3.20)** and monothioacetal **(3.21)** under the standard conditions used for N,S-acetals were unsucessful, with starting materials recovered in these cases.

3.3. Conclusion

Carbon monoxide inserts regiospecifically at the C-S bond of acyclic N,S-acetals under rhodium(I) catalyzed carbonylation conditions. The reaction proceeds in good to excellent yields affording different thiol esters depending on the nature of the substituents at sulfur, nitrogen and the acetal carbon atom. N-(Benzylthio)methyl-N,N-dialkylamines give aminoalkylthiol esters while N-(alkylthio)- or N-(benzylthio)phenylmethyl-N,N-dialkylamines yield alkyl- or benzylthiol esters of aminomethyl carboxylic acids :



R^1, R^2 = alkyl



R^1, R^2 = alkyl or $-(CH_2)_n-$

R^3 = $PhCH_2$, n-$C_{11}H_{26}$

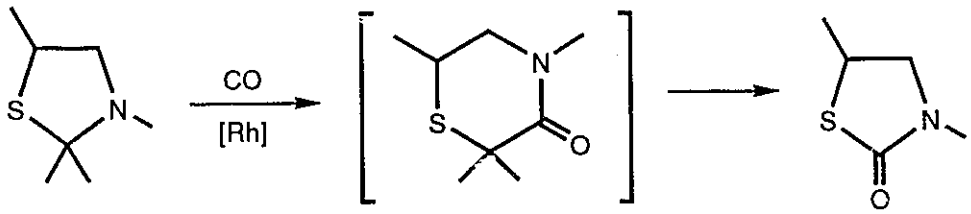
Both of these previously unknown reactions are specific for 1,3-N,S-containing acyclic molecules.

CHAPTER 4

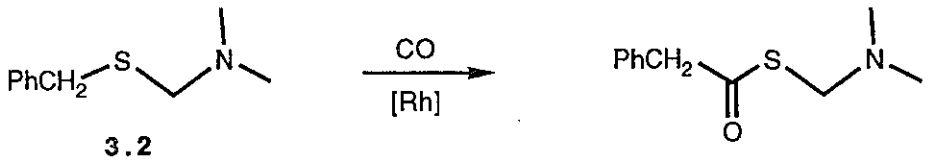
RHODIUM CATALYZED CARBONYLATION OF 2-SUBSTITUTED TETRAHYDROTHIOPHENES AND A 2-SUBSTITUTED TETRAHYDRO-FURAN

4.1. Introduction

The study of the rhodium (I) catalyzed carbonylation reaction of thiazolidines (Chapter 2) and N,S-acetals (Chapter 3) revealed that this reaction is feasible for both non-strained heterocyclic compounds and acyclic compounds containing two heteroatoms.



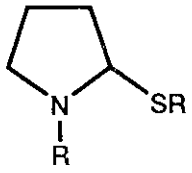
3.1



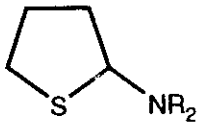
3.2

Previous studies[67, 97] also showed that the carbonylation of acyclic compounds usually requires some special functionalities (e.g. allylic or benzylic). We were surprised to find that with such functionalities, carbonylation of the acyclic system appeared to be more facile than that of 5-membered ring heterocycles. Furthermore, in the acyclic system, the C-S

bond was preferentially carbonylated while the C-N bond was carbonylated in the cyclic system. In order to determine more exactly the selectivity in the carbonylation of cyclic and acyclic C-S vs C-N bonds we attempted to prepare compounds (**4.1**) and (**4.2**). These substrates should provide some insight into the regioselectivity of the carbonylation of heterocycles containing heteroatom side chains.



4.1



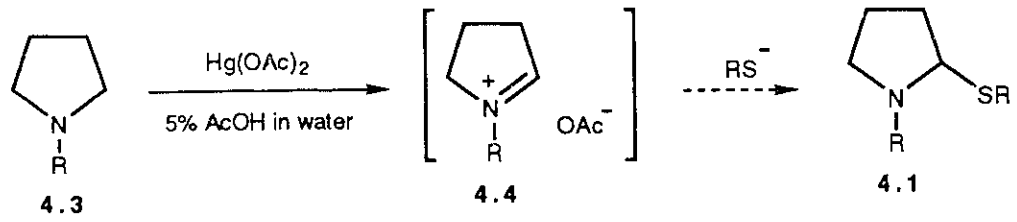
4.2

4.2. Results and Discussion

4.2.1. Synthesis of Starting Materials

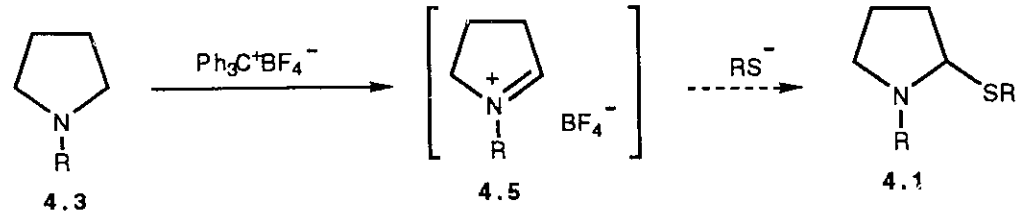
4.2.1.1. Synthesis of 2-Alkylthiopyrrolidines

Our attempts to prepare compounds of type (**4.1**) centred around the generation of the corresponding pyrrolidinium salt[104] and subsequent attack with sulfur nucleophiles. The iminium salt was prepared by a literature method via deprotonation of N-alkylpyrrolidine with $Hg(OAc)_2$.[104] The sulfur nucleophiles were added to the in situ generated iminium salt either as the thiol with added triethylamine or as the sodium salt. Neither of these methods proved successful.



4.3 4.4 4.1

Isolation of the iminium ion as its tetrafluoroborate salt[105] and exposure to various thiol nucleophiles was also unsuccessful.



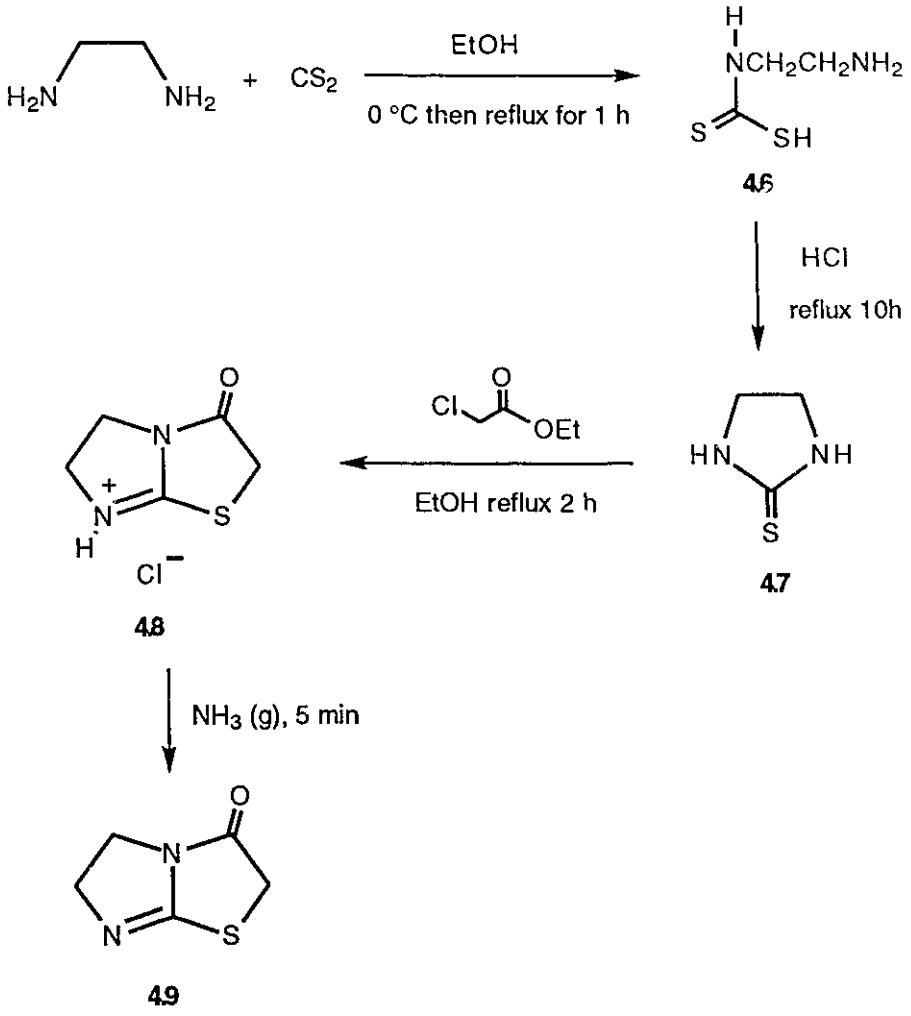
4.3 4.5 4.1

At this point we turned our attention to a bicyclic system whose partial synthesis was described in the literature.[106]

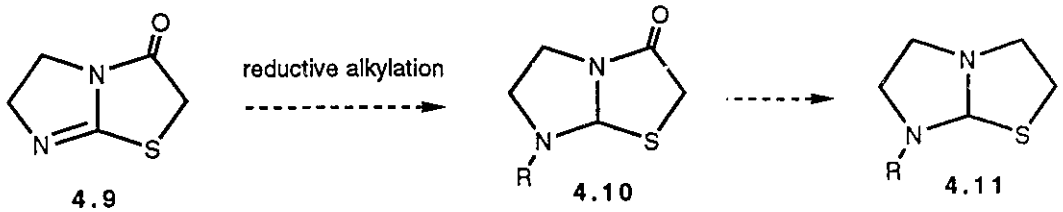
4.2.1.2. Synthesis of 5,6-Dihydroimidazo[2,1-*b*]thiazole-3(2H)-one[106]

Compound **(4.9)** was prepared in four steps starting from ethylenediamine and carbon disulfide as shown below :

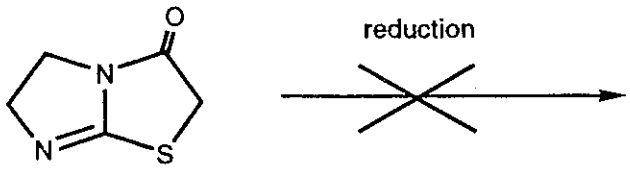
Scheme 4.1



We hoped that complete reduction of the amide and reduction/alkylation of the imine would produce a highly functionalized saturated bicyclic heterocycle **(4.11)**.



A variety of methods were examined for the reduction of the C=N functionality including borohydride reagents,[107] hydrogenation using a heterogeneous palladium catalyst, tin hydride[108] and lithium aluminium hydride :



4.9

Conditions : $NaBH_4$ / EtOH

KBH_4 / EtOH

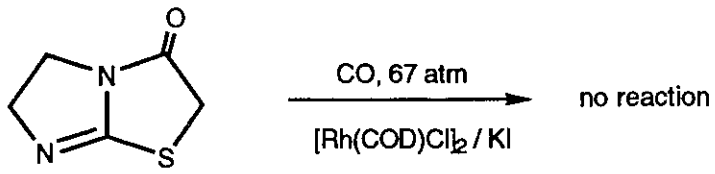
$NaBH_3CN$ / MeOH / 2 N HCl (bromocresol as indicator)

Bu_3SnH / toluene / 2% AIBN

H_2 / Pd-C / 33 atm / EtOAc-AcOH

$LiAlH_4$ / THF

Since the reduction was not feasible, we attempted to carbonylate the imine system itself.

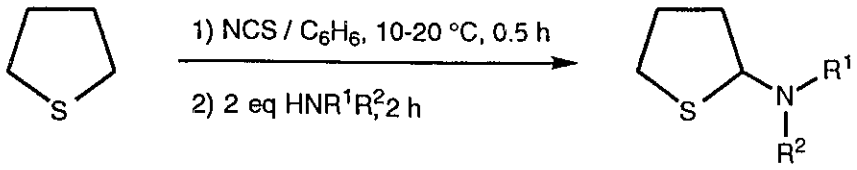


4.9

Under the previously developed optimum conditions ($[Rh(COD)Cl]_2$/KI) no carbonylation was observed even at 180 °C for 48h. Thus we abandoned this system and turned our attention to 2-aminotetrahydrothiophene.

4.2.1.3. Synthesis of 2-N,N-Dialkylaminotetrahydrothiophenes[109]

Four representative 2-N,N-dialkylaminotetrahydrothiophenes were synthesized by a modification of the procedure reported by Johnstone and Delaney.[109] Tetrahydrothiophene was chlorinated with N-chlorosuccinimide in benzene at ambient temperature (10-20 °C). After filtering off the succinimide, the crude solution was then treated with 2 equiv of the corresponding amine. This procedure yielded the desired products in good to excellent yields (based on N-chlorosuccinimide added as a limiting reagent (0.5 eq) to prevent over chlorination of tetrahydrothiophene) after purification by column chromatography using silica gel and 10% EtOAc in hexane as eluant. Characterization by ^{1}H and ^{13}C NMR confirmed the expected structures.



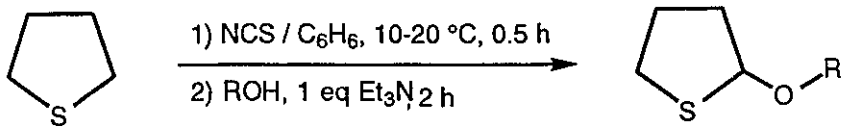
4.12-4.15

Table 4.1. Synthesis of 2-N,N-Dialkylamino tetrahydrothiophenes (**4.12-4.15**)

R^1	R^2	Product	% yield
Methyl	Benzyl	**4.12**	80
Ethyl	Ethyl	**4.13**	80
$-CH_2CH_2CH_2CH_2-$		**4.14**	65
$-CH_2CH_2OCH_2CH_2-$		**4.15**	82

4.2.1.4. Synthesis of 2-Alkoxytetrahydrothiophenes

To extend our studies to the related S,O-systems we used the same method with an alcohol in place of an amine.[109] Thus several 2-alkoxytetrahydrothiophenes were prepared in good yield as shown below.



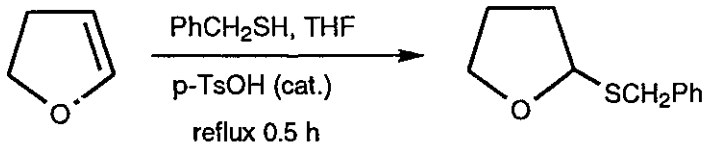
4.16-4.21

Table 4.2. Synthesis of 2-Alkoxytetrahydrothiophenes (**4.16-4.21**)

R	Product	% yield
Ethyl[110]	**4.16**	74
i-Butyl	**4.17**	81
Phenethyl[111]	**4.18**	80
m-Methylbenzyl	**4.19**	82
sec-Phenethyl	**4.20**	68
Phenyl	**4.21**	70

4.2.1.5. Synthesis of 2-Benzylthiotetrahydrofuran[112]

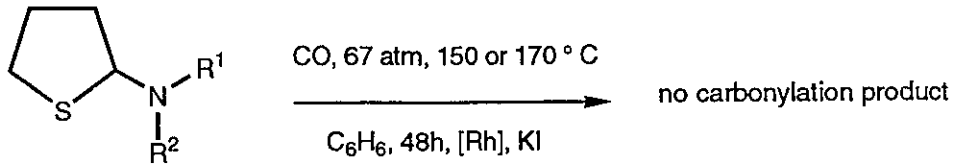
2-Benzylthiotetrahydrofuran was synthesized according to a method described in the literature.[112] Benzylmercaptan was refluxed with 2,3-dihydrofuran in the presence of a catalytic amount of p-toluenesulfonic acid for 1h. The reaction was then cooled down and extracted with CH_2Cl_2/H_2O. The crude product was chromatographed on silica gel using 10% EtOAc in hexane as the eluant affording 2-benzylthiotetrahydrofuran in 57% yield.



4.22

4.2.2. Attempted Carbonylation of 2-N,N-Dialkylaminotetrahydrothiophenes

Following the synthesis of a variety of 2-N,N-dialkylaminotetrahydrothiophenes, we attempted the carbonylation under our standard conditions, with and without KI as the promoter. At 150 °C we observed no reaction. Increasing the temperature to 170 °C caused only decomposition of the starting material, with no carbonylation products formed in the reaction.



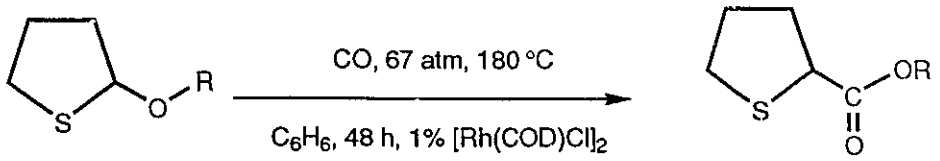
4.12-4.15

Different substituents attached to the nitrogen atom did not improve the reaction. Since the thiazolidine ring systems required at least 180 °C for carbonylation to occur (Chapter 2), the decreased stability of the 2-N,N-dialkylaminotetrahydrothiophene system at such elevated temperatures may make carbonylation impossible.

4.2.3. Carbonylation of 2-Alkoxytetrahydrothiophenes and 2-Benzylthiotetrahydrofuran Catalyzed by $[Rh(COD)Cl]_2$

As we reasoned that the corresponding 2-alkoxytetrahydrothiophene should be more stable than their amine analogs, compounds **(4.16-4.21)** were prepared and then subjected to carbonylation at 67 atm of CO and 180 °C using 1 mol% $[Rh(COD)Cl]_2$. We were gratified to observe carbonylation in moderate to good yield. Furthermore, the reaction was chemo and regiospecific yielding only the tetrahydrothiophene-2-carboxylic esters from

carbonylation of the carbon-oxygen bond connecting the side chain to the ring. The structures of the products were determined by spectroscopic methods (see Experimental Sections). Representative ^{1}H and ^{13}C NMR spectra are shown in **Fig 4.1**.



4.16-4.21 **4.23-4.28**

Table 4.3. Rhodium Catalyzed Carbonylation of 2-Alkoxytetrahydrothiophene **(4.16-4.21)**

Reactant	R	Product	% yield
4.16	Ethyl	**4.23**	73
4.17	i-Butyl	**4.24**	32
4.18	Phenethyl	**4.25**	44
4.19	m-Methylbenzyl	**4.26**	67
4.20	sec-Phenethyl	**4.27**	14
4.21	Phenyl	**4.28**	0

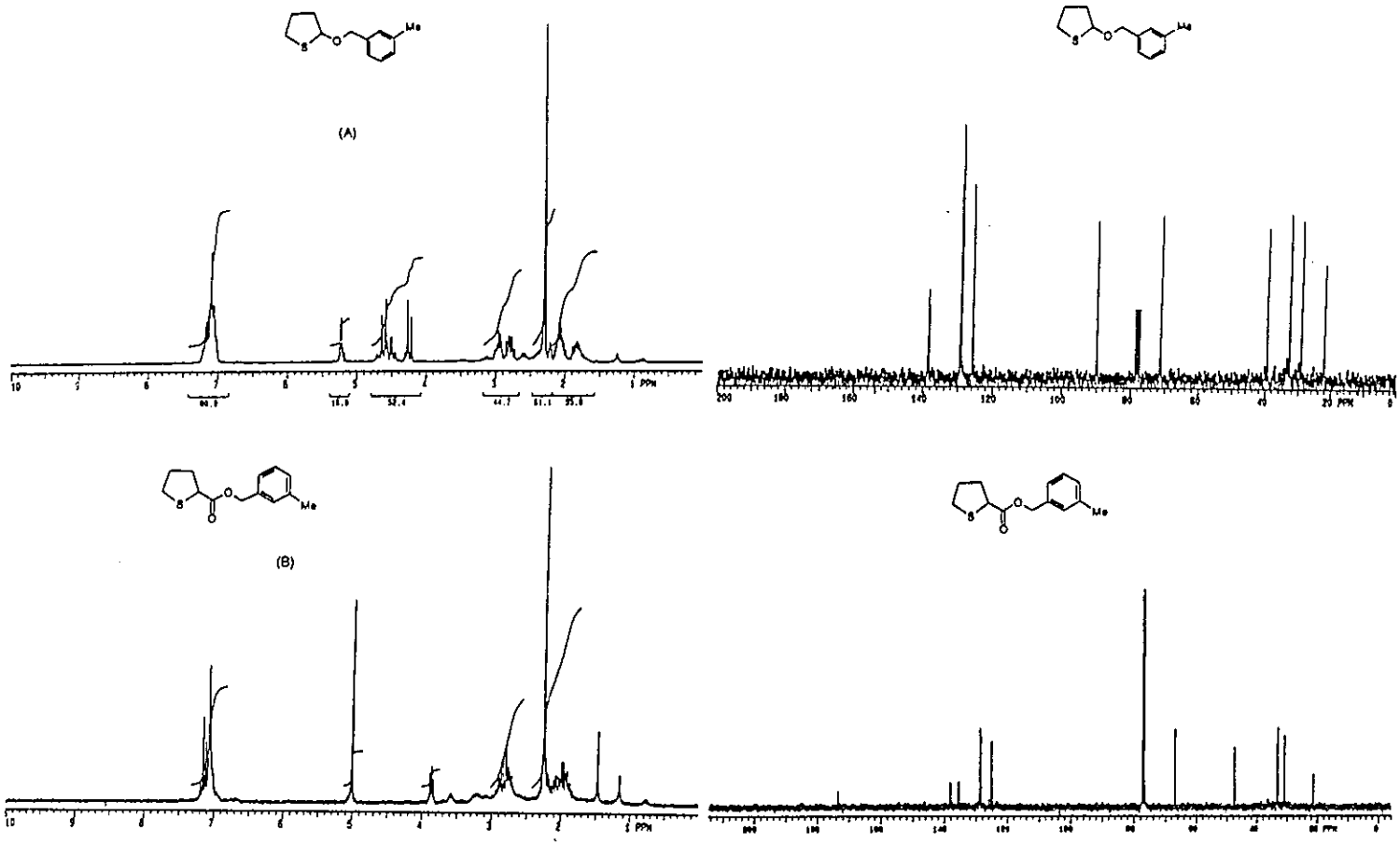
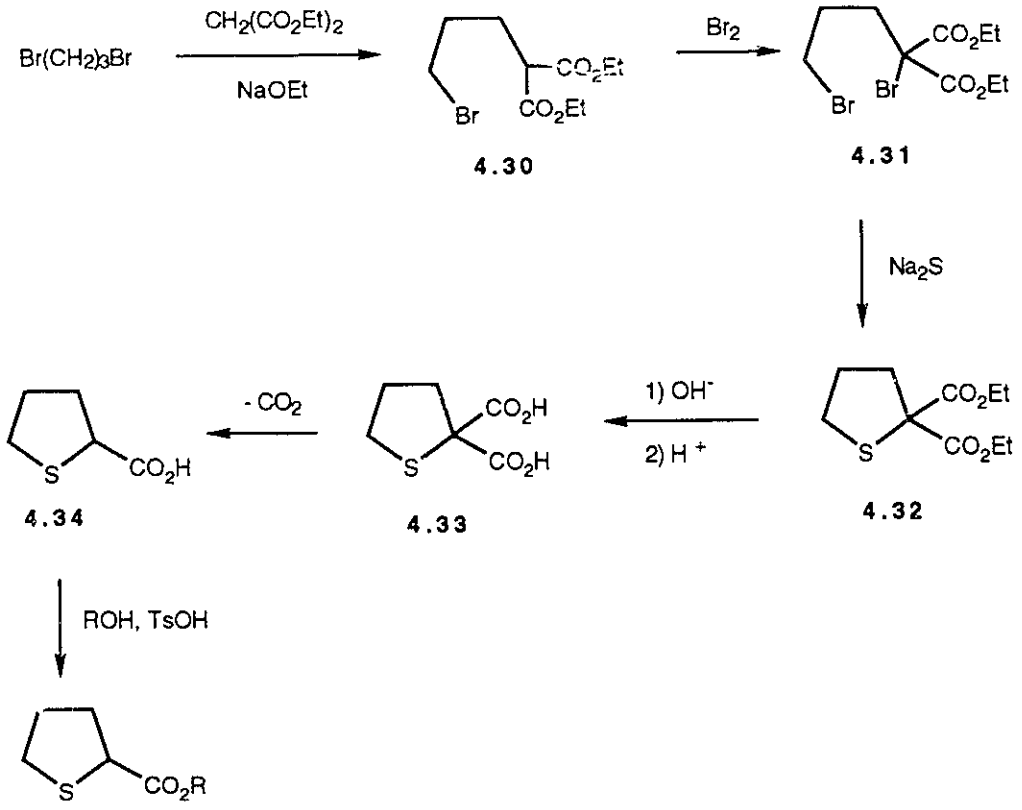


Fig. 4.1. ^{1}H and ^{13}C NMR Spectra of 2-(*m*-Methylbenzyloxy)tetrahydrothiophene (**4.19**) (A) and *m*-Methylbenzyl tetrahydrothiophene-2-carboxylate (**4.26**) (B)

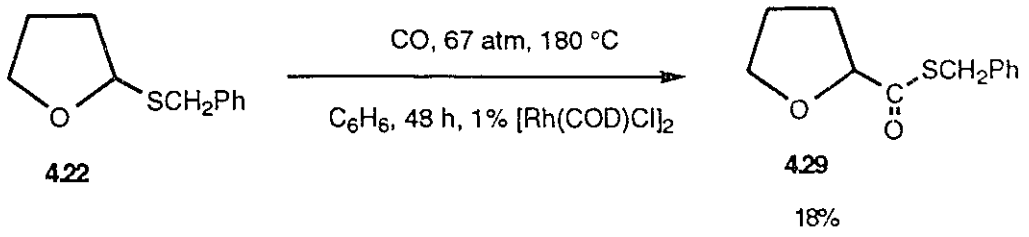
The reaction proceeds using alkyl (**4.16, 4.17**) or primary (**4.18, 4.19**) or secondary (**4.20**) benzylic ethers. Note that some starting material was recovered using (**4.20**) as the substrate. The phenoxy substituted ether (**4.21**) was unreactive under the aforementioned conditions presumably due to steric effects and resonance interaction of the π-electrons of the benzene ring with the *n*-electrons of the oxygen atom.

Although this study was undertaken primarily to determine the regio and chemoselectivity of the carbonylation of cyclic and acyclic carbon heteroatom bonds, it also represents a concise synthesis of tetrahydrothiophene-2-carboxylic esters. Conventional methods are quite lengthy (**Scheme 4.2**)[113] and our method is only three steps long. Furthermore, the carbonylation described herein requires only 1% of a commercially available rhodium catalyst.

Scheme 4.2



Finally, to further compare the carbonylation of cyclic and acyclic carbon-heteroatom bonds, we prepared 2-benzylthiotetrahydrofuran[109] and subjected it to the same conditions as mentioned above. The carbonylation product **(4.29)** was isolated in 18 % yield after 48h with starting material recovered as well. Again the carbonylation was completely selective, this time occuring at the carbon-sulfur bond connecting the side chain to the ring.



4.22

4.29

18%

4.3. Conclusion

The results described above clearly demonstrate the chemospecific for the insertion of carbon monoxide into the acyclic carbon-heteroatom (O, S) bond, given the choice between this insertion and that involving a heterocyclic carbon-heteroatom bond. Furthermore, the carbonylation is restricted to the carbon heteroatom bond attached to the ring. The carbonylation of 2-alkylthiotetrahydrofuran gave considerably lower yields than that attained using 2-alkoxytetrahydrothiophenes as substrates, but the acyclic preference was retained. Thus it appears that the choice between cyclic and acyclic carbonylation is more important than C-O versus C-S. This is probably due to the fact that the energy for the transformation of a five membered to a six membered ring is quite high. Since the CO is able to insert into the side chain, the latter process is observed exclusively.

CHAPTER 5

RHODIUM AND IRIDIUM CATALYZED REACTIONS OF CARBON MONOXIDE WITH HETEROCYCLIC COMPOUNDS CONTAINING TWO HETEROATOMS AT THE 1,2-POSITION OF A HETEROCYCLIC RING.

5.1. Introduction

As noted in the introduction, carbonylation reactions can be catalyzed by many kinds of metal complexes including complexes of rhodium and iridium. Although both metals are in the same group in the periodic table, their chemistry is often quite different.[114] This chapter describes the attempted carbonylation of heterocyclic compounds using both $[Rh(COD)Cl]_2$, which will form $[Rh(CO)_2Cl]_2$ in the presence of CO, and $IrCl_3$, which has been shown to form chlorotricarbonyliridium at elevated temperatures in the presence of CO.[115]

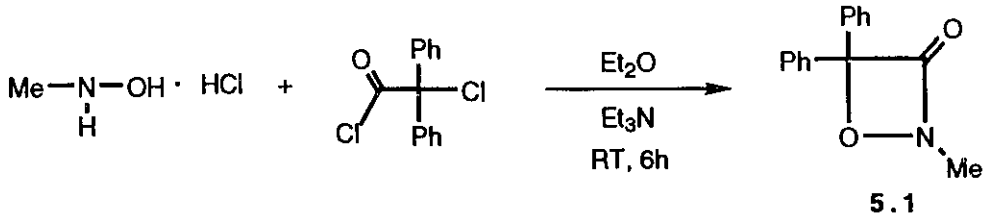
The heterocycles which were chosen for this study are those containing two heteroatoms at the 1,2-positions. Roberto and Alper[78] previously demonstrated that carbon monoxide can be inserted into the N-N bond of diaziridines (see Chapter 1 - conversion of **1.92** to **1.93**). It is likely that the facility of this process is due to the strain energy in the starting material. It was also revealed that in this system, the N-N bond is carbonylated and not the C-N bonds. We now describe our efforts to determine the reactivity and selectivity of the carbonylation of less strained ring systems containing a heteroatom-heteroatom bond. We first examined isoxazolidine derivatives since their chemistry is well studied.[116] In addition, for comparison, we studied the carbonylation of oxazetidinone[117] and pyrazolidine[118] derivatives.

5.2. Results and Discussion

5.2.1. Synthesis of Starting Materials

5.2.1.1. Synthesis of 4,4-Diphenyl-2-methyl-1,2-oxazetidine-3-one

4,4-Diphenyl-2-methyl-1,2-oxazetidine-3-one (**5.1**) was synthesized according to the literature procedure.[119] Reacting N-methylhydroxylamine hydrochloride and α-chlorodiphenylacetyl chloride in the presence of triethylamine afforded the desired product which solidified upon standing and was used without further purification.

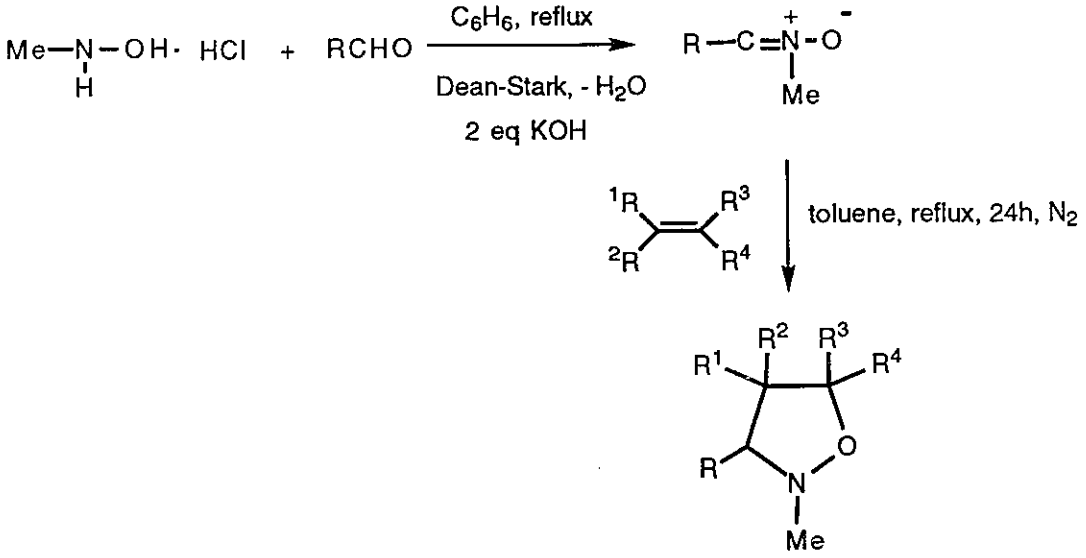


5.1

5.2.1.2. Synthesis of Isoxazolidines

The cycloaddition reaction of N-methylnitrones and dipolarophiles which has been described in the literature was used to synthesize isoxazolidines.[120] N-Methylnitrones were synthesized by a simple condensation of commercially available N-methylhydroxylamine hydrochloride and the corresponding aldehyde in the presence of KOH. The cycloaddition was effected by refluxing the nitrone and excess dipolarophile in toluene under nitrogen for 24 h (**Scheme 5.1**).

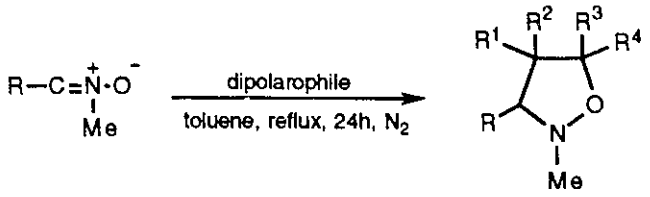
Scheme 5.1



5.2-5.8

The crude reaction mixtures were purified by silica gel chromatography using EtOAc in hexane as the eluant. The purified products were characterized by ^{1}H, ^{13}C NMR and mass spectrometry. The results of the syntheses of isoxazolidines are summarized in **Table 5.1**.

Table 5.1. Cycloaddition of Nitrones and Dipolarophiles (**5.2-5.8**)



5.2-5.8

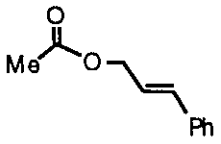
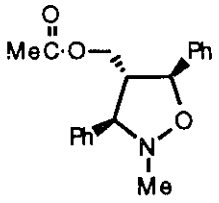
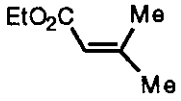
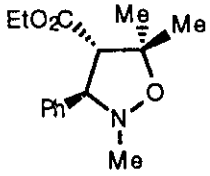
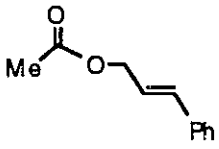
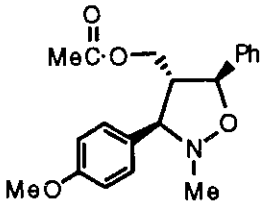
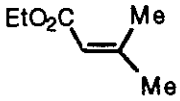
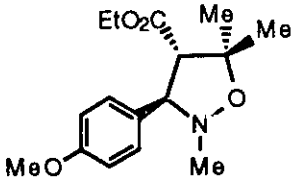
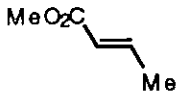
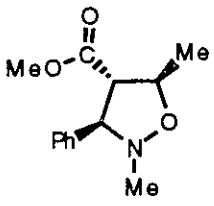
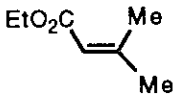
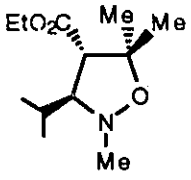
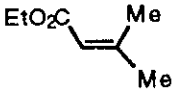
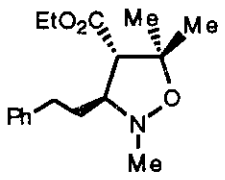
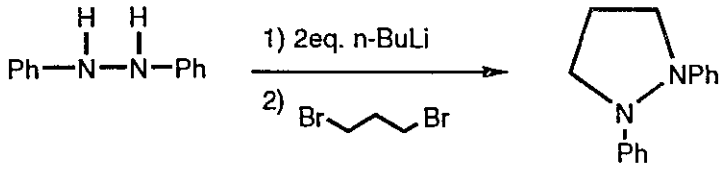
R	Dipolarophile	Product	% Isolated yield
Ph		 **5.2**	78
Ph		 **5.3**	80
4-MeO-C_6H_4		 **5.4**	67
4-MeO-C_6H_4		 **5.5**	82

Table 5.1. (continued)

R	Dipolarophile	Product	% isolated yield
Ph		 **5.6**	83
$CH(CH_3)_2$		 **5.7**	64
CH_2CH_2Ph		 **5.8**	61

5.2.1.3. Synthesis of 1,2-Diphenylpyrazolidine[118]

N,N'-Diphenylpyrazolidine (**5.9**) was prepared by alkylation of 1,2-diphenylhydrazine with 1,3-dibromopropane as described in the literature.[118] The product was isolated from the reaction mixture in 24% yield by vacuum distillation.



5.9

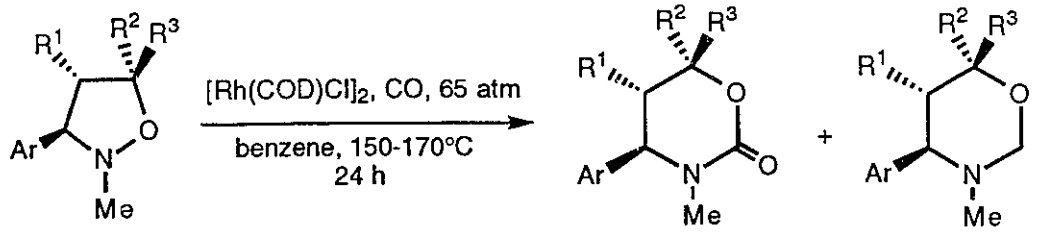
5.2.2. Reaction of 1,2-N,O-Heterocycles with Carbon Monoxide Catalyzed by Rhodium or Iridium Complexes

The carbonylations of 1,2-oxazetidin-3-one (**5.1**) and isoxazolidine derivatives (**5.2-5.8**) were carried out in dry benzene, at 65 atm of carbon monoxide and 150-170 °C for 24 h using $[Rh(COD)Cl]_2$ or $IrCl_3$ as the catalyst precursors. The concentration of the catalyst in all cases was 1 mol %. The 1,2-oxazetidin-3-one (**5.1**) did not yield any carbonylation products under the conditions described above.

The carbonylation of isoxazolidine derivatives (**5.2-5.6**) led to three different products depending on the ring substituents and the type of catalyst (**Table 5.2**). The products were isolated by column chromatography on silica gel. The structures of the carbonylation products (**5.10-5.13**) were assigned using a combination of ^1H, ^{13}C, DEPT, COSY and HMQC techniques (see **Fig 5.1, 5.2** for representative NMR spectra).

Using rhodium(I), insertion of carbon monoxide occurs into the N-O bond in all cases affording tetrahydro-1,3-oxazin-2-ones. No products of insertion into the C-N or C-O bond were detected in these reactions (**Table 5.2**). Using substrates **5.4-5.5** carbonylation of the N-O bond was also observed, but a minor product resulting from reduction of the C=O unit was also detected and this product became the only one obtained in the case of **5.6**. In the ^1H NMR spectra, the signals for the protons attached to the carbon

next to N and O (if there are protons adjacent to O) are shifted downfield by approximately 0.5 ppm. The ^{13}C NMR spectra display the carbamate carbonyl signal at the expected chemical shift of δ 153-155 ppm. Representative ^{1}H and ^{13}C NMR are shown in **Fig 5.1**.



5.2-5.6 **5.10-5.13** **5.14-5.18**

5.2, 5.10, 5.14 R^1 = $MeOCOCH_2$, R^2 = Ph, R^3 = H, Ar = Ph

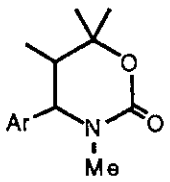
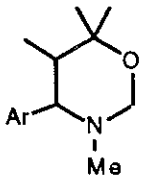
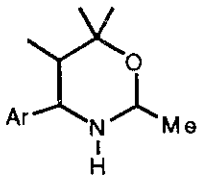
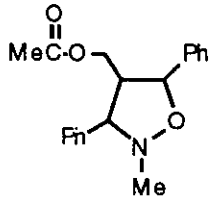
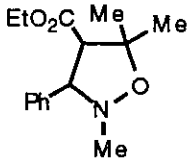
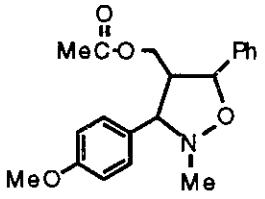
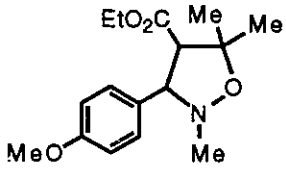
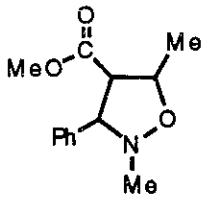
5.3, 5.11, 5.15 R^1 = EtO_2C, R^2 = R^3 = Me, Ar = Ph

5.4, 5.12, 5.16 R^1 = $MeOCOCH_2$, R^2 = Ph, R^3 = H, Ar = p-MeO-C_6H_4

5.5, 5.13, 5.17 R^1 = EtO_2C, R^2 = R^3 = Me, Ar = p-MeO-C_6H_4

5.6, 5.18 R^1 = MeO_2C, R^2 = Me, R^3 = H, Ar = Ph

Table 5.2. Carbonylation of Isoxazolidines **(5.2-5.6)**

		 5.10-5.13	(% yield)	 5.14-5.18	(% yield)	 5.19, 5.20	(% yield)
 5.2	[Rh]	5.10	(80)	-		-	
	[Ir]	-		5.14	(45)	-	
 5.3	[Rh]	5.11	(72)	-		-	
	[Ir]	-		5.15	(39)	-	
 5.4	[Rh]	5.12	(20)	5.16	(20)	-	
	[Ir]	-		5.16	(42)	-	
 5.5	[Rh]	5.13	(64)	5.17	(10)	-	
	[Ir]	-		5.17	(37)	5.19	(8)
 5.6	[Rh]	-		5.18	(24)	-	
	[Ir]	-		5.18	(35)	5.20	(7)

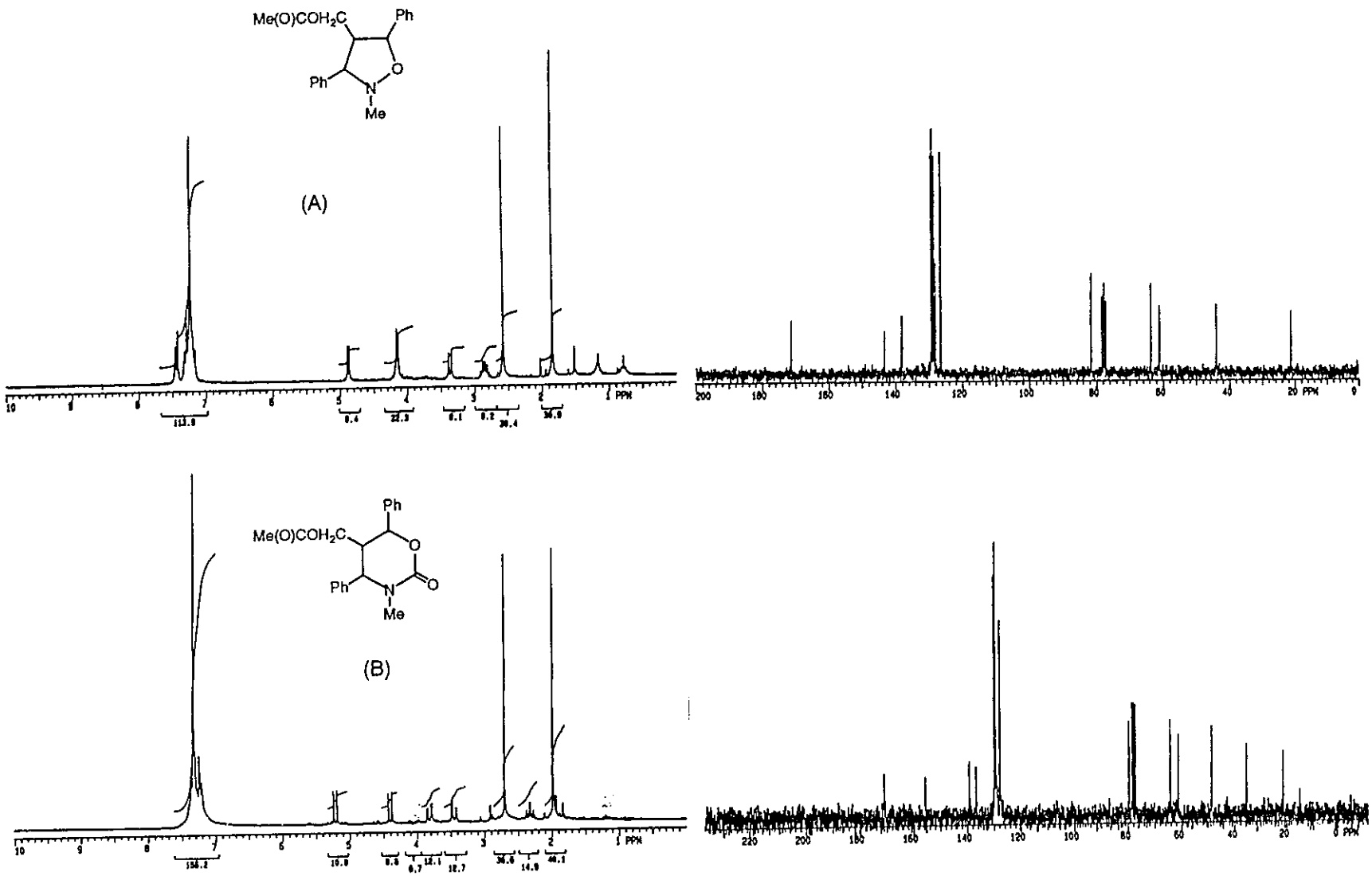
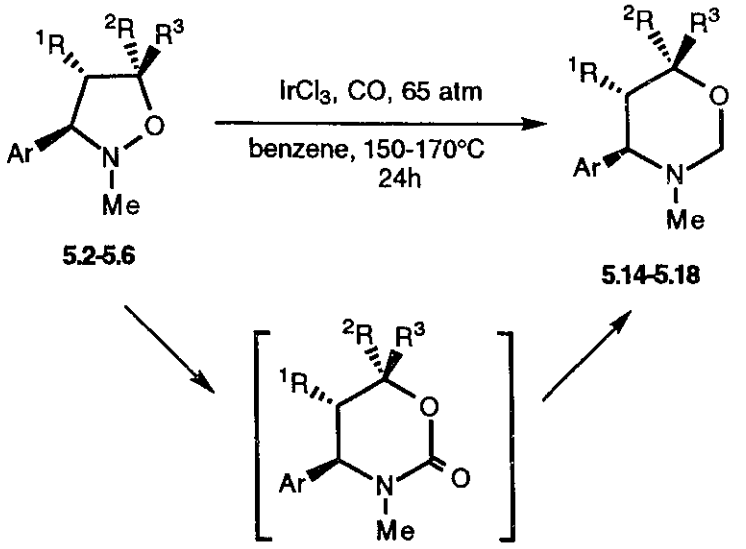


Fig. 5.1. ^{1}H and ^{13}C NMR Spectra of 4-Acetoxymethyl-3,5-diphenyl-2-methylisoxazolidine **(5.2)** (A) and 5-Acetoxymethyl-4,6-diphenyl-3-methyl-1,3-oxazin-2-one **(5.10)** (B)

It was anticipated that $IrCl_3$ would catalyze the selective transformation of isoxazolidine derivatives to 1,3-oxazin-2-ones. However, in every case, the principal or only product resulted from the net reduction of the carbonyl groups of the presumed carbamate intermediate, to a methylene group (**Table 5.2**). The 1,3-oxazine derivatives (**5.14-5.18**) were characterized by ^1H, ^{13}C NMR, COSY and HMQC. In the ^1H NMR spectra the methylene group displays an AB doublet of doublets, and shows no coupling with any other protons in the COSY, and couples with the aminal carbon in the HMQC (**Fig 5.2, 5.3**).



As previously noted, the 1,3-oxazine (reduction) product was observed in trace amounts during the rhodium catalyzed carbonylation of isoxazolidines. Using iridium, the oxazines become the dominant or only products.

We assume that the 1,3-oxazine products are secondary products, derived from the 1,3-oxazin-2-one. Since the maximum yield does not exceed 50%, it is possible that the hydrogen source is the starting heterocycle. To test

this hypothesis, we subjected oxazinone (**5.10**) to the standard carbonylation conditions. We recovered the oxazinone (**5.10**) unchanged in almost quantitative yield from this experiment. This result supports our idea that the starting material (isoxazolidine) is the source of hydrogen for the product.

It was demonstrated by Braude[121] and Entwistle[122] that cyclohexene can act as a hydrogen source in Pd-catalyzed transfer-hydrogenations of many compounds including alkenes, alkynes, and even nitroaromatics. We therefore attempted the iridium catalyzed carbonylation reaction of isoxazolidine (**5.4**) in the presence of one equivalent of cyclohexene. Under these conditions, the yield of **5.16** increased from 42% to 55%.

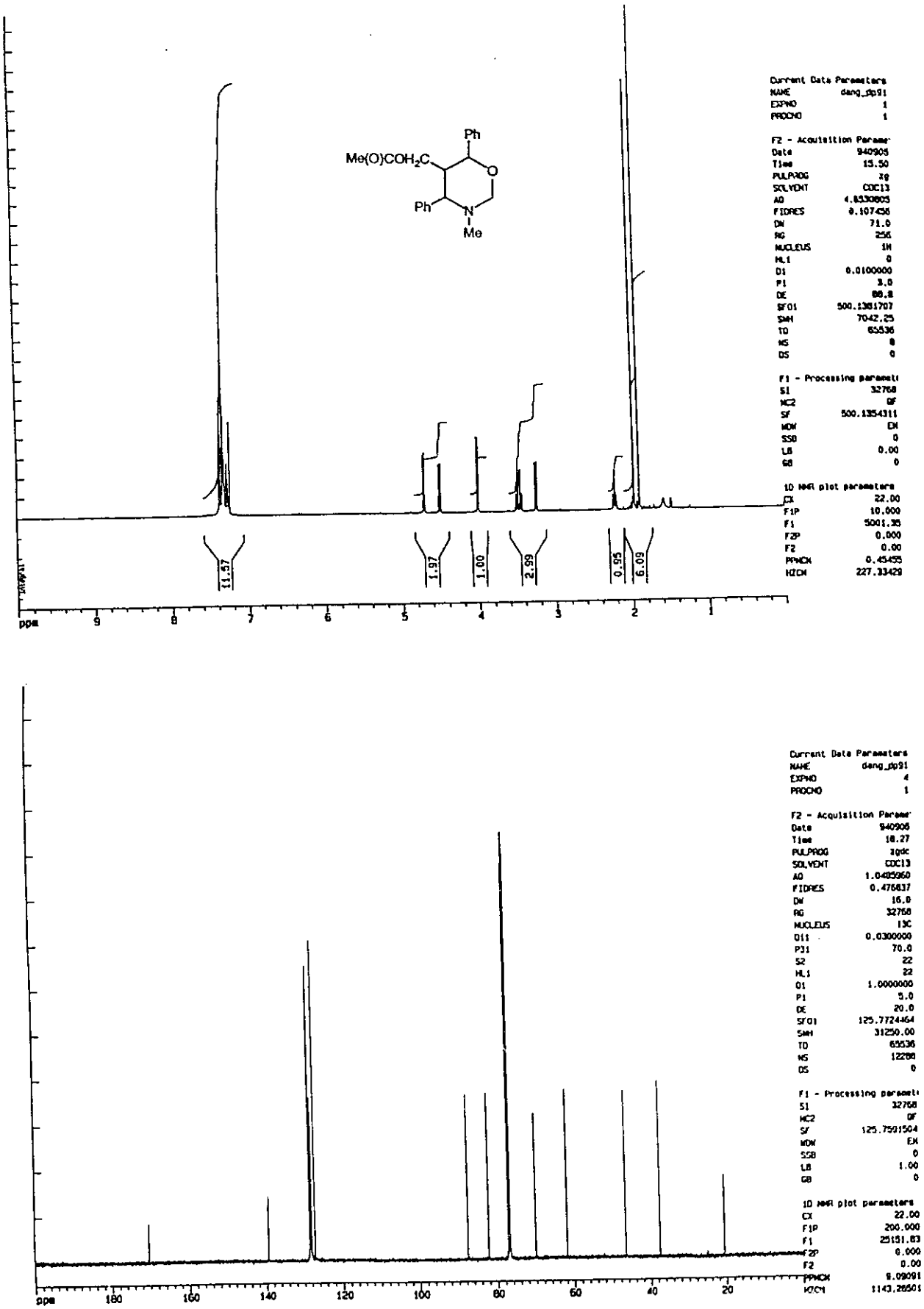


Fig. 5.2. ^{1}H and ^{13}C NMR Spectra of 5-Acetoxymethyl-4,6-diphenyl-3-methyl-1,3-oxazine **(5.14)**

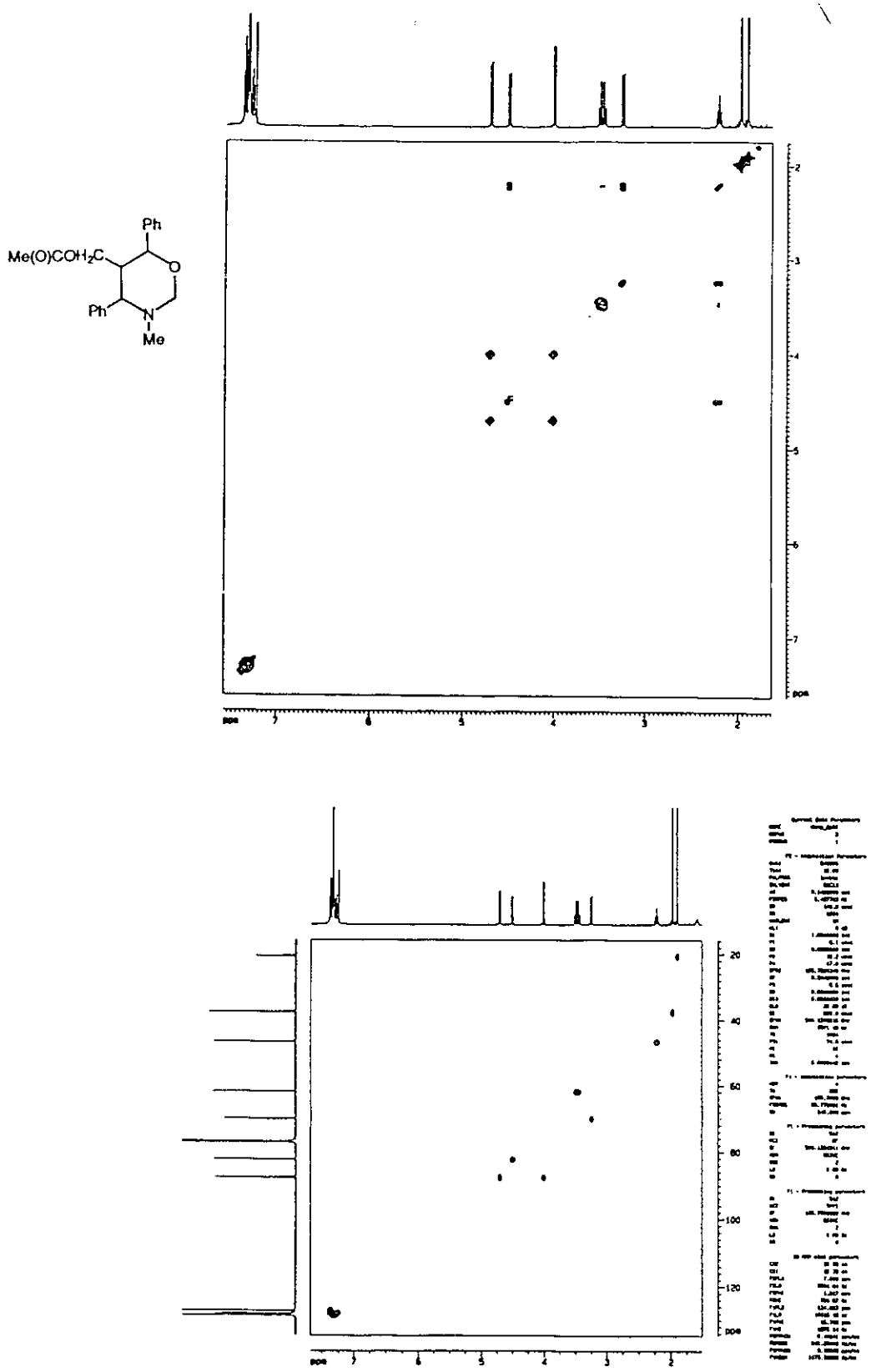
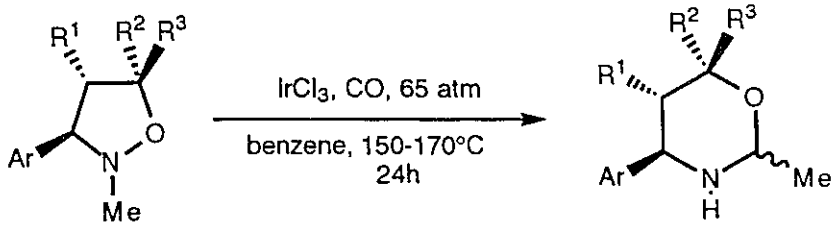


Fig. 5.3. COSY and HMQC Spectra of 5-Acetoxymethyl-4,6-diphenyl-3-methyl-1,3-oxazine (**5.14**)

In certain cases (**5.5, 5.6**), a second product was isolated in less than 10% yield in which the methyl group had migrated from nitrogen to the adjacent methylene carbon during ring expansion.



5.5, 5.19 $R^1 = EtO_2C$, $R^2 = R^3 = Me$, Ar = p-OMe-C_6H_4

5.6, 5.20 $R^1 = MeO_2C$, $R^2 = Me$, $R^3 = H$, Ar = Ph

The ^1H NMR signal of the CH-CH_3 unit comprises a multiplet at δ 4.68 which integrates to one proton (**Fig 5.4**). Note that the signal of the CH_2 unit in **5.17, 5.18** consists of an AB system centered at δ 3.93, 4.55. The signal at δ 4.68 is also coupled with the aminal carbon in the HMQC spectrum (**Fig 5.5**). Furthermore, the signal at δ 2.5 ppm observed in the spectrum of **5.5, 5.6**, which was assigned to the N-Me, disappeared and a new methyl signal was observed in the spectrum of **5.19, 5.20** as a doublet at δ 1.10-1.20 ppm. Representative spectra are shown in **Fig 5.5, 5.6**. The yield of the migration product is low (<10%) so it represents a minor pathway. Nevertheless this is a novel reaction.

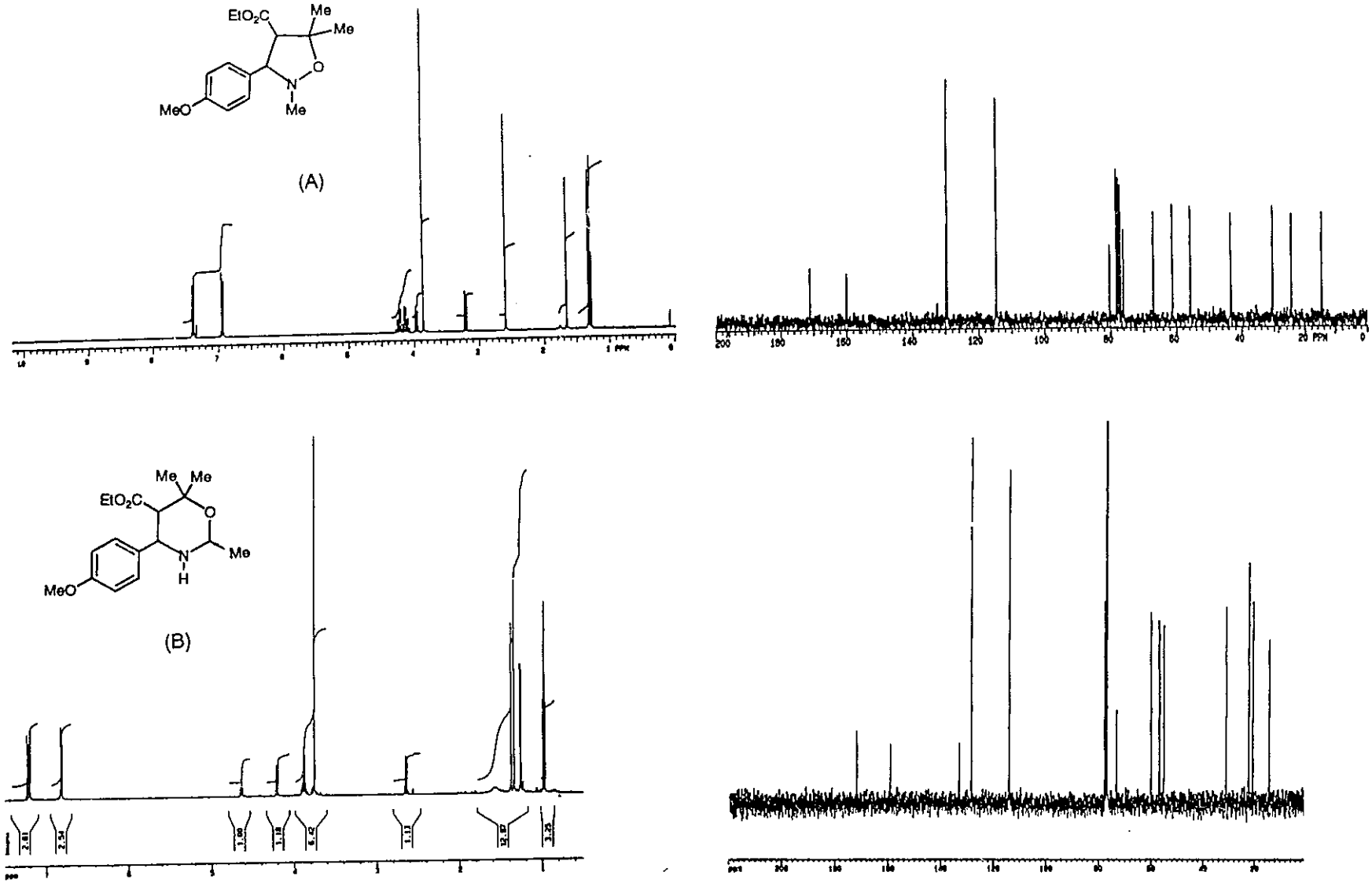


Fig. 5.4. ^{1}H and ^{13}C NMR Spectra of 4-Ethoxycarbonyl-3-(p-methoxyphenyl)-2,5,5-trimethylisoxazolidine **(5.5)** (A) and 5-Ethoxycarbonyl-4-(p-methoxyphenyl)-2,6,6-trimethyl-1,3-oxazine **(5.19)** (B)

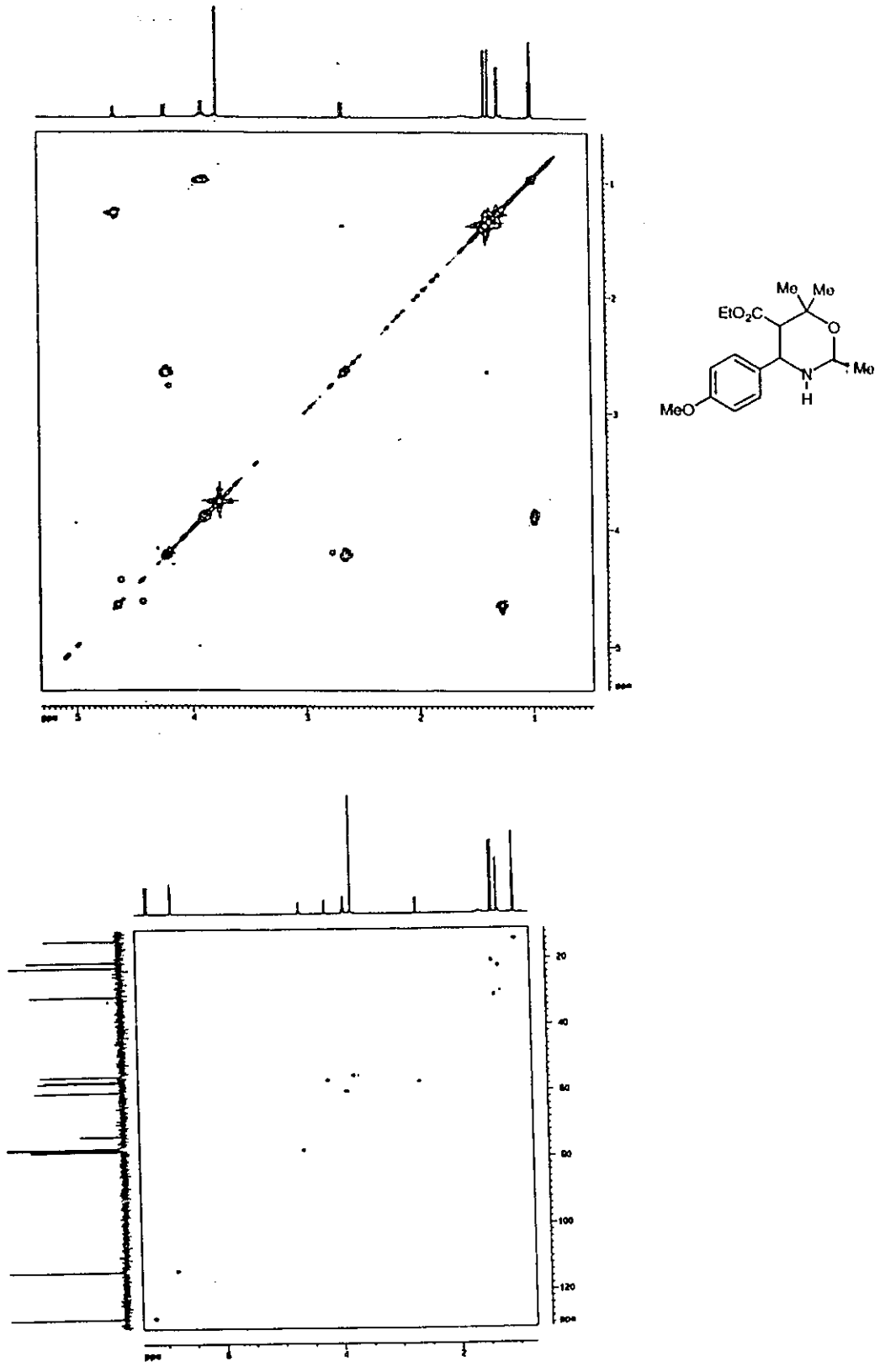
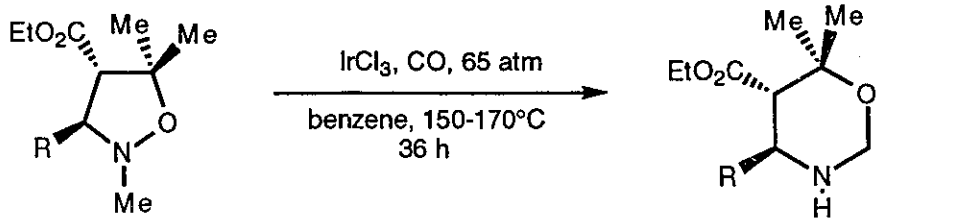


Fig. 5.5. COSY and HMQC Spectra of 5-Ethoxycarbonyl-4-(p-methoxyphenyl)-2,6,6-trimethyl-1,3-oxazine **(5.19)**

A different rearrangement was observed in the $IrCl_3$ catalyzed reaction of isoxazolidines bearing an *alkyl* substituent at the 3-position. In both substrates **(5.7, 5.8)**, the N-methyl carbon was observed to migrate *into* the ring thereby forming a 1,3-oxazine **(5.21, 5.22)** **(Fig 5.6, 5.7)**. Unlike the carbonylation/reduction observed in the aryl substituted systems, this rearrangement occured in good yields (47%, 65% respectively). It should be noted that these substrates **(5.7, 5.8)** are not as reactive as those having an aryl substituent at the 3-position [the reaction time for these substrates is somewhat longer (36 h)]. Also, these substrates **(5.7, 5.8)** are unreactive when a rhodium complex is used as the catalyst. The reason for the remarkable difference in reactivity of the alkyl and aryl substituted isoxazolidines is not clear. Additional studies are required to determine if the rearrangement is inter- or intramolecular and whether or not it is applicable to other N-alkyl isoxazolidines.



5.7 R = i-Propyl

5.8 R = CH_2CH_2Ph

5.21 R = i-Propyl

5.22 R = CH_2CH_2Ph

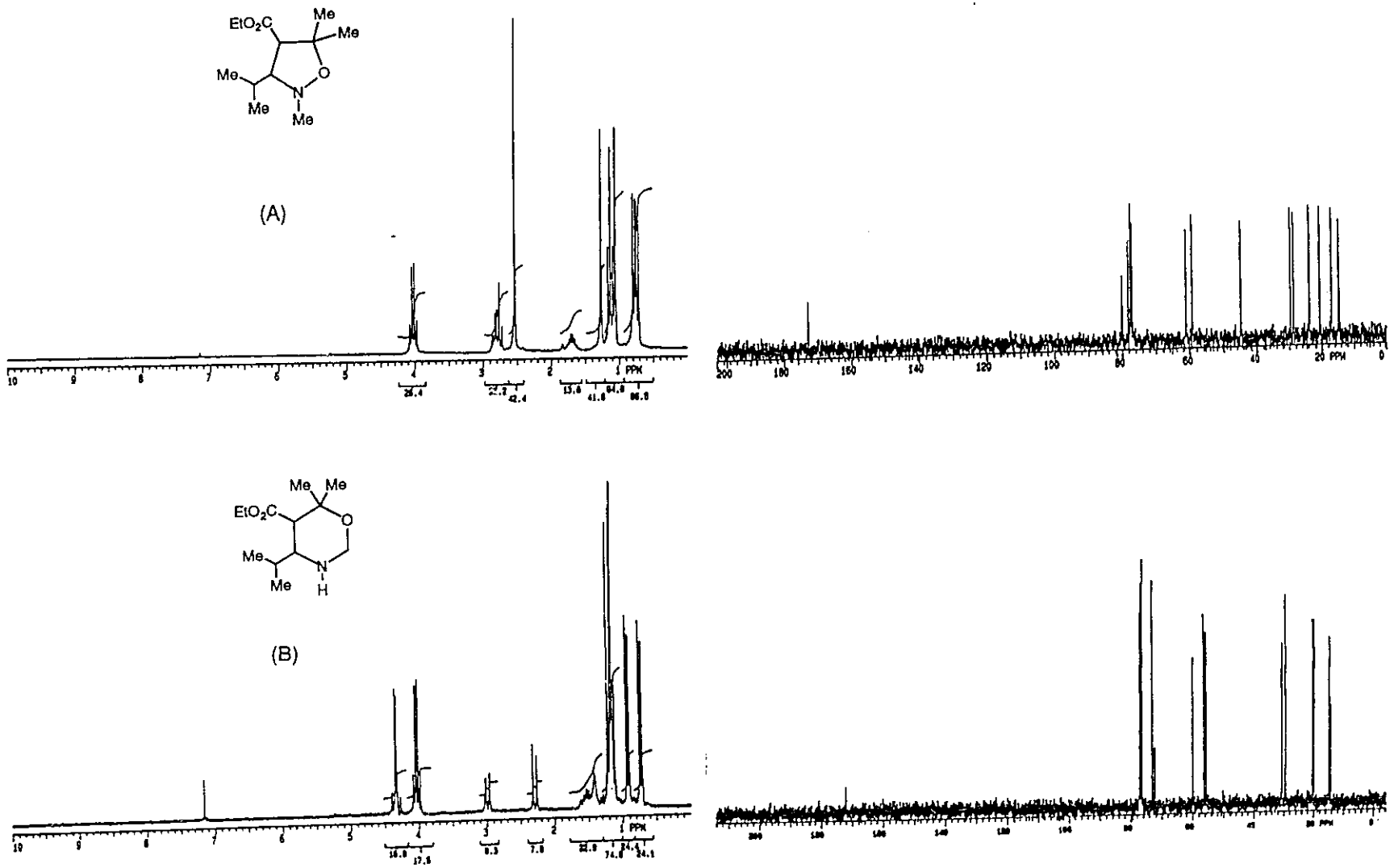


Fig. 5.6. ^{1}H and ^{13}C NMR Spectra of 4-Ethoxycarbonyl-3-isopropyl-2,5,5-trimethylisoxazolidine (**5.7**) (A) and 5-Ethoxycarbonyl-4-isopropyl-6,6-dimethyl-1,3-oxazine (**5.21**) (B)

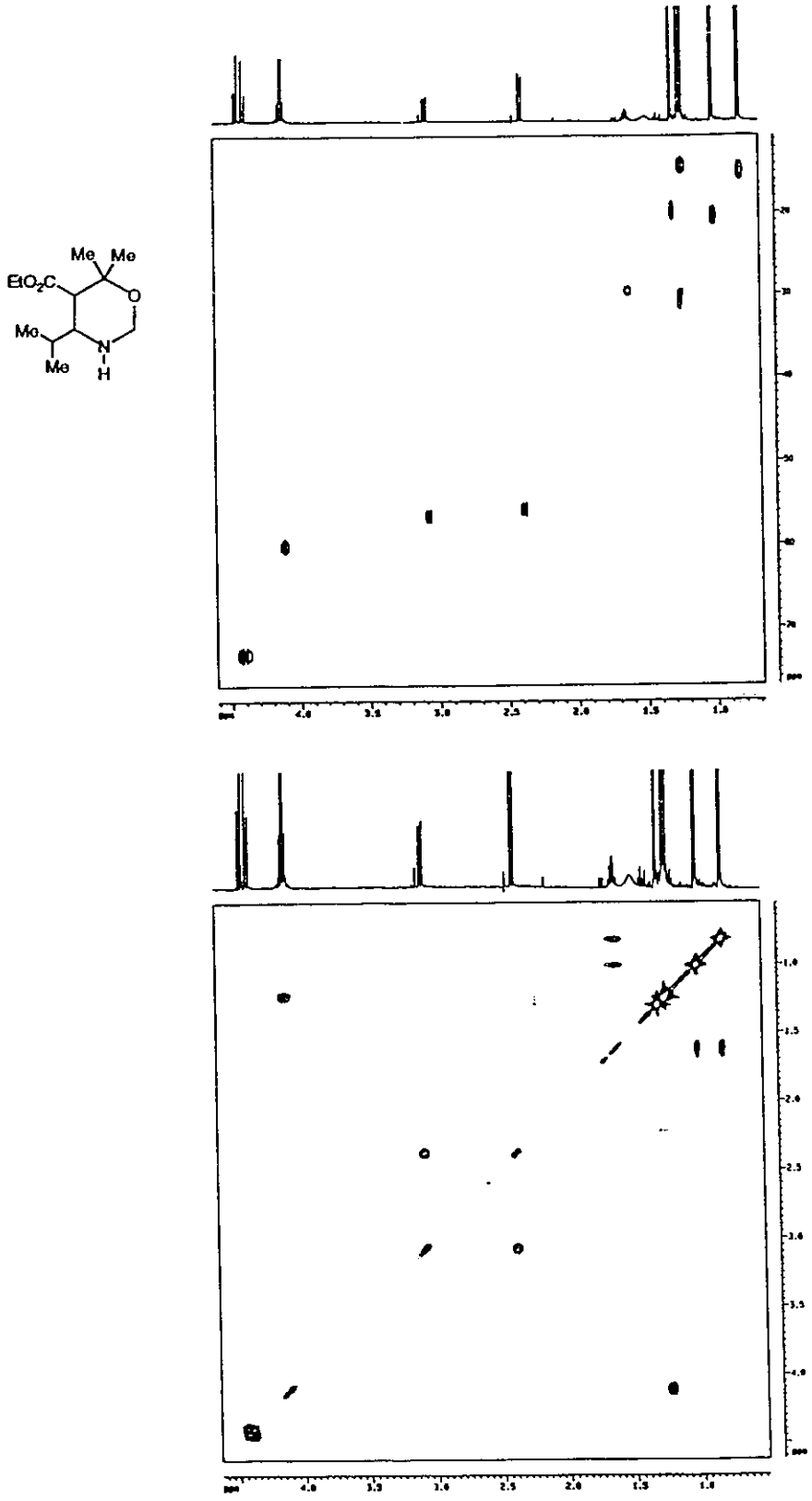
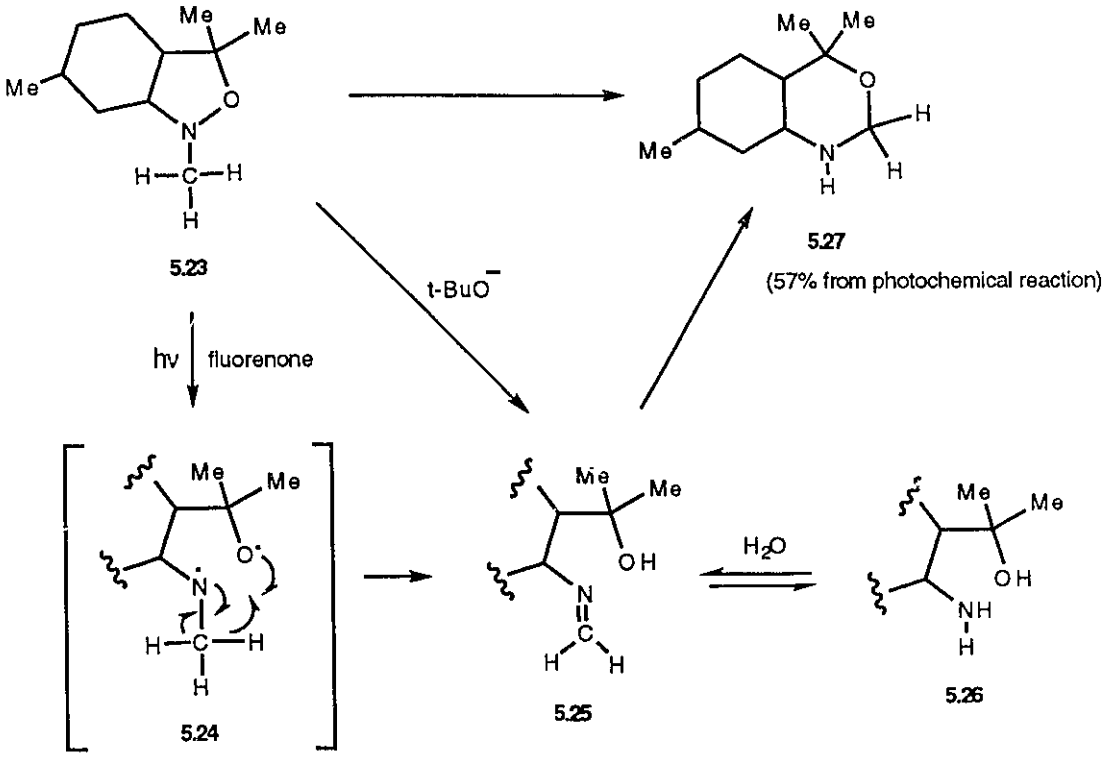


Fig. 5.7. COSY and HMQC Spectra of 5-Ethoxycarbonyl-4-isopropyl-6,6-dimethyl-1,3-oxazine (**5.21**)

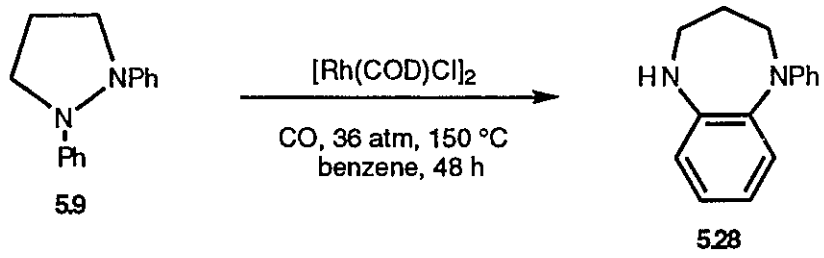
A related rearrangement was reported by Lebel et. al. for N-alkylisoxazolidine.[123] They showed that isoxazolidines isomerized to tetrahydro-1,3-oxazines when exposed to light or strong base as shown in **Scheme 5.2**.[123] It is possible that a similar pathway is also occuring in our reaction.

Scheme 5.2



5.2.3. Reaction of Pyrazolidine with Carbon Monoxide Catalyzed by Rhodium(I)

In the attempted carbonylation of 1,2-diphenylpyrazolidine (**5.9**), an unexpected product was isolated in 17% yield, which did not contain a carbonyl moiety. The ^{1}H NMR and ^{13}C spectra of (**5.28**) differ significantly from those of (**5.9**) and are in accord with the structure of 1-phenyl-[2,3-b]-benzo-1,4-diazepine (**5.28**). Signals for three non-equivalent CH_2 groups are observed in the ^{1}H NMR spectrum (**Fig 5.8**). The ^{13}C NMR spectrum shows the presence of three quaternary carbon atoms (**Fig 5.9**), and a molecular ion peak is observed in the mass spectrum which corresponds to the formula for this compound (**5.28**). The mechanism of this unusual transformation is not known.



5.9 5.28

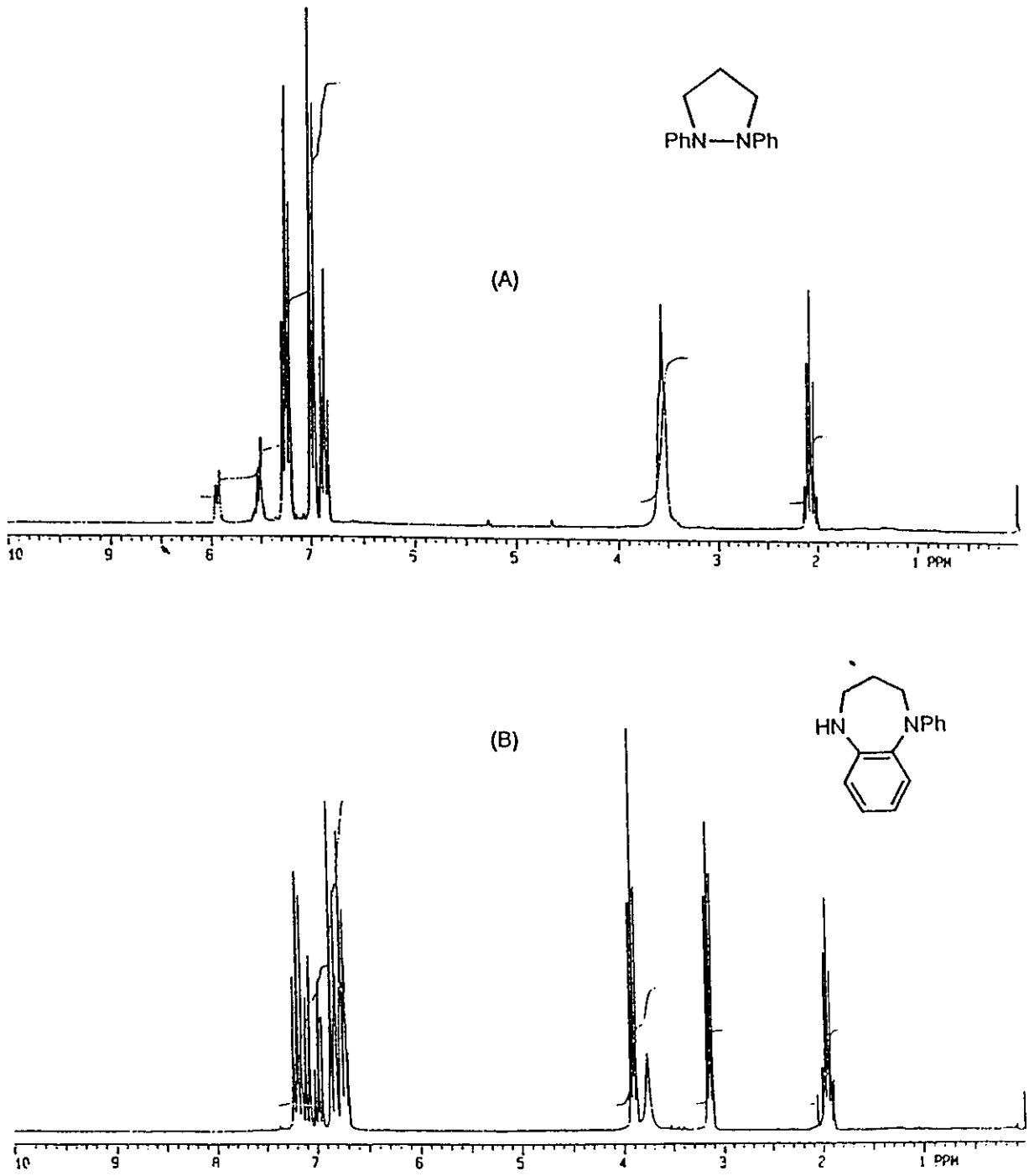


Fig. 5.8. ^{1}H NMR Spectra of 1,2-Diphenylpyrazolidine **(5.9)** (A) and 1-Phenyl-[2,3,b]-1,4-diazepin **(5.28)** (B)

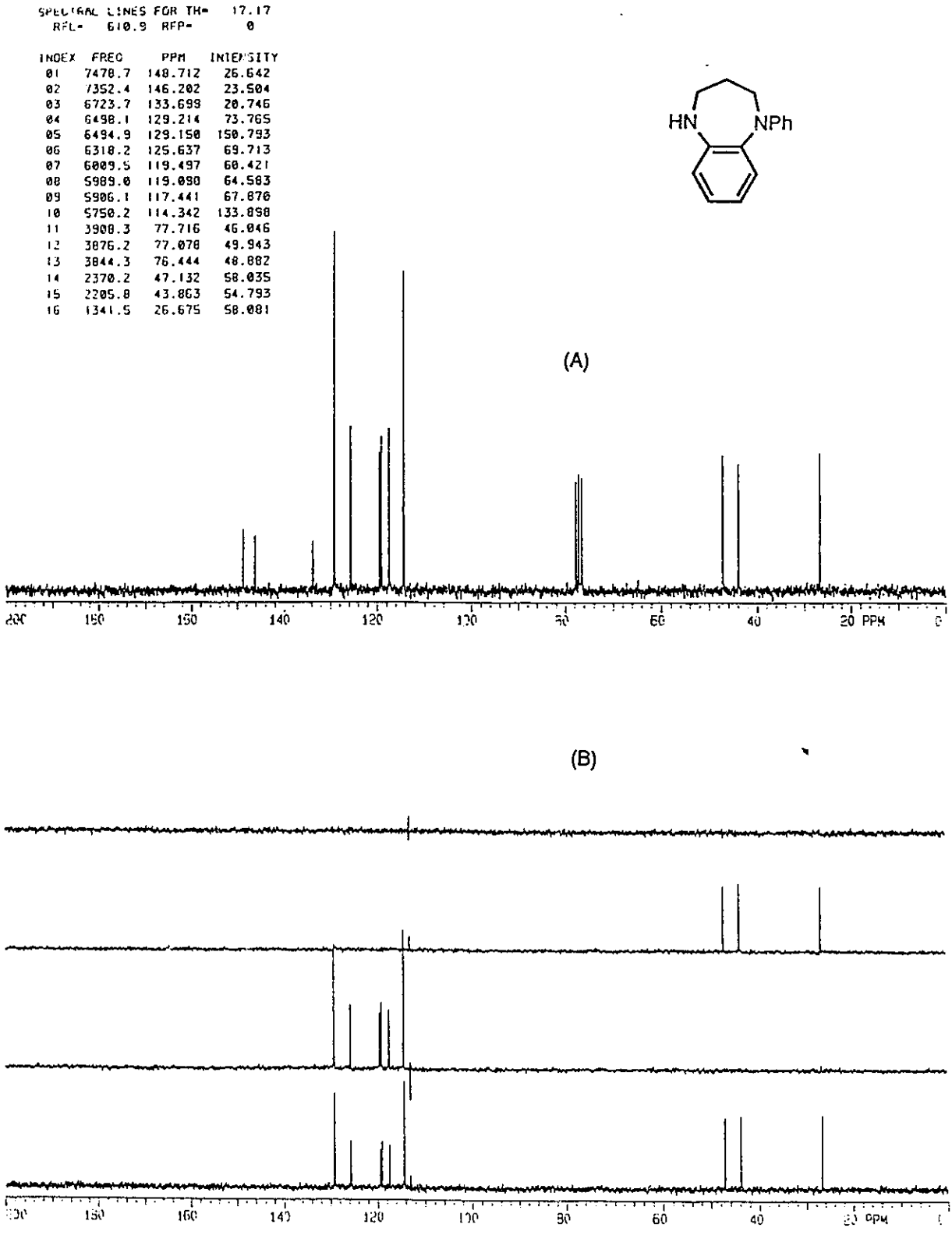
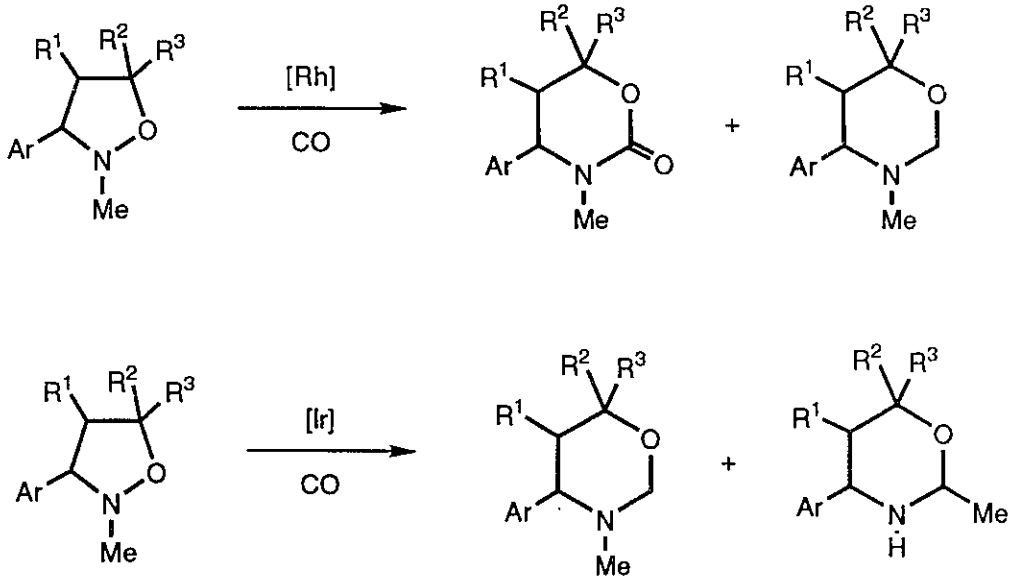
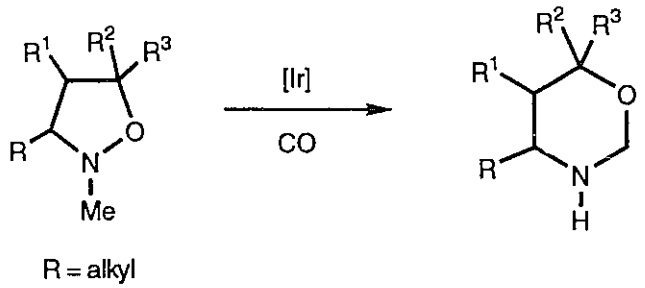


Fig. 5.9. ^{13}C NMR Spectra of 1-Phenyl-[2,3,b]-1,4-diazepin **(5.28)** (A) and DEPT (B)

5.3. Conclusion

Rhodium and iridium complex catalyzed carbonylation reactions of saturated heterocycles containing heteroatoms in the 1,2-positions proceed in both anticipated and unexpected ways. Rhodium(I) catalyses the expected insertion of carbon monoxide into isoxazolidines affording 1,3-oxazin-2-ones as the major or only product in reasonable yields. Iridium chloride is an active catalyst for the novel conversion of 3-arylisoxazolidines to isomeric 1,3-oxazines, the main product resulting from an intermolecular hydrogen transfer reaction, with a by-product formed by migration of a methyl group from nitrogen to the carbon atom arising from carbon monoxide insertion. A novel rearrangement reaction occurs for 3-alkylisoxazolidine exposed to iridium chloride.





R = alkyl

Unlike the diaziridines described by Alper et. al.,[78] the related pyrazolidines did not undergo carbonylation. Instead, an unusual ring expansion reaction was observed, in which a seven membered ring was formed.

CHAPTER 6

EXPERIMENTAL

6.1. Instrumentation

Bruker AMX 500, Varian XL 300 and Gemini 200 NMR spectrometers were used for recording ^{1}H and ^{13}C spectra. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm and referenced to residual protons in the deuterated solvents (7.24 ppm for $CDCl_3$). Chemical shifts reported upfield of zero are defined as negative.

A Bomem MB 100 FTIR spectrometer, interfaced to a NEC 286 computer was used with Bomem version 1.45 Michelson series software for all infrared analyses. The samples were run neat, or in solution.

A VG7070E spectrometer was used for mass spectral determinations. The energy of ionization was 70 eV.

A standard vacuum line equipped with a two stage Edwards pump was used for handling air and moisture sensitive materials.

Parr stainless steel autoclaves fitted with glass liners were used for all high pressure reactions. For experiments at elevated temperatures a silicone oil bath was used.

6.2. Chemicals and Solvents

All starting materials were purchased from Aldrich, Fluka, Strem Chemicals or Johnson Matthey and were used as received, unless otherwise noted. The solvents were dried, purified and distilled as described in the literature.[124]

6.3. Elemental Analysis

Elemental analyses were carried out by MHW Laboratories, Phoenix, AZ.

6.4. Catalysts

The complex $[Rh(COD)Cl]_2$ was prepared as described in the literature.[125] Dicobalt octacarbonyl and triruthenium dodecacarbonyl were purchased from Strem and Aldrich Chemical Companies, and were used as received.

EXPERIMENTAL FOR CHAPTER 2

6.5. Synthesis of Alkylating Agents

6.5.1. 2-Phenoxyethyl Bromoacetate

To a solution of 2-phenoxyethan-1-ol (1.38 g, 10 mmol) in dry benzene (10 mL) was added sodium metal (0.23 g, 10 mmol), and the mixture was stirred for 3h. The sodium salt of 2-phenoxyethan-1-ol was then added dropwise to a benzene solution of bromoacetyl bromide (4.04 g, 20 mmol). After stirring at room temperature for 2h, the reaction mixture was worked up by extraction with CH_2Cl_2 and water. The organic layer was dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to give 2.01 g (78%) of 2-phenoxyethyl bromoacetate; ^1H NMR ($CDCl_3$) δ 3.85 (s, 2H, $COCH_2Br$), 4.18 (t, 2H, $PhOCH_2$), 4.50 (t, 2H, CH_2OCO), 6.82-7.40 (m, 5H, aromatic protons). MS (m/e, relative abundance,%) 266/264 (18.4/19.0).

6.5.2. 2-(1-Adamantyloxy)ethyl Bromoacetate

The reaction was carried out with 1-adamantanemethanol using the same procedures as that for **(2.4)**. Generation of the sodium salt required refluxing the alcohol with sodium metal for 2h. Yield : 0.93 g (32%); ^{1}H NMR ($CDCl_3$) δ 1.45-2.00 (m, 15H, adamantane protons), 3.75 (s, 2H, CH_2OCO), 3.82 (s, 2H, $COCH_2Br$).

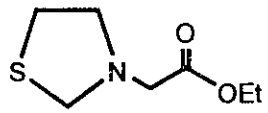
6.5.3. Methyl 3-iodopropanoate

A mixture consisting of methyl 3-bromopropanoate (8.35 g, 0.05 mol), benzene (10 mL), sodium iodide (16.6 g, 0.1 mol), water (5 mL) and tetrabutyl ammonium hydrogen sulfate (0.85 g, 2.5 mmol) was stirred magnetically at reflux temperature for 1h. The organic layer was separated, dried ($MgSO_4$), the solvent was evaporated and the residue was distilled under vacuum to give 8.4 g (79%) of methyl 3-iodopropanoate, bp. 62-64°C/0.4 mm Hg; ^{1}H NMR ($CDCl_3$) δ 2.95 (t, 2H, CH_2I), 3.30 (t, 2H, CH_2COO), 3.70 (s, 3H, OCH_3); MS (m/e) 214 [M^+].

6.6. General Procedure for the Preparation of 3-Substituted Thiazolidines (2.2-2.7).

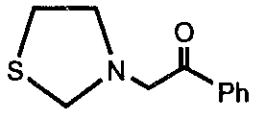
To a suspension of thiazolidine (0.89 g, 10 mmol) and potassium carbonate (1.52 g, 11 mmol) in ethanol (95%, 10 mL), was added the requisite alkylating agent as a solution in ethanol (10 mmol in 5 mL). After stirring overnight, the cloudy solution was worked up by extraction with CH_2Cl_2 and water. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel using ethyl acetate / hexanes (20/80) as the eluant to yield the thiazolidine derivatives **(2.2-2.7)** (see **Table 2.1**, Chapter 2).

6.6.1. 3-(Ethoxycarbonylmethyl)thiazolidine (2.2)



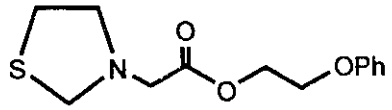
78% yield; IR (neat) ν (CO) 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (t, 3 H, CH_3CH_2O), 2.85 (t, 2H, CH_2S), 3.05 (t, 2H, CH_2N), 3.12 (s, 2H, NCH_2CO), 4.10 (s, 2H, SCH_2N), 4.18 (q, 2H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 14.02 (CH_3), 29.29 (CH_2S), 54.04 (CH_2N), 58.04 ($COCH_2N$), 60.29 (SCH_2N), 60.68 (CH_2O), 170.28 (CO); Calcd for $C_7H_{13}NO_2S$, 175.06669; HRMS, m/e 175.06491 [M^+].

6.6.2. 3-(Benzoylmethyl)thiazolidine (2.3)



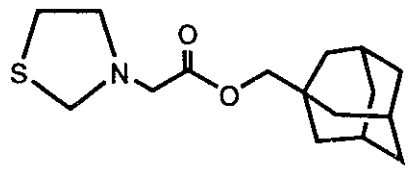
82% yield; IR (neat) ν (CO) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.95 (t, 2H, CH_2S), 3.18 (t, 2H, CH_2N), 3.90 (s, 2H, NCH_2CO), 4.18 (s, 2H, SCH_2N); 7.38-8.00 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 29.64 (CH_2S), 58.30 (CH_2N), 58.90 ($COCH_2N$), 61.38 (SCH_2N), 127.96, 128.66, 133.46, 135.65 (aromatic carbons), 195.90 (CO); CIMS, m/e 207.8 [M^++1].

6.6.3. 3-[(2-Phenoxy)ethoxycarbonyl]methylthiazolidine (2.4)



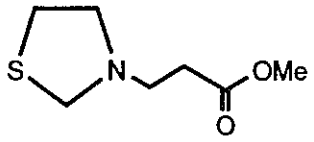
64% yield; IR (neat) ν (CO) 1742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.80 (t, 2H, CH_2S), 3.05 (t, 2H, CH_2N), 3.20 (s, 2H, NCH_2CO), 4.05 (s, 2H, SCH_2N), 4.10 (t, 2H, CH_2OPh), 4.40 (t, 2H, $COOCH_2$), 6.78-7.30 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 29.48 (CH_2S), 54.15 (CH_2N), 58.20 ($COCH_2N$), 60.89 (SCH_2N), 63.21 ($PhOCH_2$), 65.57 (CO_2CH_2), 114.51, 121.19, 129.52, 158.30 (aromatic carbons) , 170.50 (CO); Calcd for $C_{13}H_{17}NO_3S$, 267.09291; HRMS, m/e 267.09288 [M^+].

6.6.4. 3-[(1-Adamantyl)methoxycarbonyl]methylthiazolidine (2.5)



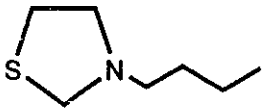
68% yield; IR (neat) ν (CO) 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45-1.95 (m, 15H, protons for 1-adamantyl), 2.85 (t, 2H, CH_2S), 3.12 (t, 2H, CH_2N), 3.22 (s, 2H, NCH_2CO), 3.70 (s, 2H, OCH_2-adamantyl), 4.13 (s, 2H, SCH_2N); ^{13}C NMR ($CDCl_3$) δ 28.00, 28.21 (CH-adamantyl), 29.59 (CH_2S), 33.21 (quaternary C-adamantyl), 36.91, 37.19, 39.05, 39.23 (CH_2-adamantyl), 54.22 (CH_2N), 58.26 ($COCH_2N$), 60.97 (CH_2O), 61.02 (SCH_2N), 170.61 (CO); Calcd for $C_{16}H_{25}NO_2S$, 295.16059; HRMS, m/e 295.16306 [M^+].

6.6.5. 3-(Methoxycarbonylethyl)thiazolidine (2.6)



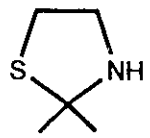
64% yield; IR (neat) ν (CO) 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.42 (t, 2H, $CH_2CO_2CH_3$), 2.65 (t, 2H, $NCH_2CH_2CO_2CH_3$), 2.85 (t, 2H, CH_2S), 3.03 (t, 2H, CH_2N), 3.68 (s, 3H, OCH_3), 4.25 (s, 2H, SCH_2N); ^{13}C NMR ($CDCl_3$) δ 30.01 (CH_2S), 34.69 ($COCH_2$), 48.96 (CH_2N side chain), 52.18 (CH_2N in ring), 58.59 (OCH_3), 60.87 (SCH_2N), 172.95 (CO); MS (m/e) 175 [M^+]

6.6.6. 3-Butylthiazolidine (2.7)[95]



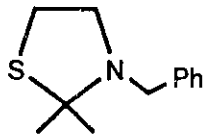
73% yield; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, $CH_3CH_2CH_2CH_2$), 1.20-1.55 (m, 4H, $CH_2CH_2CH_3$), 2.35 (t, 2H, CH_2CH_2N), 2.85 (t, 2H, CH_2S), 3.05 (t, 2H, CH_2N), 4.05 (s, 2H, SCH_2N); ^{13}C NMR ($CDCl_3$) δ 14.57 (CH_3), 21.03 (CH_2CH_3), 30.12 (CH_2S), 31.79 (CH_2CH_2N), 53.09 (CH_2N in ring), 58.59 (CH_2N), 61.60 (SCH_2N); MS (m/e) 145 [M^+].

6.6.7. 2,2-Dimethylthiazolidine (2.9)



A mixture of 2-aminoethanethiol hydrochloride (2.27 g, 20 mmol), acetone (50 mL) and potassium hydroxide (1.12 g, 20 mmol) in 100 mL of benzene was refluxed and the water was removed with a Dean-Stark apparatus. After the calculated amount of water was removed, the reaction mixture was worked up by removing the solvent and then extracting with CH_2Cl_2 and water. The organic phase was dried over $MgSO_4$, filtered and concentrated by rotary evaporation to yield 1.2 g (51%) of 2,2-dimethyl-thiazolidine. The product was purified by column chromatography using silica gel and ethyl acetate/hexane (10/90) as an eluant. ^1H NMR ($CDCl_3$) δ 1.35 (s, 6H, 2xCH_3), 2.85 (t, 2H, CH_2S), 3.13 (t, 2H, CH_2N).

6.6.8. 3-Benzyl -2,2-dimethylthiazolidine (2.10)

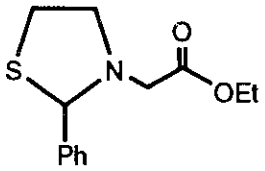


The alkylation was carried out as described above (Section 6.6). Yield 1.6 g (78%); ^1H NMR ($CDCl_3$) δ 1.60 (s, 6H, 2xCH_3), 2.95 (t, 2H, CH_2S), 3.10 (t, 2H, CH_2N), 3.62 (s, 2H, NCH_2Ph), 7.25-7.40 (m, 5H, aromatic protons); MS (m/e) 207 [M^+].

6.6.9. 2-Phenylthiazolidines (2.12, 2.13)[86] (General Procedure)

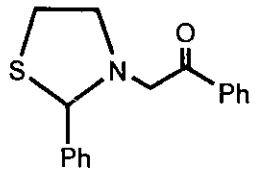
A mixture of 2-aminoethanethiol (2.27 g, 20 mmol), benzaldehyde (2.12 g, 20 mmol) and potassium hydroxide (1.12 g, 20 mmol) in 100 mL of benzene was refluxed and the water was removed with a Dean-Stark apparatus. After the calculated amount of water was removed, the reaction mixture was worked up by evaporating the solvent and then extracting with CH_2Cl_2 and water. The organic phase was dried over $MgSO_4$, filtered and concentrated by rotary evaporation to yield 84% of 2-phenylthiazolidine. The product was purified by recrystallization using CH_2Cl_2-hexane. The alkylation was carried out as described above (see Section 6.6).

6.6.9.1. 3-(Ethoxycarbonylmethyl)-2-phenylthiazolidine (2.12)



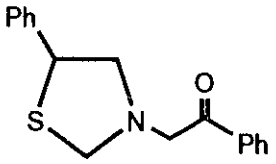
57% yield; IR (neat) ν (CO) 1737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H, CH_3CH_2O), 2.90-3.50 (m, 6H, CH_2S, CH_2N, NCH_2CO), 4.01 (s, 2H, SCH_2N) 4.25 (q, 2H, OCH_2CH_3), 5.30 (s, 1H, *CH*Ph), 7.20-7.60 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.21 (CH_3), 30.66 (CH_2S), 53.42 (CH_2N), 56.08 ($COCH_2N$), 60.72 (CH_2O), 74.75 (SCHN), 127.99, 128.18, 128.28, 140.25 (aromatic carbons) 170.46 (CO); MS (m/e) 251 [M^+].

6.6.9.2. 3-(Benzoylmethyl)-2-phenylthiazolidine (2.13)



65% yield; IR (neat) ν (CO) 1697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.95-3.20 (m, 2H, CH_2S, 1H of CH_2N), 3.30-3.42 (m, 1H of CH_2N), 3.72, 4.05 (AB system, J_{AB} 20 Hz, 2H, NCH_2CO), 5.29 (s, 1H, CHPh), 7.15-7.85 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 30.86 (CH_2S), 56.13 (CH_2N), 58.63 ($COCH_2N$), 75.92 (SCHN), 128.05, 128.17, 128.32, 128.56, 133.35, , 136.56, 140.25 (aromatic carbons), 170.46 (CO); MS (m/e) 283 [M^+].

6.6.10. 3-(Benzoylmethyl)-5-phenylthiazolidine (2.17)[87,88]



An aqueous solution of 1-phenyl-2-amino-1-ethanol (6.85 g, 50mmol) was neutralized to a methyl red end-point with 50% aqueous sulfuric acid, followed by addition of an equal volume of acid. Water was removed by heating the solution to 130°C at 10-15mm. The product was heated at 120-130 °C under reduced pressure to constant weight. The sulfate ester was then added to 300 mL of 2N NaOH at 0 °C and the mixture was slowly heated to 90 °C for 2h. The reaction mixture was then separated from solution by steam distillation to give 2-phenylaziridine in 72% yield

To a solution of 2-phenylaziridine (4.16 g, 35 mmol) in 20 mL of 95% ethanol at 0 °C was added dropwise a 37% formaldehyde solution (1.05 g, 35 mmol). The mixture was then saturated with hydrogen sulfide for 1 h., and was left stirring overnight at room temperature. The mixture was worked up by extracting with water and CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered and the solvent was removed *in vacuo* affording 5-phenylthiazolidine (37%) which was used in the next step without further purification.

The alkylation was carried out as described above (see Section 6.6) to form **(2.17)** which was purified by recrystallization from ethanol.77% yield; IR (neat) ν (CO) 1696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.01, 3.04 (dd, *J* =12.65, 9.5 Hz, 1H, CH_2N), 3.64 (dq, *J* = 12.65, 6.4, 1.9 Hz, 1H, PhCHCH_2N), 4.04, 4.22 (AB, *J* = 17.2 Hz, 2H, NCH_2CO) 4.30 (dd, *J* = 9.5, 1.9 Hz, 1H, SCH_2N), 4.66 (d, *J* = 9.5 Hz, 1H, SCH_2N), 4.68, 4.69 (dd, *J* = 9.5, 6.4 Hz, 1H, PhCHS), 7.23-8.00 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 52.34 (PhCHS), 60.13 (NCH_2CO), 63.38 (SCH_2N), 68.41 (PhCHCH_2N), 127.95, 128.47, 128.63, 129.25, 129.33, 134.17, 136.20, 141.26 (aromatic carbons), 196.43 (CO). The structure assignment is also based on HMQC, COSY, TOCSY and NOESY experiments. MS (m/e) 283 [M^+] (see Appendices).

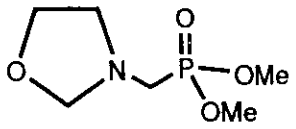
6.7. Synthesis of N-Substituted Oxazolidines (2.21, 2.22, 2.25, 2.26)

6.7.1. General Procedure for the Synthesis of 3-(Dimethyl / phenyl / phosphonylmethyl)oxazolidines[89]

Formaldehyde (40%, 20 mL) was added at room temperature to a stirred solution of requisite 2-aminoethanol (0.05 mol) and dialkylphosphite (0.06 mol) in 20 mL of methanol. The mixture was refluxed for 3h, cooled,

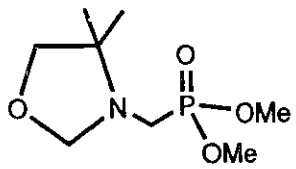
poured into water, and then extracted with diethyl ether. The organic layer was dried ($MgSO_4$) and evaporated under vacuum to give 3-(phosphinylalkyl)-oxazolidine. Compounds **(2.21)** and **(2.22)** were purified by vacumm distillation. Product **(2.25)** was purified by silica gel column chromatography using ethyl acetate / hexane (20/80) as the eluant.

6.7.1.1. 3-(Dimethylphosphonylmethyl)oxazolidine (2.21)



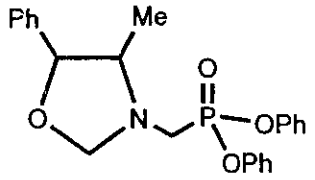
46% yield; ^1H NMR (CDCl3) δ 2.85 (d, 2H, $CH_2P{=}O$), 2.95 (t, 2H, CH_2N), 3.65 (t, 2H, CH_2O), 3.70 (d, 6H, 2xOCH_3), 4.22 (s, 2H, OCH_2N), ^{13}C NMR ($CDCl_3$) δ 47.82 (CH_2N), 51.18 (CH_2O), 52.83, 52.96 (OCH_3), 53.88, 54.37 ($NCH_2P{=}O$), 87.91, 88.18 (OCH_2N); MS (m/e) 195 [M^+].

6.7.1.2. 4,4-Dimethyl-3-(dimethylphosphonylmethyl)oxazolidine (2.22)



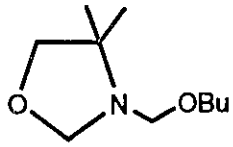
67% yield; ^1H NMR (CDCl3) δ 1.05 (s, 2H, 2x CH_3), 2.85 (d, 2H, $CH_2P{=}O$), 3.60 (t, 2H, CH_2O), 3.75 (d, 6H, 2xOCH_3), 4.50 (s, 2H, OCH_2N), ^{13}C NMR ($CDCl_3$) δ 20.81 (2xCH_3), 42.92 (CH_2O), 52.96, 54.00 (OCH_3), 59.94, 60.27 ($NCH_2P{=}O$), 78.08 ($NC(CH_3)_2$), 85.33 (OCH_2N), MS (m/e) 223 [M^+].

6.7.1.3. 3-(Diphenylphosphonylmethyl)-4-methyl-5-phenyloxazolidine (2.25)



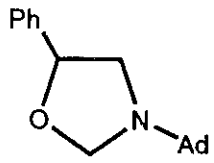
37% yield; ^{1}H NMR (CDCl3) δ 0.98 (d, 3H, CH_3), 3.12-3.54 (m, 3H, CH_2P=O, NC*H*CH_3), 4.38 (d, 1H, NCH_2O), 5.08 (d, 1H, NCH_2O), 5.11 (d, 1H, O*CH*Ph), 7.10-7.40 (m, 15H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.51 (CH_3), 46.53, 49.92 (NCH_2P=O), 63.47, 63.75 (*CH*CH_3), 80.54 (O*CH*Ph), 87.24, 87.39 (OCH_2N), 120.57, 120.65, 125.31, 126.69, 127.46, 128.05, 129.78, 139.09, 150.11, 150.28 (aromatic carbons); MS (m/e) 409 [M^+].

6.7.2. 3-(Butoxymethyl)-4,4-dimethyloxazolidine (2.26)[90]



To a mixture of 1-butanol (7.4 g, 0.1 mol), paraformaldehyde (6.0 g, 0.2 mol) and benzene (40 mL) was added dropwise 8.9 g (0.1 mol) of 2-amino-2-methyl-1-propanol. The mixture was refluxed and water removed as an azeotrope using a Dean-Stark trap. After removal of the theoretical amount of water, the solvent were removed by vacuum and the remaining crude oil was distilled under high vacuum. 92% yield; ^{1}H NMR (CDCl3) δ 0.75 (t, 3H, CH_2CH_3), 1.05 (s, 6H, 2xCH_3), 1.15-1.50 (m, 4H, $CH_2CH_2CH_3$), 3.20 (t, 2H, OCH_2), 3.38 (s, 2H, OCH_2), 4.05 (s, 2H, NCH_2O), 4.50 (s, 2H, OCH_2N in ring)

6.7.3. 3-(1-Adamantyl)-5-phenyloxazolidine (2.28)

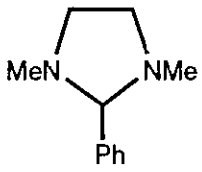


A mixture of aminoalcohol[91] **(2.27)** (2.71 g, 10 mmol) and paraformaldehyde (3.3 g, 11 mmol) in benzene (100 mL) was heated for 3h under reflux and the water formed was removed using a Dean-Stark trap. Evaporation of the solvent followed by column chromatography on silica gel using 20/80 ethyl acetate / hexanes as the eluant gave 2.2 g (78%) of the product. IR (neat) (CO) cm^{-1}; ^1H NMR (CDCl3) δ 1.50–2.25 (m, 15H, adamantane protons), 2.78 (t, 1H, NCH_2), 3.48 (dd, 1H, NCH_2), 4.75 (dd, 2H, OCH_2N), 4.95 (m, 1H, OCHPh), 7.2-7.6 (m, 5H, aromatic protons); MS (m/e) 283 [M^+].

6.8. Preparation of 1,3-Dimethyl-2-Substituted Imidazolidines (2.33-2.35). (General Procedure)

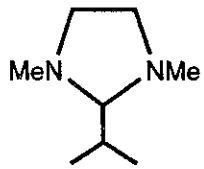
A mixture of N,N'-dimethylethylene diamine (1.76 g, 20 mmol) and the corresponding aldehyde (20 mmol) in 100 mL of benzene was refluxed for 3h and the water was removed with a Dean-Stark apparatus. After the calculated amount of water was removed, the reaction mixture was worked up by evaporating the solvent and then extracting with methylene chloride and water. The organic phase was dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by vacuum distillation to yield the 1,3-dimethyl-2-substituted imidazolidines.

6.8.1. 1,3-Dimethyl-2-phenylimidazolidine (2.33)[92]



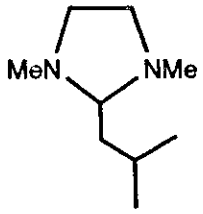
88% yield; ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H, CH_3N), 2.50 (m, 2H, CH_2N), 3.20 (m, 1H, N*CH*N), 3.35 (m, 2H, CH_2N), 7.2-7.5 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 39.46 (NCH_3), 53.29 (CH_2N), 92.39 (NCHN), 128.19, 128.45, 128.78, 139.70 (aromatic carbons); MS, m/e 176 [M^+] (see Appendices for ^{1}H NMR and the three bond coupling spectra).

6.8.2. 1,3-Dimethyl-2-isopropylimidazolidine (2.34)[93]



91% yield; ^{1}H NMR ($CDCl_3$) δ 0.74 (d, 6H, 2xCH_3CH), 1.50-1.60 (m, 2H, $CH(CH_3)_2$), 2.21 (s, 6H, NCH_3), 2.34 (m, 3H, CH_2N), 2.82 (m, 2H, CH_2N, N*CH*N); MS, m/e 142 [M^+].

6.8.3. 1,3-Dimethyl-2-isobutylimidazolidine (2.35)



78% yield; ^{1}H NMR ($CDCl_3$) δ 0.80 (d, 6H, 2xCH_3CH), 1.25 (m, 1H, CH_2(CH)), 1.65 (m, 1H, $CH(CH_3)_2$), 2.22 (s, 6H, NCH_3), 2.33 (m, 2H, CH_2N), 2.50 (m, 1H, CH_2N), 2.95 (m, 2H, CH_2N, NCHN); ^{13}C NMR ($CDCl_3$) δ 23.27 (CH_3), 24.83 ($CH$$CH_2$), 41.08 ($NCH_3$), 42.07 ($CHCH_2$), 53.15 ($CH_2N$), 86.83 (NCHN); MS, m/e 156 [M^+].

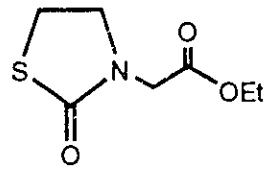
6.9. Carbonylation of Thiazolidines and Related Compounds

6.9.1. General Procedure for the Carbonylation of N-Substituted Thiazolidines (2.2-2.7, 2.45, 2.46, 2.51-2.53, 2.57, 2.61)

A mixture of the thiazolidine (5 mmol), $[Rh(COD)Cl]_2$ (0.025 g, 0.05 mmol), potassium iodide (if used) (0.017 g, 0.10 mmol) and benzene (10 mL) was placed in an autoclave containing a glass liner and stirring bar. The autoclave was purged several times with carbon monoxide and pressurized to 65 atm. The reaction mixture was stirred at 160-180 °C for 48h (96h for (**2.7**)). The reaction was then cooled to room temperature, filtered through acidic alumina using CH_2Cl_2 and then ethyl acetate as eluant. The more polar fraction (containing the product) was purified by preparative thin-layer chromatography using 30% ethyl acetate in hexane as the developer.

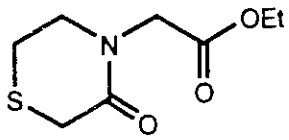
The carbonylation of **(2.45)** was carried out following the general procedure except for a reaction time of 24h in this case. After work up, **(2.39)** was obtained in quantitative yield.

6.9.1.1. 3-(Ethoxycarbonylmethyl)thiazolidin-2-one (2.39)



80% yield (with KI), 30% yield (without KI); IR (neat) ν (CO) 1738, 1671 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H, CH_3CH_2O), 3.25 (t, 2H, CH_2S), 3.70 (t, 2H, CH_2N), 4.02 (s, 2H, NCH_2CO), 4.15 (q, 2H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 14.06 (CH_3), 25.69 (CH_2S), 45.68 (CH_2N), 48.81 ($COCH_2N$), 61.41 (CH_2O), 168.15 (COOEt), 172.93 (SCON); MS (m/e) 189 [M^+]. Anal. Calcd for $C_7H_{11}NO_3S$: C, 44.44; H, 5.82; N, 7.4. Found: C, 44.71; H, 6.02; N, 7.30.

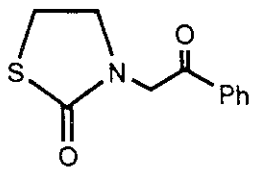
6.9.1.2. 4-(Ethoxycarbonylmethyl)-1,4-thiazin-3-one (2.45)



28% yield; IR (neat) ν(CO) 1738, 1653 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H, CH_3CH_2O), 2.89 (t, 2H, CH_2S), 3.32 (s, 2H, SCH_2CO), 3.65 (t, 2H, CH_2N), 4.12 (s, 2H, NCH_2CO), 4.15 (q, 2H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 14.07 (CH_3), 26.07 (CH_2S), 30.11 (SCH_2CO), 49.25 (CH_2N), 50.75 ($COCH_2N$), 61.32

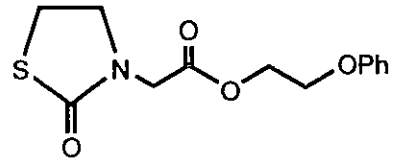
(CH_2O), 166.79 (COOEt), 168.83 (CON); MS (m/e) 203 [M^+]. Anal. Calcd for $C_8H_{13}NO_3S$: C, 47.29; H, 6.40; N, 6.89. Found: C, 47.57; H, 6.33; N, 6.49.

6.9.1.3. 3-(Benzoylmethyl)thiazolidin-2-one (2.40)



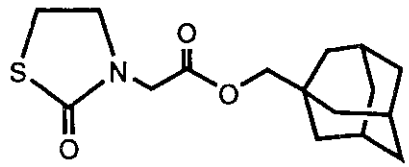
82% yield (with KI), 65% yield (without KI); IR (neat) ν (CO) 1696, 1667 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.35 (t, 2H, CH_2S), 3.75 (t, 2H, CH_2N), 4.75 (s, 2H, NCH_2CO), 7.38-7.95 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 25.93 (CH_2S), 49.01 (CH_2N), 50.72 ($COCH_2N$), 127.98, 128.87, 133.95, 134.63 (aromatic carbons), 173.05 (SCON), 195.90 (CO); MS (m/e) 221 [M^+]. Anal. Calcd for $C_{11}H_{11}NO_2S$: C, 59.73; H, 4.98; N, 6.33. Found: C, 59.45; H, 5.17; N, 5.99. For X-ray crystallography data see **Fig 2.2** (Chapter 2) and Appendices.

6.9.1.4. 3-[(2-Phenoxy)ethoxycarbonyl]methylthiazolidin-2-one (2.41)



70% yield; IR (neat) ν (CO) 1744, 1667 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.29 (t, 2H, CH_2S), 3.71 (t, 2H, CH_2N), 4.10 (s, 2H, NCH_2CO), 4.18 (t, 2H, CH_2OPh), 4.47 (t, 2H, $COOCH_2$), 6.82-7.32 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 25.70 (CH_2S), 45.63 (CH_2N), 48.76 ($COCH_2N$), 63.70 ($PhOCH_2$), 65.45 (CO_2CH_2), 114.51, 121.28, 129.52, 158.23 (aromatic carbons), 168.15 (CO), 173.03 (SCON); MS (m/e) 281 [M^+]. Anal. Calcd for $C_{13}H_{15}NO_4S$: C, 55.52; H, 5.34; N, 4.98. Found: C, 55.37; H, 5.44; N, 5.03.

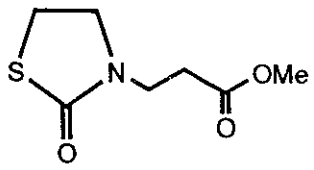
6.9.1.5. 3-[(1-Adamantyl)methoxycarbonyl]methylthiazolidin-2-one (2.42)



68% yield; IR (neat) ν (CO) 1740, 1672 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50-1.95 (m, 15H, protons for 1-adamantyl), 3.30 (t, 2H, CH_2S), 3.70 (s, 2H, OCH_2-adamantyl), 3.72 (t, 2H, CH_2N), 4.10 (s, 2H, NCH_2CO); ^{13}C NMR ($CDCl_3$) δ 25.71 (CH_2S), 27.87, 28.11, 28,30 (CH-adamantyl), 33.06 (quaternary C-adamantyl), 36.79, 38.96, 39.10, (CH_2-adamantyl), 45.71 (CH_2N), 48.90 ($COCH_2N$), 73.77 (CH_2O), 168.34 (CO), 172.70 (SCON); MS (m/e) 309 [M^+].

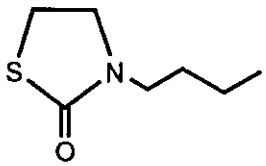
Anal. Calcd for $C_{16}H_{23}NO_3S$: C, 62.13; H, 7.44; N, 4.53. Found: C, 61.98; H, 7.48; N, 4.27.

6.9.1.6. 3-(Methoxycarbonylethyl)thiazolidin-2-one (2.43)



56% yield (without KI); IR (neat) ν (CO) 1734, 1666 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60 (t, 2H, $CH_2CO_2CH_3$), 3.25 (t, 2H, CH_2S), 3.58 (t, 2H, $NCH_2CH_2CO_2CH_3$), 3.65 (t, 2H, CH_2N), 3.70 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 26.56 (CH_2S), 33.14 (CH_2CO), 41.37 (CH_2N side chain), 49.96 (CH_2N in ring), 52.53 (OCH_3), 172.71 ($COOCH_3$), 172.90 (SCON); MS (m/e) 189 [M^+]. Anal. Calcd for $C_7H_{11}NO_3S$: C, 44.44; H, 5.82; N, 7.41. Found: C, 44.38; H, 5.85; N, 7.71 (see Appendices for ^1H NMR spectra).

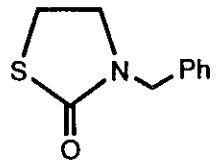
6.9.1.7. 3-Butylthiazolidin-2-one (2.44)[95]



88% yield; IR (neat) ν (CO) 1662 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, $CH_3CH_2CH_2CH_2$), 1.25-1.60 (m, 4H, $CH_2CH_2CH_3$), 3.25 (m, 4H, CH_2CH_2N and CH_2S), 3.58 (t, 2H, CH_2N); ^{13}C NMR ($CDCl_3$) δ 13.71 (CH_3), 19.92

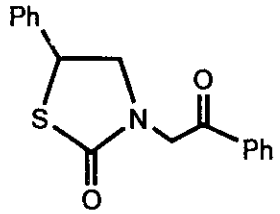
(CH_2CH_3), 25.67 (CH_2S), 29.53 (NCH_2CH_2), 44.58 (NCH_2 in ring), 48.51 (NCH_2), 171.68 (CO); MS (m/e) 159 [M^+].

6.9.1.8. 3-Benzylthiazolidin-2-one (2.47)



86% yield; IR (neat) ν (CO) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.28 (t, 1H, CH_2S), 3.49 (t, 2H, CH_2N), 4.45 (s, 2H, NCH_2Ph), 7.28-7.50 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 26.09 (CH_2S), 48.55 (NCH_2), 49.23 (NCH_2Ph), 128.46, 128.71, 129.41, 136.60 (aromatic carbons), 172.81 (CO); MS (m/e) 193 [M^+]. Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.18; H, 5.70; N, 7.25. Found: C, 62.05; H, 6.13; N, 7.31.

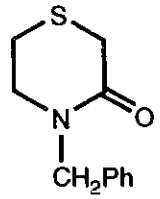
6.9.1.9. 3-(Benzoylmethyl)-5-phenylthiazolidin-2-one (2.54)



72% yield (with KI), 44% yield (without KI); IR (neat) ν (CO) 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.79 (dd, 1H, CH_2N), 4.01 (m, 1H, CH_2N), 4.82 (dd, 2H, NCH_2CO), 4.95 (dd, 1H, PhCHS), 7.15-8.00 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 46.69 (PhCHS), 51.31 ($PhCHCH_2N$), 57.32 (NCH_2CO), 128.22, 128.62, 129.01, 129.53, 129.58, 134.62, 135.23, 139.51 (aromatic carbons), 173.04

(SCON), 193.82 (CO). MS (m/e) 297 [M^+]. Anal. Calcd for $C_{17}H_{15}NO_2S$: C, 68.69; H, 5.05; N, 4.71. Found: C, 68.71; H, 4.81; N, 4.63.

6.10. N-Benzyl-1,4-thiazin-3-one (2.56).



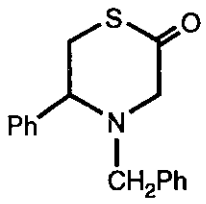
To a solution of 2-aminoethanethiol hydrochloride (1.13 g, 10 mmol) and potassium hydroxide (1.12 g, 20 mmol) in ethanol (95%, 20 mL) was added ethyl bromoacetate (1.84 g, 11 mmol) in ethanol (10 mL). The solution was left stirring overnight at room temperature. The reaction was then extracted with 2N HCl and CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield 1,4-thiazin-3-one **(2.55)** (84%). The crude product was used in the next step without further purification.

To the solution of **(2.55)** (0.59 g, 0.5 mmol) in dried THF (10 mL) was added sodium hydride (80% in mineral oil, 0.01 g, 0.5 mmol). After stirring at room temperature for 0.5h, benzyl bromide was then added to the solution (0.09 g, 0.5 mmol) in dried THF (5 mL). The reaction mixture was stirred for 3h, and then worked up by extraction with CH_2Cl_2 and water. The organic layer was dried and the solvent was removed under vacuum. Purification by column chromatography using silica gel yielded **(2.56)** in 74% yield. ^{1}H NMR ($CDCl_3$) δ 2.75 (t, 2H, CH_2S), 3.37 (s, 2H, COCH_2S), 3.52 (t, 2H, CH_2CH_2N), 4.63 (s, 2H, NCH_2Ph), 7.20-7.42 (m, 5H, aromatic protons), ^{13}C NMR ($CDCl_3$) δ 26.98 (CH_2S), 31.04 (COCH_2S), 49.19 (CH_2N), 51.29 (NCH_2Ph), 128.25, 128.62,

129.33, 137.33 (aromatic carbons); MS (m/e) 207 [M^+]. Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.77; H, 6.28; N, 6.76. Found: C, 63.72; H, 6.44; N, 7.01.

The carbonylation of **(2.56)** was carried out and worked up according to the general procedure described above (24 h reaction time) affording **(2.47)** in 86% yield.

6.11. 4-Benzyl-5-phenyl-1,4-thiazin-2-one (2.60)



2-Phenylthiirane was prepared as described in the literature.[97] To the solution of 2-phenylthiirane (2.72 g, 20 mmol) in ethanol (95%, 20 mL) was added dropwise HBr in acetic acid (30% wt, 6.5 g, 22 mmol) at 0 °C. After stirring at room temperature for 4h, the reaction mixture was extracted with CH_2Cl_2 and saturated $NaHCO_3$ solution, then water. The organic layer, after drying ($MgSO_4$) and removing the solvent under *vacuo*, yielded the crude product **(2.58)** (78%). This product was used in the next step without further purification.

To the solution of bromothiol **(2.58)** (2.17 g, 10 mmol) in dry THF (20 mL) was added sodium hydride (80% in mineral oil, 0.2 g, 10 mmol). The reaction mixture was left stirring at room temperature for 1h. To the solution of bromoacetyl bromide (4.02 g, 20 mmol) in dry benzene (10 mL) was added, drop by drop, 10 mmol of sodium thiolate. The reaction mixture was stirred for 3h and then worked up by extraction with CH_2Cl_2, saturated $NaHCO_3$ solution, followed by water. After drying ($MgSO_4$) and removing the solvent,

the dibromo compound **(2.59)** was obtained in 55% yield. ^{1}H NMR ($CDCl_3$) δ 3.75-3.90 (m, 2H, *CH_2*S), 4.02 (s, 2H, CO*CH_2*Br), 5.10 (dd, 1H, Ph*CH*Br), 7.28-7.55 (m, 5H, aromatic protons). ^{13}C NMR ($CDCl_3$) δ 33.96 (CH_2S), 39.17 (CO*CH_2*Br), 51.73 (Ph*CH*Br), 128.18, 129.52, 129.71, 140.26 (aromatic carbons), 192.11 (CO).

To the mixture of dibromo compound **(2.59)** (0.68 g, 2 mmol) and potassium carbonate (0.28 g, 2 mmol) in ethanol 10 mL was added benzylamine (0.11 g, 1 mmol) in 5 mL of ethanol. The reaction mixture was stirred at room temperature overnight, then worked up by extraction with CH_2Cl_2 and water. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo* to form 62.5 mg (22%) of **(2.60)**. ^{1}H NMR ($CDCl_3$) δ 2.72, 2.85 (AB, 2H, *CH_2*S), 3.32 (s, 2H, CO*CH_2*N), 3.85 (s, 2H, N*CH_2*Ph), 4.45 (m, 1H, Ph*CH*Br), 7.15-7.45 (m, 10H, aromatic protons). ^{13}C NMR ($CDCl_3$) δ 33.86 (CH_2S), 40.19 (N*CH_2*Ph), 43.89 (N*CH_2*CO), 59.98 (Ph*CH*N), 128.96, 129.08, 129.11, 129.18, 129.40, 129.51, 130.05, 130.19, 139.18 (aromatic carbons), 201.55 (CO). MS (m/e) 283 [M^+]. Anal. Calcd for $C_{17}H_{17}NOS$: C, 72.08; H, 6.01; N, 4.95. Found: C, 72.40; H, 5.75; N, 4.59.

6.12. Carbonylation of Oxazolidines (2.21, 2.22, 2.25, 2.26, 2.28), Imidazolidines (2.33-2.35) (General Procedure)

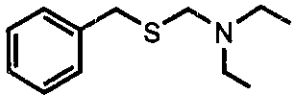
Reactions of the title compounds with carbon monoxide were carried out as described for N-substituted thiazolidines (see Section **6.10.1**) at 130 °C and 36 atm of CO for 48 h. In all cases starting materials were recovered unchanged.

EXPERIMENTAL FOR CHAPTER 3

6.13. General Procedure for the Preparation of N,S-Acetals (3.3-3.9, 3.10-3.18).[100]

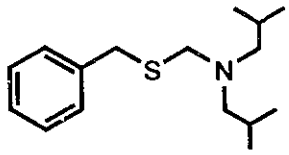
To the thiol (10 mmol), was added the amine (10 mmol). An exothermic reaction commenced immediately with the solution temperature rising to 65 °C. The aldehyde (40% aq. formaldehyde or neat benzaldehyde) was introduced in one portion into the reaction mixture (10 mmol) and the reaction was then refluxed for 15 min (1h in the case of benzaldehyde). After cooling, the reaction mixture was washed with 10% NaOH and CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by distillation under reduced pressure. In the cases where benzaldehyde was employed, the crude products were used in the next step without distillation due to decomposition resulting from the distillation.

6.13.1. N-(Benzylthio)methyl-N,N-diethylamine (3.3)



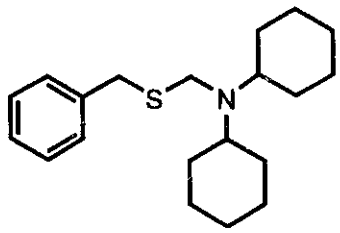
92% yield; ^1H NMR ($CDCl_3$) δ 1.05 (t, 6H, 2xCH_3CH_2), 2.58 (q, 4H, 2xCH_2CH_3), 3.75 (s, 2H, PhCH_2S), 4.10 (s, 2H, SCH_2N), 7.13-7.47 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 13.32 (CH_3), 37.09 ($PhCH_2S$), 46.92 (NCH_2CH_3), 58.20 (SCH_2N), 127.47, 128.99, 129.05, 129.36, 129.42, 139.76 (aromatic carbons); MS, m/e 209 [M^+].

6.13.2. N-(Benzylthio)methyl-N,N-diisobutylamine (3.4)



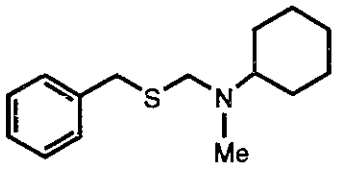
98% yield; ^{1}H NMR ($CDCl_3$) δ 0.87 (d, 12H, 4xCH_3CH), 1.63 (m, 2H, 2xCH(CH_3)$_2$), 2.24 (d, 4H, 2xCH_2CH), 3.75 (s, 2H, PhCH_2S), 4.05 (s, 2H, SCH_2N), 7.20-7.44 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 20.74 (CH_3), 26.13 (CH(CH_3)$_2$), 36.73 (PhCH$_2$S), 60.49 (NCH_2CH), 61.76 (SCH$_2$N), 126.80, 128.42, 128.77, 139.36 (aromatic carbons); MS, m/e 265 [M$^+$].

6.13.3. N-(Benzylthio)methyl-N,N-dicyclohexylamine (3.5)



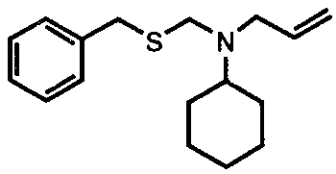
73% yield; ^{1}H NMR ($CDCl_3$) δ 1.10-1.90 (m, 20H, 2xcyclohexyl protons), 2.65 (m, 2H, 2xNCH), 3.75 (s, 2H, PhCH_2S), 4.15 (s, 2H, SCH_2N), 7.14-7.40 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 25.93, 26.64, 26.82, 26.93, 32.95 (cyclohexyl carbons), 36.14 (PhCH$_2$S), 54.57 (NCH), 57.95 (SCH$_2$N), 127.16, 128.94, 129.42, 140.15 (aromatic carbons); MS, m/e 317 [M$^+$].

6.13.4. N-(Benzylthio)methyl-N-cyclohexyl-N-methylamine (3.6)



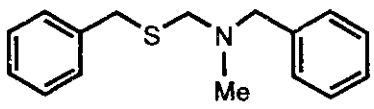
80% yield; ^{1}H NMR ($CDCl_3$) δ 1.10-1.90 (m, 10H, cyclohexyl protons), 2.35 (s, 3H, N*CH*$_3$), 2.45 (m, 1H, N*CH*), 3.75 (s, 2H, Ph*CH*$_2$S), 3.97 (s, 2H, S*CH*$_2$N), 7.25-7.35 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 26.16, 26.66, 30.67 (cyclohexyl carbons), 36.69 ($PhCH_2S$), 37.81 (NCH_3), 59.95 (NCH), 61.27 (SCH_2N), 127.37, 128.99, 129.47, 139.79 (aromatic carbons); MS, m/e 249 [M^+].

6.13.5. N-Allyl-N-(benzylthio)methyl-N-cyclohexylamine (3.7)



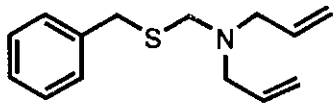
80% yield; ^{1}H NMR ($CDCl_3$) δ 1.10-1.90 (m, 10H, cyclohexyl protons), 2.58 (m, 1H, N*CH*), 3.28 (d, 2H, N*CH*$_2$CH=CH_2), 3.70 (s, 2H, Ph*CH*$_2$S), 4.04 (s, 2H, S*CH*$_2$N), 5.10-5.30 (ABC, 2H, *CH*$_2$=CH), 5.80 (ABC, 1H, *CH*=CH_2), 7.15-7.40 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 26.50, 26.73, 31.24 (cyclohexyl carbons), 36.59 ($PhCH_2S$), 52.28 (N*CH*$_2$CH=CH_2), 56.77 (NCH), 60.57 (SCH_2N), 117.38 (*CH*$_2$=CH), 127.32, 128.99, 129.41, 137.51, 139.94 (aromatic carbons and *CH*=CH_2); MS, m/e 275 [M^+].

6.13.6. N-Benzyl-N-(benzylthio)methyl-N-methylamine (3.8)



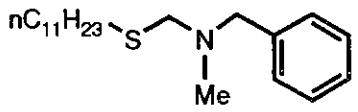
84% yield; ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H, N*CH*$_3$), 3.65 (s, 2H, N*CH*$_2$Ph), 3.75 (s, 2H, Ph*CH*$_2$S), 3.92 (s, 2H, S*CH*$_2$N), 7.20-7.40 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 36.70 ($PhCH_2S$), 40.88 (NCH_3), 59.19 (NCH_2Ph), 61.02 (SCH_2N), 126.88, 127.17, 128.37, 128.47, 128.91, 129.03, 138.48, 138.98 (aromatic carbons); MS, m/e 257 [M^+]

6.13.7. N-(Benzylthio)methyl-N,N-diallylamine (3.9)



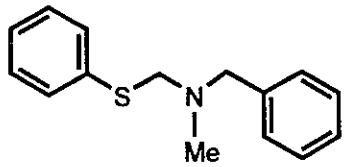
76% yield; ^{1}H NMR ($CDCl_3$) δ 3.28 (d, 4H, N*CH*$_2$CH=CH_2), 3.75 (s, 2H, Ph*CH*$_2$S), 4.02 (s, 2H, S*CH*$_2$N), 5.10-5.30 (ABC, 4H, *CH*$_2$=CH), 5.70-5.90 (ABC, 2H, *CH*=CH_2), 7.15-7.45 (m, 5H, aromatic protons); CIMS, m/e 234 [M^++1].

6.13.8. N-Benzyl-N-methyl-N-(undecylthio)methylamine (3.10)



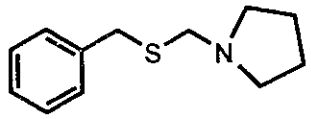
74% yield; ^{1}H NMR ($CDCl_3$) δ 0.85 (2d, 3H, CH_3), 1.23 (br s, 17H, CH_2), 1.55 (m, 2H, CH_2), 2.26 (d, 3H, N*CH*$_3$) 2.53 (m, 2H, S*CH*$_2$), 3.63 (s, 2H, $PhCH_2N$), 3.97 (s, 2H, S*CH*$_2$N), 7.38 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.17 (CH_3), 22.73, 28.97, 29.29, 29.38, 29.58, 29.65, 30.57, 31.95 (CH_2), 33.47 (SCH_2), 40.81 (NCH_3), 59.04 ($PhCH_2N$), 62.36 (NCH_2S), 127.11, 128.28, 129.01, 138.51 (aromatic carbons); MS, m/e 321 [M$^+$].

6.13.9. N-Benzyl-N-methyl-N-(phenylthio)methylamine (3.11)



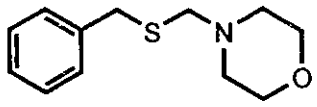
68% yield; ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H, N*CH*$_3$), 3.68 (s, 2H, N*CH*$_2$Ph), 4.53 (s, 2H, S*CH*$_2$N), 7.20-7.55 (m, 10H, aromatic protons); MS, m/e 243 [M$^+$].

6.13.10. 1-[(Benzylthio)methyl]pyrrolidine (3.12)



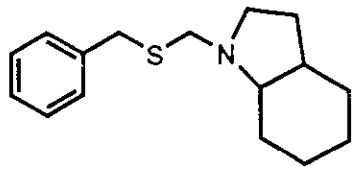
80% yield; ^{1}H NMR ($CDCl_3$) δ 1.78 (m, 4H, 2xCH_2CH_2N), 2.66 (m, 4H, 2xNCH_2CH_2), 3.75 (s, 2H, $PhCH_2S$), 3.97 (s, 2H, SCH_2N), 7.20-7.40 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 24.51 (CH_2CH_2N), 37.67 ($PhCH_2S$), 51.55 (NCH_2CH_2), 58.28 (SCH_2N), 127.47, 129.04, 129.25, 129.54, 139.58 (aromatic carbons); MS, m/e 207 [M^+].

6.13.11. 1-[(Benzylthio)methyl]morpholine (3.13)



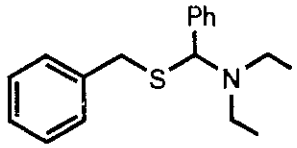
82% yield; ^{1}H NMR ($CDCl_3$) δ 2.55 (m, 4H, 2xNCH_2CH_2O), 3.70 (m, 6H, 2xOCH_2CH_2N, $PhCH_2S$), 3.80 (s, 2H, SCH_2N), 7.20-7.45 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 36.80 (NCH_2CH_2O), 51.87 ($PhCH_2S$), 61.69 (SCH_2N), 67.54 (OCH_2CH_2N), 127.55, 129.05, 129.21, 129.62, 139.22 (aromatic carbons); MS, m/e 223 [M^+].

6.13.12. 1-[(Benzylthio)methyl]perhydroindoline (3.14)



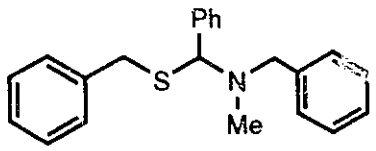
80% yield; ^{1}H NMR ($CDCl_3$) δ 1.10-2.00 (m, 11H,*CH_2*, *CH* of saturated ring), 2.70 (m, 2H, N*CH_2* ring), 2.96 (m, 1H, N*CH* ring), 3.75 (s, 2H, Ph*CH_2*S), 4.10 (s, 2H, S*CH_2*N), 7.20-7.40 (m, 5H, aromatic protons); MS, m/e 261 [M^+].

6.13.13. N-(Benzylthio)(phenyl)methyl-N,N-diethylamine (3.15)



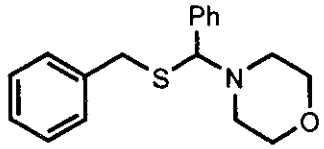
89% yield; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 6H, 2xCH_3), 2.60 (q, 4H, 2xCH_2), 3.65 (AB, 2H, Ph*CH_2*S), 5.10 (s, 1H, S*CH*(Ph)N), 7.10-7.80 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.32 (CH_3), 36.34 ($PhCH_2S$), 44.41 (NCH_2), 73.43 (SCH(Ph)N), 127.46, 127.97, 128.68, 128.95, 128.99, 129.56, 129.63, 129.68, 139.57, 140.51 (aromatic carbons); MS, m/e 285 [M^+].

6.13.14. N-Benzyl-N-[(benzylthio)(phenyl)]methyl-N-methylamine (3.16)



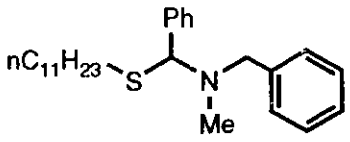
68% yield; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H, NC*H*$_3$), 3.75 (m, 4H, 2x*C*H_2Ph), 5.10 (s, 1H, S*CH*(Ph)N), 7.20-7.70 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 36.39 ($PhCH_2S$), 38.15 (NCH_3), 58.66 (NCH_2Ph), 75.62 (SCH(Ph)N), 127.59, 127.69, 128.35, 128.82, 129.02, 129.12, 129.30, 129.36, 129.50, 129.62, 139.21, 139.40, 139.85 (aromatic carbons); MS, m/e 333 [M^+].

6.13.15. N-[(Benzylthio)(phenyl)]methylmorpholine (3.17)



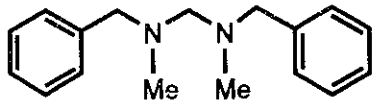
78% yield; ^{1}H NMR ($CDCl_3$) δ 2.58 (m, 4H, 2x*C*H_2N), 3.52-3.88 (m, 6H, 2x*C*H_2O, *C*H_2S), 4.68 (s, 1H, S*CH*(Ph)N), 7.18-7.50 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 36.04 ($PhCH_2S$), 49.99 (NCH_2), 67.69 (CH_2O), 75.07 (SCH(Ph)N), 127.55, 128.51, 128.64, 128.76, 129.02, 129.34, 129.62, 137.79, 139.10 (aromatic carbons); MS, m/e 299 [M^+].

6.13.16. N-Benzyl-N-methyl-N-[(n-undecylthio)(phenyl)]methylamine (3.18)



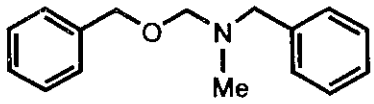
82% yield; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3H, CH_3), 1.24 (br s, 18H, CH_2), 1.53 (m, 1H, CH_2), 2.20 (s, 3H, N*CH*$_3$), 2.48 (m, 2H, S*CH*$_2$), 3.70 (AB, 2H, Ph*CH*$_2$N), 5.05 (s, 1H, S*CH*Ph), 7.20-7.65 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.77 (CH_3), 23.32, 29.62, 29.71, 29.34, 29.85, 29.97, 30.16, 30.24, 30.40, 30.75, 32.55 (CH_2), 38.07 (NCH_3), 58.71 (NCH_2Ph), 76.47 (SCH(Ph)N), 127.63, 128,09, 128.63, 128.78, 128.90, 129.44, 129.59, 139.86, 139.92 (aromatic carbons); MS, m/e 397 [M^+].

6.14. Bis(N-benzyl-N-methyl)methylenediamine (3.19)



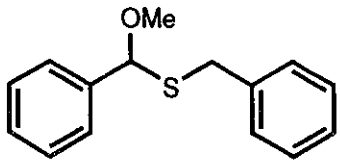
Compound **(3.19)** was prepared from N-benzyl-N-methylamine and 40% aq. formaldehyde using general procedure described in Section 5.14. ^{1}H NMR ($CDCl_3$) 2.25 (s, 6H, 2xCH_3), 3.05 (s, 2H, NCH_2N), 3.65 (s, 4H, $PhCH_2N$), 7.20-7.40 (m, 10H, aromatic protons); MS, m/e 254 [M^+].

6.15. N-Benzyl-N-(benzyloxy)methyl-N-methylamine (3.20)



Compound (3.20) was prepared by reacting equimolar amounts of N-benzyl-N-methylamine and benzyl alcohol with excess 40% aq. formaldehyde, using the general procedure described in Section **6.14**. ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H, CH_3), 3.87 (s, 2H, $PhCH_2N$), 4.38 (s, 2H, OCH_2N), 4.60 (s, 2H, $PhCH_2O$), 7.25-7.50 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 39.61 (NCH_3), 58.15 (NCH_2Ph), 70.15 (OCH_2Ph), 87.15 (OCH_2N), 126.98, 127.12, 127.57, 127.61, 128.38, 128.47, 128,96, 138.95, 139.14 (aromatic carbons); MS, m/e 241 [M^+].

6.16. Benzyl α-methoxybenzyl sulfide (3.21)[101]



A mixture of benzyl mercaptan (1.24 g, 10 mmol) and benzaldehyde (1.06 g, 10 mmol) in 90% MeOH / H_2O containing 0.1 M HCl (50 mL) was stirred at room temperature. The product seperated as an oil after several hours and 10 mL of 1M NaOH was added. After standing overnight the oil was separated and distilled to obtain **(3.21)** 1.7 g (67%). ^{1}H NMR ($CDCl_3$) δ 3.42 (s, 3H, OCH_3), 3.75 (dd, 2H, SCH_2Ph), 5.40 (s, 1H, $PhCHOCH_3$), 7.20-7.50 (aromatic protons); ^{13}C NMR ($CDCl_3$) δ 34.18 (OCH_3), 56.59 (SCH_2Ph), 87.41

(Ph*C*HOCH$_3$), 127.20, 127.55, 128.65, 128.93, 129.10, 129.68, 138.80, 139.81 (aromatic carbons).

6.17. Synthesis of N,N-Dibenzyl-N-(benzylthio)ethylamine (3.22)

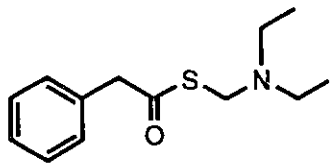
To a solution of 2-aminoethanethiol hydrochloride (1.14 g, 10 mmol) in ethanol (100 mL) was added KOH (2.24 g, 40 mmol) and then benzyl bromide (5.13 g, 30 mmol), and the mixture was stirred overnight at room temperature. Dilution with water, extraction with CH_2Cl_2, drying ($MgSO_4$) and evaporation of the solvent afforded a solid product which was recrystallized from ethanol to give **(3.22)** in 56% yield; ^{1}H NMR ($CDCl_3$) δ 2.50 (t, 2H, CH_2S), 2.62 (t, 2H, CH_2N), 3.52 (s, 6H, 2xNCH_2Ph, SCH_2Ph), 7.1-7.4 (m, 15H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 29.45 (CH_2S), 36.69 ($PhCH_2S$), 53.47 (CH_2N), 58.95 (2x$PhCH_2N$), 127.54, 127.62, 128.36, 128.91, 129.11, 139.12, 140.14 (aromatic carbons); MS (m/e) 335 [M$^+$].

6.18. Carbonylation of N,S-Acetals (3.3-3.18) and Related Compounds (3.19-3.22, 3.29) (General Procedure)

A mixture of the N,S-acetal (5 mmol), $[Rh(COD)Cl]_2$ (0.025 g, 0.05 mmol) and benzene (10 ml) was placed in an autoclave containing a glass liner and stirring bar. The autoclave was purged several times with carbon monoxide, pressurized to 53 atm, and the reaction mixture was stirred at 140 °C for 24h. The reaction mixture was then cooled to room temperature and filtered through acidic alumina using CH_2Cl_2 and then ethyl acetate as eluants. In all cases, except **(3.8)**, the less polar fraction contains the product. In the case of **(3.8)**, the product is in the ethyl acetate fraction. The

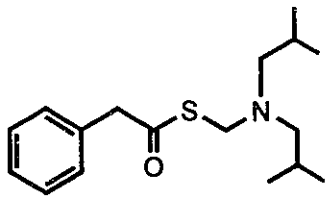
fraction containing the product was then purified by preparative thin-layer chromatography using 20% ethyl acetate in hexane as developper.

6.18.1. (N,N-Diethylamino)methyl 2-phenylethanethiolate (3.23)



74% yield; IR (neat) ν(CO) 1686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (t, 6H, 2xCH_3CH_2), 2.66 (q, 4H, 2xCH_2CH_3), 3.32 (s, 2H, PhCH_2CO), 4.07 (s, 2H, SCH_2N), 7.13-7.40 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 12.58 (CH_3), 33.58 ($PhCH_2S$), 48.72 (NCH_2CH_3), 63.24 (SCH_2N), 127.63, 128.07, 129.13, 129.49, 130.02, 138.58 (aromatic carbons), 202.93 (CO); MS, m/e 237 [M^+]. *Anal.* Calcd. for $C_{13}H_{19}NOS$, C, 65.82; H, 8.02; N, 5.91. Found C, 66.20; H, 8.04; N, 5.99.

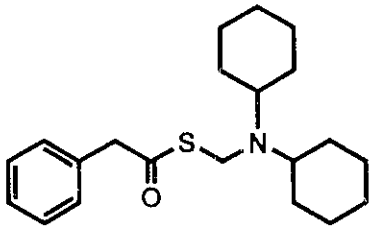
6.18.2. (N,N-Diisopropylamino)methyl 2-phenylethanethiolate (3.24)



82% yield; IR (neat) ν(CO) 1681 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, 12H, 4xCH_3CH), 1.72 (m, 2H, 2x$CH(CH_3)_2$), 2.22 (d, 4H, 2xCH_2CH), 3.30 (s, 2H, PhCH_2CO), 4.05 (s, 2H, SCH_2N), 7.20-7.35 (m, 5H, aromatic protons); ^{13}C

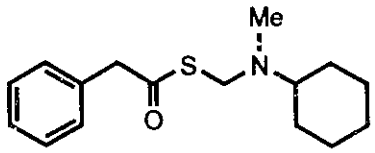
NMR ($CDCl_3$) δ 20.89 (CH_3), 26.61 ($CH(CH_3)_2$), 32.76 ($PhCH_2S$), 63.88 (NCH_2CH), 65.79 (SCH_2N), 126.97, 128.47, 128.73, 128.84, 129.40, 138.04 (aromatic carbons), 201.89 (CO); MS, m/e 293 [M^+]. *Anal.* Calcd. for $C_{17}H_{27}NOS$, C, 69.62; H, 9.22; N, 4.78. Found C, 69.61; H, 9.33; N, 5.01.

6.18.3. (N,N-Dicyclohexylamino)methyl 2-phenylethanethiolate (3.25)



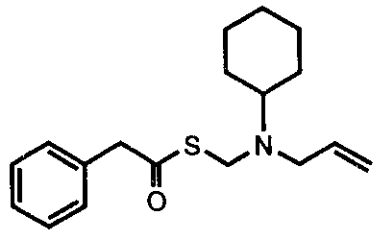
92% yield; IR (neat) ν(CO) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10-1.90 (m, 20H, 2xcyclohexyl protons), 2.55 (m, 2H, 2xN*CH*), 3.43 (s, 2H, PhCH_2CO), 4.00 (s, 2H, SCH_2N), 7.20-7.45 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 26.66, 26.90, 32.14 (cyclohexyl carbons), 33.70 ($PhCH_2S$), 57.54 (NCH), 59.54 (SCH_2N), 127.43, 129.03, 129.47, 138.99 (aromatic carbons), 207.22 (CO); MS, m/e 345 [M^+]. *Anal.* Calcd. for $C_{21}H_{31}NOS$, C, 73.04; H, 8.99; N, 4.06. Found C, 73.23; H, 8.96; N, 3.96.

6.18.4. (N-Cyclohexyl-N-methylamino)methyl 2-phenylethanethiolate (3.26)



81% yield; IR (neat) ν(CO) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10-1.90 (m, 10H, cyclohexyl protons), 2.33 (s, 3H, N*CH*$_3$), 2.45 (m, 1H, N*CH*), 3.35 (s, 2H, Ph*CH*$_2$CO), 4.05 (s, 2H, S*CH*$_2$N), 7.10-7.40 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 26.37, 26.67, 29.48 (cyclohexyl carbons), 33.53 ($PhCH_2S$), 43.86 (NCH_3), 63.61 (NCH), 63.70 (SCH_2N), 127.61, 129.12, 129.50, 130.02, 138.65 (aromatic carbons), 203.48 (CO); MS, m/e 277 [M^+]. *Anal.* Calcd. for $C_{16}H_{23}NOS$, C, 69.31; H, 8.30; N, 5.05. Found C, 69.58; H, 8.01; N, 5.32.

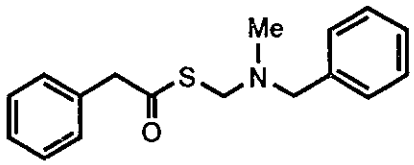
6.18.5. (N-Allyl-N-cyclohexylamino)methyl 2-phenylethanethiolate (3.27)



80% yield; IR (neat) ν(CO) 1684 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10-1.95 (m, 10H, cyclohexyl protons), 2.55 (m, 1H, N*CH*), 3.21 (d, N*CH*$_2$CH=CH_2), 3.35 (s, 2H, Ph*CH*$_2$CO), 4.02 (s, 2H, S*CH*$_2$N), 5.18 (ABC, 2H, *CH*$_2$=CH), 5.90 (ABC, 1H, *CH*=CH_2), 7.15-7.45 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 26.54, 26.74, 29.65 (cyclohexyl carbons), 33.65 ($PhCH_2S$), 55.35 (N*CH*$_2$CH=CH_2), 60.02 (NCH), 61.13 (SCH_2N), 118.00 (*CH*$_2$=CH), 127.52, 129.07, 129.50, 129.60, 137.08,

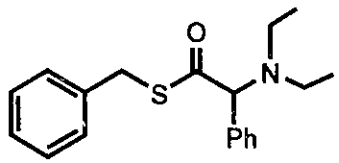
138.77 (aromatic carbons and *CH*=CH_2), 205.06 (CO); MS, m/e 303 [M^+]. *Anal.* Calcd. for $C_{18}H_{25}NOS$, C, 71.29; H, 8.25; N, 4.62. Found C, 71.25; H, 8.33; N, 4.47.

6.18.6. (N-Benzyl-N-methylamino)methyl 2-phenylethanethiolate (3.28)



85% yield; IR (neat) ν(CO) 1686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3H, NCH_3), 3.31 (s, 2H, Ph*CH*$_2$CO), 3.65 (s, 2H, Ph*CH*$_2$N), 4.08 (s, 2H, S*CH*$_2$N), 7.15-7.45 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 32.75 ($PhCH_2S$), 42.87 (NCH_3), 62.05 (NCH_2Ph), 66.25 (SCH_2N), 127.09, 127.35, 128.35, 128.55, 128.80, 128.90, 137.85, 138.02, (aromatic carbons), 200.91 (CO); MS, m/e 285 [M^+]. *Anal.* Calcd. for $C_{17}H_{19}NOS$, C, 71.58; H, 6.67; N, 4.91. Found C, 71.27; H, 6.92; N, 4.98.

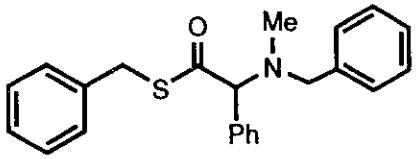
6.18.7. Benzyl 2-(N,N-diethylamino)-2-phenylethanethiolate (3.30)



83% yield; IR (neat) ν(CO) 1686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (t, 6H, 2xCH_3), 2.48 (m, 2H, CH_2), 2.70 (m, 2H, CH_2), 4.10 (s, 2H, SCH_2Ph), 4.60 (s, 1H, CO*CH*(Ph)N), 7.15-7.40 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ

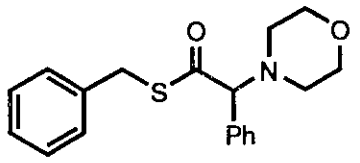
12.56 (CH_3), 34.00 ($PhCH_2S$), 44.47 (NCH_2), 76.75 (CO*CH*(Ph)N), 127.67, 128.68, 128.93, 129.15, 129.52, 130.21, 136.14, 138.52 (aromatic carbons), 202.68 (CO); MS, m/e 313 [M^+]. *Anal.* Calcd. for $C_{19}H_{23}NOS$, C, 72.84; H, 7.35; N, 4.47. Found C, 73.07; H, 7.13; N, 4.47.

6.18.8. Benzyl 2-(N-benzyl-N-methyl)amino-2-phenylethanethiolate (3.31)



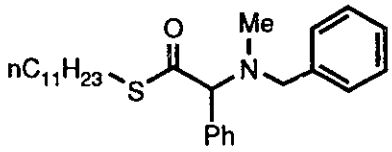
46% yield; IR (neat) ν(CO) 1688 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (s, 3H, N*CH*$_3$), 3.60 (AB, 2H, N*CH*$_2$Ph), 4.12 (s, 2H, SCH_2Ph), 4.43 (s, 1H, CO*CH*(Ph)N), 7.15-7.50 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 33.87 ($PhCH_2S$), 40.19 (NCH_3), 59.98 (NCH_2Ph), 79.72 (COCH(Ph)N), 127.75, 127.80, 127.93, 128.06, 128.96, 129.07, 129.11, 129.17, 129.40, 129.51, 129.63, 129.79, 130.05, 130.19, 135.40, 137.99, 138.32, 139.55 (aromatic carbons), 201.55 (CO); MS, m/e 361 [M^+]. *Anal.* Calcd. for $C_{23}H_{23}NOS$, C, 76.45; H, 6.37; N, 3.88. Found C, 76.09; H, 6.42; N, 3.84.

6.18.9. Benzyl 2-(1-morpholino)-2-phenylethanethiolate (3.32)



80% yield; IR (neat) ν(CO) 1686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.55 (m, 4H, 2xCH_2N), 3.73 (m, 6H, 2xCH_2O), 4.05 (s, 2H, SCH_2Ph), 4.15 (s, 1H, COCH(Ph)N), 7.20-7.50 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 33.16 ($PhCH_2S$), 51.87 (NCH_2), 66.81 (CH_2O), 81.16 (COCH(Ph)N), 127.18, 128.56, 128.61, 128.81, 129.29, 134.39, 137.33 (aromatic carbons), 199.89 (CO); MS, m/e 327 [M^+]. *Anal.* Calcd. for $C_{19}H_{21}NO_2S$, C, 69.72; H, 5.70; N, 7.25. Found C, 69.46; H, 5.55; N, 7.25.

6.18.10. n-Undecyl 2-(N-benzyl-N-methyl)amino-2-phenylethanethiolate (3.33)



55% yield; IR (neat) ν(CO) 1686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, CH_3), 1.20-1.40 (m, 18H, CH_2), 1.55 (m, 1H, CH_2), 2.16 (s, 3H, NCH_3), 2.85 (t, 2H, SCH_2), 3.55 (AB, 2H, PhCH_2N), 4.35 (s, 1H, SCHPh), 7.20-7.50 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.73 (CH_3), 23.29, 28.99, 29.32, 29.46, 29.71, 29.94, 30.08, 30.20, 32.51, 34.67, (CH_2), 40.16 (NCH_3), 59.88 (NCH_2Ph), 80.17 (COCH(Ph)N), 127.70, 128,80, 128.89, 129.01, 129.38, 130.00, 136.01, 139.33, (aromatic carbons), 201.82 (CO); MS, m/e 425 [M^+]. *Anal.* Calcd. for $C_{27}H_{39}NOS$, C, 76.24; H, 9.18; N, 3.29. Found C, 76.29; H, 9.34; N, 3.14.

6.19. Ethyl benzyl sulfide (3.29)

A mixture of benzyl mercaptan (1.24 g, 10 mmol), ethyl iodide (2.34 g, 15 mmol), sodium hydroxide (2 g, 50 mmol) and 18-crown-6 (0.13 g, 0.5 mmol) was stirred overnight in benzene (10 mL). The reaction mixture was then worked up by extraction with CH_2Cl_2. The organic phase was washed with water, dried over $MgSO_4$, filtered, and concentrated under vacuum. The product was separated from the crown ether by column chromatography using silica gel and 10% of ethyl acetate in hexane as the eluant to yield **(3.29)** in 92% yield ; ^1H NMR ($CDCl_3$) δ 1.24 (t, 3H, CH_3), 2.42 (q, 2H, CH_2), 3.75 (s, 2H, SCH_2), 7.20-7.40 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.42 (CH_3), 25.21 (CH_2CH_3), 35.89 ($PhCH_2S$), 126.87, 128.46, 128.82, 138.61 (aromatic carbons); MS, m/e 152 [M^+].

EXPERIMENTAL FOR CHAPTER 4

6.20. Synthesis of 2-Alkylthio-N-methylpyrrolidine (4.1)

6.20.1. By Mercuric Acetate Oxidation[104]

A mixture of 8.5 g (0.10 mol) of N-methylpyrrolidine and 150 g (0.48 mol) of mercuric acetate in 400 mL of 5% acetic acid (95% water) was heated at 100 °C for 2h. The reaction mixture was cooled and the precipitated mercurous acetate was collected by filtration and washed with 5% acetic acid. The filtrate was saturated with hydrogen sulfide, and filtration again. The filtrate was basified by adding K_2CO_3 in small portions. When gas

evolution ceased, the aqueous layer was extracted with ether (3 x 100 mL), the combined extracts were dried over $MgSO_4$, and the solvent was removed *in vacuo*.

The residue was dissolved in 95% EtOH (50 mL) and then added to a mixture of 12.4 g (0.10 mol) of benzylmercaptan and 8.9 g (0.01 mol) of NEt_3 in EtOH (20 mL). After stirring for 4h at room temperature the reaction mixture was worked up by extraction with CH_2Cl_2 and water. The organic layer was dried over $MgSO_4$, and the solvent was removed by rotary evaporation. Analysis of the crude product by ^1H NMR showed none of the signals anticipated for the desired product.

An alternative method involving the generation of sodium benzylthiolate (by stirring benzylmercaptan with sodium metal in benzene at room temperature for 2h) before addition to the iminium salt also did not result in the formation of the desired product.

6.20.2. By Hydride Abstraction Using Triphenylcarbenium tetrafluoroborate[105]

7.13 g (20.8 mmol) of triphenylcarbenium tetrafluoroborate was suspended in 30 mL of dry CH_2Cl_2. The mixture was cooled in ice water and added dropwise to a solution of 1.79 g (21 mmol) of N-methylpyrrolidine in 20 mL dry CH_2Cl_2. After stirring for 15 min, the reaction was added to 300 mL of dry CCl_4, the iminium salt precipitated out and was collected by vacuum filtration. The salt was then dissolved in 20 mL of dry dioxane and treated with a mixture of 2.48 g (20 mmol) of benzylmercaptan and 1.89 g (20 mmol) of NEt_3. After stirring at room temperature for 3 h the reaction mixture was

then washed with CH_2Cl_2 and water. The ^1H NMR of the crude reaction mixture showed no signals for the desired product.

An alternative method using sodium benzylthiolate (see 6.20.1) also did not give the desired product.

6.21. Synthesis of Ethylene thiourea (4.7)[106a]

To a solution of 6.0 g (100 mmol) of ethylenediamine in 20 mL of 95% EtOH and 20 mL of water in a 2-neck flask attached to an efficient reflux condenser, was added, dropwise, 6 mL of carbon disulfide. After the reaction began, the solution was heated to 60 °C and the balance of the carbon disulfide was added at such a rate that the vapors refluxed about one-third the way up the condenser. After all the carbon disulfide was added the oil bath temperature was raised to 100 °C. The reaction mixture was refluxed for 1h, 1 mL of concentrated HCl was added, and the mixture was refluxed for an additional 10h. The mixture was cooled in an ice bath, and the product was filtered and washed with cold acetone. White crystals of ethylene thiourea were obtained in 6.3 g (66%), and were used in the next step without further purification.

6.22. Synthesis of 5,6-Dihydroimidazo[2,1-b]thiazole-3(2H)-one (4.9)[106b]

A solution of 6.0 g (59 mmol) of ethylene thiourea and 7.2 g (59 mmol) of ethyl chloroacetate in 20 mL of absolute EtOH was refluxed for 2h. The solution was then cooled in an ice bath and was treated with ammonia gas for 5 minutes. The precipitated ammonium chloride was filtered, and removal of ethanol under reduced pressure at room temperature gave 4.2 g

(53% overall yield) of the bicyclic heterocycle.; ^{1}H NMR ($CDCl_3$) δ 3.70 (t, 2H, CH_2NCO), 4.15 (s, 2H, CH_2S), 4.35 (t, 2H, $CH_2N=C$); ^{13}C NMR ($CDCl_3$) δ 165.33 (CO), 162.36 (C=N), 62.43 ($CH_2N=C$), 42.18 (CH_2S), 40.34 (CH_2N).

6.23. Attempted Reduction of 5,6-Dihydroimidazo[2,1-b]thiazole-3(2H)-one (4.9)

6.23.1. By $NaBH_4$

To 0.13 g (1 mmol) of **(4.9)** in 95% EtOH was added in portions 0.076 g (2 mmol) of $NaBH_4$. After stirring for 2h, the reaction mixture was acidified with dilute HCl (pH 6 by pH paper), extracted with CH_2Cl_2 and washed with water. The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo* to give 18 mg of an unidentified compound. Starting material was recovered from the aqueous phase.

6.23.2. By KBH_4

The reaction was carried out using the procedure described in 6.23.1 except that one equivalent of KBH_4 (0.054g) was used instead of $NaBH_4$. The crude residue amounted to 23 mg of unidentified product.

6.23.3. By $NaBH_3CN$[107]

To a solution of 0.13 g (1 mmol) of **(4.9)** in 5 mL of methanol at room temperature was added a trace of bromocresol green. A methanolic 2N HCl solution was added until the color turned turned yellow, followed by 0.065 g (1

mmol) of $NaBH_3CN$. More of the HCl-methanol solution was added dropwise in order to restore the yellow color, and stirring was then continued for 1h. The solution was poured into 0.1N NaOH (100 mL), saturated with NaCl and extracted with ether (3 x 10 mL). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give 7 mg of crude unidentified product.

6.23.4. By Bu_3SnH[108]

A mixture of 0.13 g (1 mmol) of **(4.9)**, Bu_3SnH (1.1 eq) and AIBN (2%) in dry toluene (5 mL) was refluxed for 15h. The solvent was evaporated. An ^1H NMR of the crude residue shows a complex mixture of products.

6.23.5. By H_2 and Pd on carbon

A mixture of 0.13 g (1 mmol) of **(4.9)** and Pd on carbon (1%) in 10 mL of EtOAc was placed in an autoclave. The autoclave was purged three times with hydrogen and pressurized to 33 atm. The reaction mixture was then stirred at 100 °C for 12h and then cooled to room temperature. Thin layer chromatography showed that the starting material was still present in almost quantitative yield. The reaction mixture was then treated with 1 mL of glacial acetic acid and pressurized again to 33 atm H_2. The reaction was left stirring at 100 °C for 24 h, cooled to room temperature, and extracted with a satd. $NaHCO_3$ solution. After removal of the solvent, it was found that the starting material was recovered almost quantitatively.

6.23.6. By $LiAlH_4$

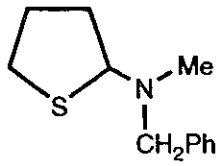
To a solution of 0.13 g (1 mmol) of **(4.9)** in dry THF (10 ml) was added in small portions, 0.057 g (1.5 mmol) of $LiAlH_4$. The reaction was refluxed for 2h, and then cooled. Water (1 mL) was added to the reaction mixture which was then extracted with CH_2Cl_2-water. The organic layer was dried ($MgSO_4$) and removed under reduced pressure. The crude product was obtained in 16 mg and the ^1H NMR did not show any of the desired product.

6.24. General Procedure for the Preparation of 2-N,N-Dialkylamino-tetrahydrothiophenes (4.12-4.15)[109]

To a stirred solution of 8.0 g (0.09 mol) of tetrahydrothiophene in 60 mL of dry benzene was added 6.0 g (0.045 mol) of N-chlorosuccinimide in small portions over a 15 minute period. The reaction temperature was maintained at 20-25 °C using an ice bath. After addition of all the N-chlorosuccinimide, stirring was continued at 20-25 °C for 2h after which the solution was filtered to remove succinimide. The yellow filtrate contained 2-chlorotetrahydro-thiophene of at least 90% purity which was used for the next step without further purification.

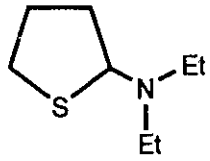
To the solution of 2-chlorotetrahydrothiophene was added 2 equivalents. of the requisite secondary amine. The reaction was stirred for 2h at room temperature, the ammonium salt was filtered, and then the filtrate was concentrated by rotary evaporation. The crude reaction mixture was then chromatographed on silica gel using 10% EtOAc in hexane as the eluant to yield the 2-N,N-dialkylaminotetrahydrothiophene **(4.12-4.15)** (see **Table 4.1**, Chapter 4).

6.24.1. 2-(N-Benzyl-N-methylamino)tetrahydrothiophene (4.12)



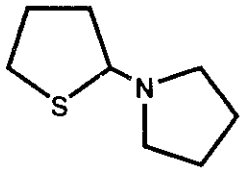
80% yield : ^{1}H NMR δ 1.79-2.20 (m, 4H, *CH*$_2$*CH*$_2$), 2.23 (s, 3H, N*CH*$_3$), 2.85 (m, 2H, *CH*$_2$S), 3.55 (dd, 2H, *J* = 12, 36 Hz, *CH*$_2$Ph), 5.10 (t, 1H, *J* = 6.4 Hz, S*CH*N), 7.30 (m, 5H, aromatic protons); ^{13}C NMR δ 30.83, 32.79 (CH_2CH_2), 35.00 (CH_2S), 37.77 (CH_3N), 60.25 (CH_2N), 79.25 (SCHN), 127.68, 128.91, 129.57, 139.35 (aromatic carbons); Calcd for $C_{12}H_{17}NS$, 207.10816; HRMS (m/e) 207.10610 [M^+].

6.24.2. 2-(N,N-Diethylamino)tetrahydrothiophene (4.13)



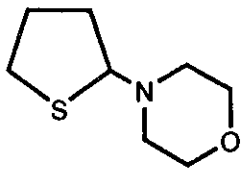
80% yield : ^{1}H NMR δ 1.06, 1.04 (2xt, 6H, *J* = 10.7 Hz, 2x*CH*$_3$), 1.73 (m, 2H, *CH*$_2$CH$_2$), 2.12 (m, 2H, *CH*$_2$CH$_2$), 2.40 (m, 2H, *CH*$_2$CH$_3$), 2.67 (m, 2H, *CH*$_2$CH$_3$), 2.85 (m, 2H, *CH*$_2$S), 5.17 (t, 1H, *J* = 8.9 Hz, S*CH*N); ^{13}C NMR δ 13.63 (2xCH$_3$), 29.58, 32.09 (CH_2CH_2), 34.76 (CH_2S), 45.13 (2xCH_2N), 77.34 (SCHN); Calcd for $C_8H_{17}NS$, 159.10816; HRMS (m/e) 159.10831 [M^+].

6.24.3. N-(2-Tetrahydrothiophenyl)pyrrolidine (4.14)



65% yield : ^{1}H NMR δ 1.65 (m, 4H, *CH2CH2* pyrrolidine), 1.76 (m, 2H, *CH2* tetrahydrothiophene), 2.02 (m, 2H, *CH2* tetrahydrothiophene), 2.40 (m, 2H, *CH2*N), 2.65 (m, 2H, *CH2*N), 2.75 (m, 2H, *CH2*S), 5.10 (t, 2H, *J* = 9 Hz, S*CH*N); ^{13}C NMR δ 24.12 (CH_2CH_2 pyrrolidine), 30.61, 32.57 (CH_2CH_2 tetrahydrothiophene), 35.97 (CH_2S), 49.97 (2xCH_2N), 76.72 (SCHN); Calcd for $C_8H_{15}NS$, 157.09251; HRMS (m/e) 157.09227 [M^+].

6.24.4. N-(2-Tetrahydrothiophenyl)morpholine (4.15)

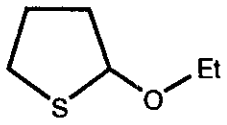


82% yield : ^{1}H NMR δ 1.60-2.00 (m, 4H, *CH2CH2* tetrahydrothiophene), 2.32 (m, 4H, 2xN*CH2*), 2.60 (m, 2H, *CH2*S), 3.50 (m, 4H, *CH2*O), 4.65 (t, 1H, *J* = 10 Hz, S*CH*N); ^{13}C NMR δ 30.08, 31.99 (CH_2CH_2), 33.17 (CH_2S), 49.29 (2xCH_2N), 66.45 (2xCH_2O), 78.52 (SCHN); Calcd for $C_8H_{15}NOS$, 173.08743; HRMS (m/e) 173.08594 [M^+].

6.25. General Procedure for the Preparation of 2-Alkoxytetrahydrothiophenes (4.16-4.21)[109]

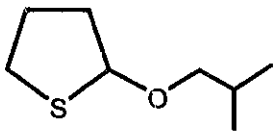
Generation of 2-chlorotetrahydrothiophene was carried out using the same procedure as that for **(4.12-4.15)**. To a solution of 2-chlorotetrahydrothiophene was added the requisite alcohol (1 equiv) and triethylamine (1 equiv). After stirring for 2h, the reaction mixture was worked up in the above manner.

6.25.1. 2-Ethoxytetrahydrothiophene (4.16)[110]



74% yield : ^{1}H NMR δ 1.10 (t, 2H, *J* = 7 Hz, *CH*$_3$CH$_2$), 1.65-2.27 (m, 4H, *CH*$_2$*CH*$_2$), 2.60-2.92 (m, 2H, *CH*$_2$S), 3.17 (m, 1H, *CH*$_2$O), 3.50 (m, 1H, *CH*$_2$O), 5.10 (dd, 1H, *J* = 1.7, 4.9 Hz, S*CH*O); ^{13}C δ NMR 15.45 (CH_3), 28.96, 32.50 (CH_2CH_2), 39.23 (CH_2S), 64.87 (CH_2O), 90.32 (SCHO); MS (m/e) 132 [M^+].

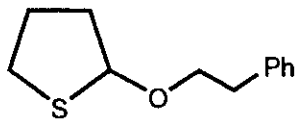
6.25.2. 2-Isobutyloxytetrahydrothiophene (4.17)



81% yield : ^{1}H NMR δ 0.75 (d, 6H, *J* = 8 Hz, 2x*CH*$_3$), 1.57-2.18 (m, 5H, 2x*CH*$_2$, *CH*), 2.60-3.25 (m, 4H, S*CH*$_2$, O*CH*$_2$), 5.05 (dd, 1H, *J* = 3.8, 10.9 Hz, S*CH*O); ^{13}C NMR δ 20.07 (2xCH_3), 28.75 (*CH*(CH_3)$_2$), 28.90, 32.33 (CH_2CH_2),

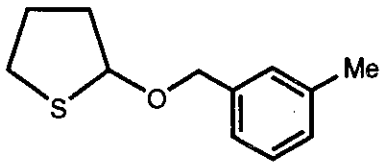
39.18 (CH_2S), 76.17 (CH_2O), 90.53 (SCHO); Calcd for $C_8H_{16}OS$, 160.09218; HRMS (m/e) 160.08965 [M^+].

6.25.3. 2-Phenethoxytetrahydrothiophene (4.18)[111]



80% yield : ^1H NMR δ 1.75-2.25 (m, 4H, *CH_2CH_2*), 2.70-2.98 (m, 4H, *CH_2*S, *CH_2*Ph), 3.37 (dd, 1H, *J* = 7, 17 Hz, O*CH_2*), 3.75 (dd, 1H, *J* = 7, 17 Hz, O*CH_2*), 5.27 (dd, 1H, *J* = 3.5, 4.8 Hz, S*CH*O), 7.08-7.30 (m, 5H, aromatic protons); ^{13}C NMR δ 28.97, 32.55 (CH_2CH_2), 36.57 (CH_2Ph), 39.33 (CH_2S), 70.22 (CH_2O), 90.62 (SCHO), 126.83, 128.95, 129.57, 139.45 (aromatic carbons); Calcd for $C_{12}H_{16}OS$, 208.09218; HRMS (m/e) 208.09159 [M^+].

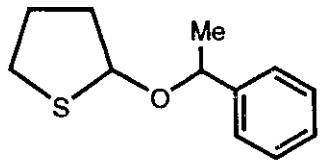
6.25.4. 2-(*m*-Methylbenzyloxy)tetrahydrothiophene (4.19)



82% yield : ^1H NMR δ 1.72-1.90 (m, 2H, *CH_2*CH_2), 2.00-2.15 (m, 2H, *CH_2*CH_2), 2.32 (s, 3H, *CH_3*), 2.75-2.85 (m, 1H, *CH_2*S), 2.87-3.00 (m, 1H, *CH_2*S), 4.22-4.70 (dd, 2H, *J* = 12, 76 Hz, *CH_2*Ph), 5.25 (dd, 1H, *J* = 3.5, 12 Hz, S*CH*O), 6.98-7.21 (m, 5H, aromatic protons); ^{13}C NMR δ 22.11 (CH_3), 29.06, 32.58 (CH_2CH_2), 39.38 (CH_2S), 71.11 (OCH_2Ph), 89.83 (SCHO), 125.87, 128.96, 129.02,

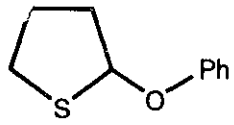
129.09, 129.52, 138.60 (aromatic carbons); Calcd for $C_{12}H_{16}OS$, 208.09218; HRMS (m/e) 208.09102 [M^+].

6.25.5. 2-(*sec*-Phenethoxy)tetrahydrothiophene (4.20)



68% yield : (two diastereoisomers were formed in a 1:1 mixture) ^1H NMR δ 1.32 (2d, 3H, J = 6.4 Hz, CH_3CH), 1.60-1.80 (m, 2H, CH_2CH_2), 1.95-2.10 (m, 2H, CH_2CH_2), 2.70, 2.90 (2xm, 2H, CH_2S), 4.52 (m, 1H, $CHCH_3$), 4.91, 5.23 (2xdd, 1H, J = 1.8, 0.9 Hz, SCHO), 7.20 (m, 5H, aromatic protons); ^{13}C NMR δ 24.87 (CH_3), 29.07, 32.42 (CH_2CH_2), 39.28 (CH_2S), 75.92 ($CHCH_3$), 87.53 (SCHO), 126.92, 127.33, 128.90, 128.22, 129.05, 129.14, 143.52 (aromatic carbons); Calcd for $C_{12}H_{16}OS$, 208.09218; HRMS (m/e) 208.09161 [M^+].

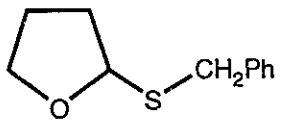
6.25.6. 2-Phenoxytetrahydrothiophene (4.21)



70% yield : ^1H NMR δ 1.90-2.20 (m, 4H, CH_2CH_2), 2.85 (m, 2H, CH_2S), 5.80 (dd, 1H, SCHO), 6.70-7.30 (m, 5H, aromatic H); MS (m/e) 180.

6.26. Synthesis of 2-Benzylthiotetrahydrofuran (4.22)[112]

A mixture of 3.5 g (0.05 mol) of 2,3-dihydrofuran, 6.2 g (0.05 mol) of benzylmercaptan, and a few crystals of p-toluenesulfonic acid were dissolved in 50 mL of THF and refluxed for 1h. The reaction mixture was cooled and extracted with CH_2Cl_2 and water. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel) using 10% EtOAc in hexane as the eluant affording 2-benzylthiotetrahydrofuran in 57% yield.



^{1}H NMR δ 1.61-2.20 (m, 4H, *CH2CH2*), 3.60-3.95 (m, 4H, *CH2*S, *CH2*O), 5.25 (m, 1H, SC*H*O), 7.22 (m, 5H, aromatic protons); ^{13}C NMR δ 25.47, 32.66 (CH_2CH_2), 35.61 (CH_2S), 67.36 (CH_2O), 83.53 (SCHO), 127.43, 129.08, 129.59, 139.21 (aromatic carbons); MS (m/e) 194.

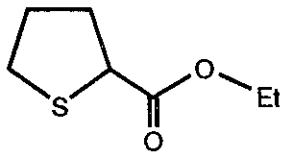
6.27. Carbonylation of 5,6-Dihydroimidazo[2,1-b]thiazole-3(2H)-one (4.9), 2-Substituted Tetrahydrothiophenes (4.12-4.21) and 2-Benzylthiotetrahydrofuran (4.22) (General Procedure)

A mixture of the substrate (5 mmol), $[Rh(COD)Cl]_2$ (0.025g, 0.05 mmol), potassium iodide (if used) (0.017 g, 0.1 mmol) and dry benzene (10 mL) was placed in an autoclave containing a glass liner and a stirring bar. The autoclave was purged several times with carbon monoxide, pressurized to 67 atm, and the reaction mixture was stirred at 150 °C (for 2-N,N-

dialkylaminotetrahydrothiophenes) or 180 °C (for the other substrates) for 48h. The reaction was then cooled to room temperature and filtered through acidic alumina using CH_2Cl_2 and then EtOAc as eluants.

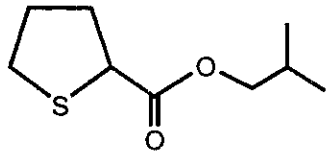
The substrates **(4.9, 4.12-4.15)** were unreactive under the aforementioned conditions (using TLC and ^1H NMR). The 2-alkoxytetrahydrothiophenes **4.16-4.21** and 2-benzylthiotetrahydrofuran **(4.22)** were carbonylated and the products were isolated by using preparative thin layer chromatography with 25% EtOAc in hexane as the developing solvent.

6.27.1. Ethyl tetrahydrothiophene-2-carboxylate (4.23)[113]



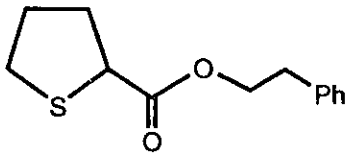
73% yield : ^1H NMR δ 1.15 (t, 3H, J = 8.5 Hz, CH_3CH_2), 1.80-2.22 (m, 4H, CH_2CH_2), 2.65-2.92 (m, 2H, CH_2S), 3.78 (dd, 1H, J = 5.5, 7.4 Hz, SCHCO), 4.05 (q, 2H, J = 8.5 Hz, CH_3CH_2OCO); ^{13}C NMR δ 14.72 (CH_3), 31.51, 33.70 (CH_2CH_2), 33.88 (CH_2S), 48.09 (SCHCO), 61.75 (CH_2O), 174.24 (CO); MS (m/e) 160.

6.27.2. i-Butyl tetrahydrothiophene-2-carboxylate (4.24)



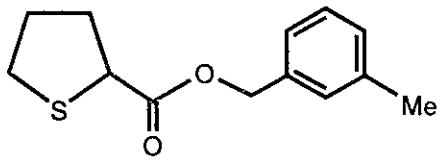
32% yield : ^{1}H NMR δ 0.85 (d, 6H, *J* = 8.5 Hz, 2x*CH3*), 1.80-2.30 (m, 5H, 2x*CH2*, *CH*), 2.75-2.95 (m, 2H, S*CH2*,), 3.70-3.90 (m, 2H, *CH2*OCO); ^{13}C NMR δ 19.03 (2xCH3), 27.71 (*CH*(CH3)2), 30.82, 30.90 (CH_2CH_2), 33.25 (CH_2S), 47.50 (SCHCO),71.79 (CH_2O), 173.67 (CO); HRMS (m/e) 188.08706 (M^+), calcd for $C_9H_{16}O_2S$ 188.08709.

6.27.3. Phenethyl tetrahydrothiophene-2-carboxylate (4.25)



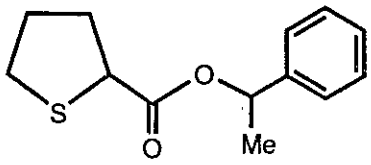
44% yield : ^{1}H NMR δ 1.80-2.30 (m, 4H, *CH2CH2*), 2.70-3.00 (m, 4H, *CH2*S, *CH2*Ph), 3.87 (dd, 1H, *J* = 6.8, 10.4 Hz, S*CH*CO), 4.15-4.21 (m, 2H, O*CH2*), 7.05-7.30 (m, 5H, aromatic H); ^{13}C NMR δ 31.48, 33.72 (CH_2CH_2), 33.88 (CH_2Ph), 35.60 (CH_2S), 48.10 (S*CH*CO), 66.22 (CH_2O), 127.17, 129.09, 129.56, 138.27 (aromatic C), 174.17 (CO); MS (m/e) 236 (M^+), Anal. Calcd for $C_{13}H_{16}O_2S$: C, 66.10; H, 6.78. Found: C, 66.07; H, 6.44.

6.27.4. *m*-Methylbenzyl tetrahydrothiophene-2-carboxylate (4.26)



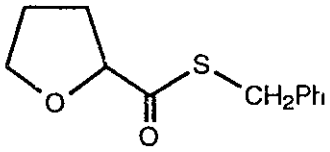
67% yield : ^{1}H NMR δ 1.85-2.25 (m, 4H, *CH*$_2$CH$_2$), 2.25 (s, 3H, *CH*$_3$), 2.70-2.92 (m, 2H, CH$_2$S), 3.85 (dd, 1H, *J* = 5.5, 9.6 Hz, SCHCO), 5.00 (s, 2H, O*CH*$_2$C$_6$H$_4$CH$_3$-*m*), 6.98-7.20 (m, 4H, aromatic H); ^{13}C NMR δ 21.27 (CH$_3$), 30.82, 33.05 (CH$_2$CH$_2$), 33.24 (CH$_2$S), 47.40 (SCHCO), 66.83 (OCH$_2$Ph), 124.52, 129.22, 129.38, 129.74, 137.99, 139.02 (aromatic C), 173.42 (CO); MS (m/e) 236 (M$^+$), Anal. Calcd for C$_{13}$H$_{16}$O$_2$S: C, 66.10; H, 6.78. Found: C, 66.00; H, 6.83.

6.27.5. *sec*-Phenethyl tetrahydrothiophene-2-carboxylate (4.27)



14% yield : ^{1}H NMR δ 1.50 (d, 3H, *J* = 8 Hz, *CH*$_3$CH), 1.80-2.20 (m, 4H, *CH*$_2$*CH*$_2$), 2.80 (m, 2H, CH$_2$S), 3.85 (m, 1H, SCHCO), 5.80 (q, 1H, *J* = 8 Hz, *CH*CH$_3$), 7.25 (m, 5H, aromatic H); ^{13}C NMR δ 21.91 (CH$_3$), 30.85, 33.03 (CH$_2$CH$_2$), 33.11 (CH$_2$S), 47.58 (SCHCO), 72.99 (*CH*CH$_3$), 126.02, 127.83, 128.42, 141.36 (aromatic C), 172.80 (CO); MS (m/e) 236 (see Appendices for ^{1}H NMR spectra).

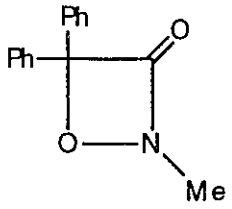
6.27.6. Benzyl tetrahydrofuran-2-thiocarboxylate(4.29)



18% yield : ^{1}H NMR δ 1.65 (m, 4H, *CH2CH2*), 3.38 (m, 2H, *CH2*O), 3.70 (m, 3H, *CH2*S, *CH*O), 7.20 (m, 5H, aromatic H); ^{13}C NMR δ 30.78, 32.42 (CH_2CH_2), 35.38 (CH_2S), 50.72 (CH_2O), 62.64 (OCHCO), 127.59, 129.13, 129.63, 138.77 (aromatic C), 202.73 (CO); MS (m/e) 222; Anal Calcd for $C_{12}H_{14}O_2S$: C, 64.86; H, 6.31. Found: C, 65.04; H, 6.35.

EXPERIMENTAL FOR CHAPTER 5

6.28. Synthesis of 4,4-Diphenyl-2-methyl-1,2-oxazetidine-3-one (5.1)[119]



A mixture of N-methylhydroxylamine hydrochloride (2.49 g, 3.0 mmol) and triethylamine (3.0 g) in 100 mL of dry ether was stirred for 1h and α-chlorodiphenylacetyl chloride (2.65 g, 10 mmol) in 50 mL of dry ether was added. After 6h of stirring the solution was filtered and evaporated. The oily residue solidified upon standing and was used without further purification; 74% yield; ^{1}H NMR ($CDCl_3$) δ 3.37 (s, 3H, NCH_3), 7.40 (m, 10H, aromatics

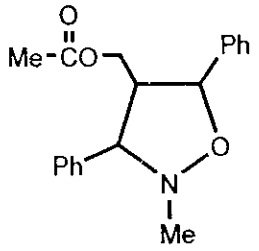
protons); ^{13}C NMR ($CDCl_3$) δ 35.58 (NCH_3), 101.60 ($C(Ph)_2$), 126.28, 128.63, 128.97, 136.41 (aromatic carbons), 171.08 (CO).

6.29. General Procedure for the Preparation of Isoxazolidines (5.2-5.8)[120]

To a suspension of N-methylhydroxylamine hydrochloride (16.6 g, 20 mmol) in benzene (100 mL), was added potassium hydroxide (2.24 g, 40 mmol) and the requisite aldehyde (20 mmol). The reaction mixture was refluxed and the water was removed with a Dean-Stark apparatus. After the calculated amount of water was removed, the reaction mixture was worked up by removing the solvent and then extracting with CH_2Cl_2 and water. The organic phase was dried over $MgSO_4$, filtered and concentrated by rotary evaporation to yield nitrones which were used in the next step without purification.

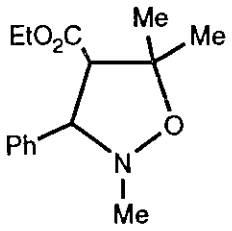
A mixture of the nitrones (10 mmol) and the requisite dipolarophile (10 mmol) in dry toluene was refluxed under a slow stream of nitrogen for 24h. The reaction mixture was concentrated by rotary evaporation affording a crude oily material. This oily material was then chomatographed using silica gel column and 10-25% ethyl acetate in hexane as the eluant to yield the isoxazolidine derivative **(5.2-8.8)** (see **Table 5.1**, Chapter 5).

6.29.1. 4-Acetoxymethyl-3,5-diphenyl-2-methylisoxazolidine (5.2)



78% yield; IR (neat) ν (CO) 1738 cm^{-1}; ^1H NMR δ 1.95 (s, 3H, CH_3CO), 2.68 (s, 3H, NCH_3), 2.96 (m, 1H, $CHCH_2OCO$), 3.47 (d, J = 10 Hz, 1H, PhCHN), 4.25 (dd, J = 1.2, 8 Hz, 2H, CH_2OCO), 4.98 (d, J = 8 Hz, 1H, PhCH(O)), 7.25-7.65 (m, 10H, aromatic H); ^{13}C NMR δ 21.28 (CH_3CO), 44.08 (NCH_3), 61.16 ($CHCH_2CO$), 63.77 (CH_2OCO), 76.80 (PhCHN), 81.67 (PhCHO), 126.56, 128.09, 128.59, 128.83, 128.94, 129.16, 129.36, 138.18 (aromatic C), 171.41 (CO); MS (m/e) 311 [M^+].

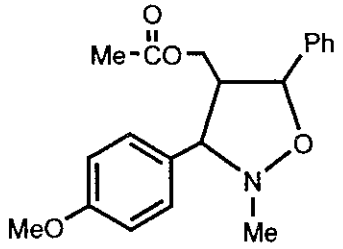
6.29.2. 4-Ethoxycarbonyl-3-phenyl-2,5,5-trimethylisoxazolidine (5.3)



80% yield; IR (neat) ν (CO) 1736 cm^{-1}; ^1H NMR δ 1.22 (t, J = 8 Hz, 3H, CH_3CH_2), 1.29 (s, 3H,CH_3), 1.60 (s, 3H, CH_3), 2.55 (s, 3H, NCH_3), 3.17 (d, J = 11 Hz, 1H, CHCOOEt), 3.95 (d, J = 11 Hz, 1H, PhCHN), 4.12 (q, J = 8 Hz, 2H, CH_2CH_3), 7.35 (m, 5H, aromatic H); ^{13}C NMR δ 14.77 (CH_3CH_2), 24.50 (CH_3), 30.51 (CH_3), 43.61 (NCH_3), 61.32 (CHCOOEt), 67.26 (CH_3CH_2OCO), 76.72

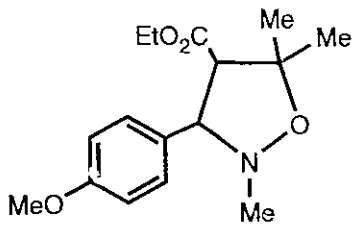
(PhCHN), 80.57 ($OC(Me)_2$), 128.52, 128.71, 129.28, 138.16 (aromatic C), 171.18 (CO); MS (m/e) 263 [M^+].

6.29.3. 4-Acetoxymethyl-3-(*p*-methoxyphenyl)-2-methyl-5-phenylisoxazolidine (5.4)



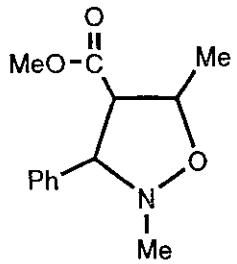
67% yield; IR (neat) ν (CO) 1738 cm^{-1}; ^1H NMR δ 1.89 (s, 3H, CH_3CO), 2.55 (s, 3H, NCH_3), 2.82 (tt, 1H, $CHCH_2OCO$), 3.31 (d, J = 10 Hz, 1H, p-$OMeC_6H_4CHN$), 3.68 (s, 3H, OCH_3), 4.15 (dd, J = 10 Hz, 2H, CH_2OCO), 4.88 (d, J = 8 Hz, 1H, PhCH(O)), 6.75-7.50 (m, 9H, aromatic H); ^{13}C NMR δ 20.42 (CH_3CO), 43.01 (NCH_3), 54.97 (OCH_3), 60.01 ($CHCH_2CO$), 62.91 (CH_2OCO), 76.21 (p-$OMeC_6H_4CHN$), 80.72 (PhCHO), 114.67, 125.63, 128.24, 128.83, 128.92, 142.57, 159.23 (aromatic C), 170.52 (CO); MS (m/e) 341 [M^+].

6.29.4. 4-Ethoxycarbonyl-3-(*p*-methoxyphenyl)-2,5,5-trimethylisoxazolidine (5.5)



82% yield; IR (neat) ν (CO) 1732 cm^{-1}; ^1H NMR δ 1.12 (t, J = 8 Hz, 6H, CH_3CH_2, CH_3), 1.29 (s, 3H,CH_3), 2.49 (s, 3H, NCH_3), 3.02 (d, J = 12 Hz, 1H, *CH*COOEt), 3.29 (s, 3H, OCH_3), 3.78 (d, J = 12 Hz, 1H, p-$OMeC_6H_4CHN$), 4.00 (q, J = 8 Hz, 2H, CH_2CH_3), 6.75, 7.20 (q, 4H, aromatic H); ^{13}C NMR δ 14.77 (CH_3CH_2), 24.56 (CH_3), 30.51 (CH_3), 43.49 (NCH_3), 55.81 (OCH_3), 61.26 (*CH*COOEt), 67.07 (CH_3CH_2OCO), 76.23 (p-$OMeC_6H_4CHN$), 80.37 ($OC(Me)_2$), 114.64, 129.64, 129.90, 132.57, 160.05 (aromatic C), 171.20 (CO); Calcd for $C_{16}H_{23}NO_4$, 293.16269, HRMS (m/e) 293.16368 [M^+]. Anal. Calcd. for $C_{16}H_{23}NO_4$, C, 65.53; H, 7.85; N, 4.78. Found: C, 65.22; H, 7.72; N, 4.62.

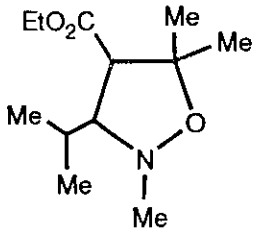
6.29.5. 2,5-Dimethyl-4-methoxycarbonyl-3-phenylisoxazolidine (5.6)



83% yield; IR (neat) ν (CO) 1738 cm^{-1}; ^1H NMR δ 1.40 (d, J = 8 Hz, 3H, CH_3CH), 2.55 (s, 3H, NCH_3), 2.98 (t, J = 2, 8 Hz, 1H, *CH*CO), 3.68 (s, 3H,

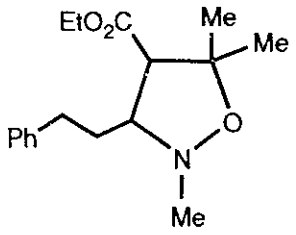
OCH_3), 3.88 (d, J = 8 Hz, 1H, PhCHN), 4.40 (quintet, J = 8 Hz, 1H, CH_3CHO), 7.25 (m, 5H, aromatic H); ^{13}C NMR δ 21.65 (CH_3CH), 43.86 (NCH_3), 51.78 (OCH_3), 52.65 (CHCOOCH_3), 61.76 (PhCHN), 76.77 ((O)CMe), 128.12, 128.73, 129.24, 139.03 (aromatic C), 172.46 (CO); Calcd for $C_{13}H_{17}NO_3$, 235.12083, HRMS (m/e) 235.12186 [M$^+$]. Anal. Calcd. for $C_{13}H_{17}NO_3$, C, 66.38; H, 7.23; N, 5.96. Found: C, 66.26; H, 7.23; N, 6.15.

6.29.6. 4-Ethoxycarbonyl-3-isopropyl-2,5,5-trimethylisoxazolidine (5.7)



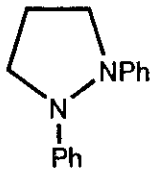
64% yield; IR (neat) ν (CO) 1739 cm^{-1}; ^{1}H NMR δ 0.72 (d, J = 9.7 Hz, 3H, CH_3CH), 0.79 (d, J = 9.7 Hz, 3H,CH_3CH), 1.08 (s, 3H, CCH_3), 1.12 (t, J = 10 Hz, 3H, CH_3CH_2), 1.29 (s, 3H, CCH_3), 1.70 (m, 1H, $CH(CH_3)_2$), 2.53 (s, 3H, NCH_3), 2.79 (m, 2H, CHCOOEt, NCH), 4.02 (q, J = 10 Hz, 2H, CH_2CH_3); ^{13}C NMR δ 14.80 (CH_3CH_2), 17.13 (CH_3), 20.76 (CH_3), 24.02 (CH_3), 28.86 (CH_3), 29.79 ($CH(CH_3)_2$), 44.84 (NCH_3), 59.35 (CHCOOEt), 61.19 (CH_3CH_2OCO), 77.49 (CHN), 80.10 ($OC(Me)_2$), 172.72 (CO); MS (m/e) 291 [M$^+$].

6.29.7. 4-Ethoxycarbonyl-3-phenethyl-2,5,5-trimethylisoxazolidine (5.8)



61% yield; IR (neat) ν (CO) 1737 cm^{-1}; ^1H NMR δ 1.12 (s, 3H, *CH3*), 1.18 (t, *J* = 10 Hz, 3H,*CH3*CH2), 1.40 (s, 3H, *CH3*), 1.75 (m, 2H, *CH2*CH2Ph), 2.50 (m, 2H, CH2*CH2*Ph), 2.61 (s, 3H, N*CH3*), 2.82 (d, *J* = 12 Hz, 1H, *CH*COOEt), 3.00 (m, 1H, *CH*N), 4.10 (q, *J* = 10 Hz, 2H, *CH2*CH3), 7.15 (m, 5H, aromatic protons); ^{13}C NMR δ 14.86 (*CH3*CH2), 24.34 (CH3), 30.19 (CH3), 32.74 (*CH2*CH2Ph), 34.00 (CH2*CH2*Ph), 44.42 (NCH3), 61.40 (*CH*COOEt), 63.94 (CH3*CH2*OCO), 71.99 (CHN), 80.28 (OC(Me)2), 126.62, 128.77, 129.04, 142.14 (aromatic carbons), 172.07 (CO); MS (m/e) 311 [M^+] (see Appendices). Anal. Calcd. for $C_{17}H_{25}NO_3$, C, 70.10; H, 8.59; N, 4.81. Found: C, 69.93; H, 8.21; N, 4.90.

6.30. Synthesis of 1,2-Diphenylpyrazolidine (5.9)[118]



To a solution of 1,2-diphenylhydrazine (1.84 g, 10 mmol) in THF (150 mL) cooled to -78 °C, was added n-BuLi (2M, in hexane solution, 2 eq) and the reaction mixture was stirred at this temperature for 0.5h. Then, a solution of 1,3-dibromopropane (2.02 g, 10 mmol) in THF (50 mL) was added dropwise

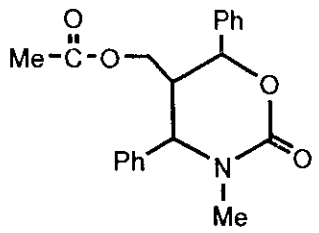
and the mixture was allowed to warm to room temperature and was stirred overnight. Quenching with saturated aq. NH_4Cl and extraction with methylene chloride followed by drying and vacuum distillation gave 1.2 g (24%) of **(5.9)**; ^1H NMR ($CDCl_3$) δ 2.08 (m, 2H, $CH_2CH_2CH_2$), 3.55 (br t, 4H, $2xCH_2N$), 6.80-6.95 (m, 10H, aromatic protons) (see also **Fig 5.8**, Chapter 5).

6.31. Carbonylation of Isoxazolidines (5.2-5.8) and 1,2-Diphenylpyrazolidine (5.9)

6.31.1. Carbonylation of Isoxazolidines (5.2-5.6) and 1,2-Diphenylpyrazolidine (5.9) using $[Rh(COD)Cl]_2$ as a Catalyst (General Procedure)

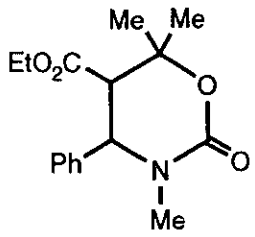
A mixture of the isoxazolidines or pyrazolidine (5 mmol), $[Rh(COD)Cl]_2$ (0.025g, 0.05 mmol) and dry benzene (10 mL) was placed in an autoclave containing a glass liner and stirring bar. The autoclave was purged several times with carbon monoxide, pressurized to 65 atm, and the reaction mixture was stirred at 150-170 °C for 24h. The reaction was then cooled to room temperature and filtered through acidic alumina using CH_2Cl_2 and then ethyl acetate as eluants. The ethyl acetate fraction which contains the product was purified by preparative thin-layer chromatography using 35% ethyl acetate in hexane as developper. It should be noted that the 1,3-oxazin-2-one product is quite polar. The product is usually found close to the base line on the chromatogram.

6.31.1.1. 5-Acetoxymethyl-4,6-diphenyl-3-methyltetrahydro-1,3-oxazin-2-one (5.10)



80% yield; IR (neat) ν (CO) 1704, 1738 cm^{-1}; ^1H NMR δ 2.02 (s, 3H, CH_3CO), 2.33 (m, 1H, $CHCH_2OCO$), 2.70 (s, 3H, NCH_3), 3.75 (ddd, J = 2, 15, 90 Hz, 2H, CH_2OCO), 4.42 (d, J = 11 Hz, 1H, PhCHN), 5.23 (d, J = 12 Hz, 1H, PhCH(O)), 7.30 (m, 10H, aromatic H); ^{13}C NMR δ 21.22 (CH_3CO), 35.31 (NCH_3), 48.52 ($CHCH_2CO$), 61.08 (CH_2OCO), 64.07 (PhCHN), 79.58 (PhCHO), 127.63, 127.89, 129.34, 129.56, 129.82, 129.88, 136.64, 139.19 (aromatic C), 155.55 (NCOO), 170.84 (CO); MS (m/e) 339 [M^+]. Anal. Calcd. for $C_{20}H_{21}NO_4$, C, 70.80; H, 6.19; N, 4.13. Found: C, 71.22; H, 6.04; N, 4.06.

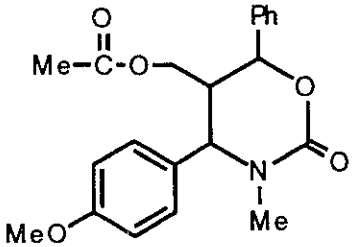
6.31.1.2. 5-Ethoxycarbonyl-4-phenyl-3,6,6-trimethyltetrahydro-1,3-oxazin-2-one (5.11)



72% yield; IR (neat) ν (CO) 1705, 1733 cm^{-1}; ^1H NMR δ 0.95 (t, J = 8 Hz, 3H, CH_3CH_2), 1.35 (s, 3H,CH_3), 1.45 (s, 3H, CH_3), 2.62 (s, 3H, NCH_3), 2.87 (d, J

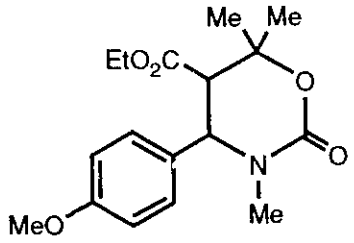
= 15 Hz, 1H, *CH*COOEt), 3.90 (q, *J* = 8 Hz, 2H, CH_2CH_3), 4.58 (d, *J* = 15 Hz, 1H, Ph*CH*N), 7.20 (m, 5H, aromatic H); ^{13}C NMR δ 13.98 (CH_3CH_2), 21.66 (CH_3), 27.95 (CH_3), 34.11 (NCH_3), 57.82 (*CH*COOEt), 61.23 (CH_3CH_2OCO), 61.74 (PhCHN), 77.75 ($OC(Me)_2$), 127.20, 128.46, 129.04, 137.89 (aromatic C), 153.48 (NCOO), 171.46 (CO); MS (m/e) 291 [M+]. Anal. Calcd. for $C_{16}H_{21}NO_4$, C, 65.98; H, 7.22; N, 4.81. Found: C, 65.83; H, 7.65; N, 4.75.

6.31.1.3. 5-Acetoxymethyl-4-(*p*-methoxyphenyl)-3-methyl-6-phenyltetrahydro-1,3-oxazin-2-one (5.12)



20% yield; IR (neat) ν (CO) 1702, 1738 cm^{-1}; ^1H NMR δ 1.95 (s, 3H, CH_3CO), 2.42 (m, 1H, $CHCH_2OCO$), 2.70 (s, 3H, NCH_3), 3.70 (s, 3H, OCH_3), 3.75 (ddd, *J* = 2, 15, 90 Hz, 2H, CH_2OCO), 4.47 (d, *J* = 11 Hz, 1H, Ph*CH*N), 5.25 (d, *J* = 12 Hz, 1H, p-$MeOC_6H_4CH(O)$), 7.35 (m, 9H, aromatic H); ^{13}C NMR δ 21.22 (CH_3CO), 35.31 (NCH_3), 48.52 ($CHCH_2CO$), 56.56 (OCH_3), 61.06 (CH_2OCO), 64.07 (p-$MeOC_6H_4CH$N), 80.45 (Ph*CH*O), 127.54, 127.88, 129.32, 129.47, 129.78, 129.88, 136.64, 139.19 (aromatic C), 158.75 (NCOO), 170.84 (CO); MS (m/e) 369 [M+].

6.31.1.4. 5-Ethoxycarbonyl-4-(p-methoxyphenyl)-3,6,6-trimethyltetrahydro-1,3-oxazin-2-one (5.13)

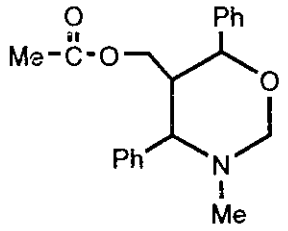


64% yield; IR (neat) ν (CO) 1706, 1735 cm^{-1}; ^1H NMR δ 1.05 (t, J = 8 Hz, 3H, CH_3CH_2), 1.45 (s, 3H,CH_3), 1.50 (s, 3H, CH_3), 2.70 (s, 3H, NCH_3), 2.87 (d, J = 10 Hz, 1H, CHCOOEt), 3.80 (s, 3H, OCH_3), 4.05 (q, J = 8 Hz, 2H, CH_2CH_3), 4.77 (d, J = 10 Hz, 1H, p-$OMeC_6H_4CH$N), 6.85, 7.22 (m, 4H, aromatic H); ^{13}C NMR δ 13.98 (CH_3CH_2), 19.73 (CH_3), 27.95 (CH_3), 34.94 (NCH_3), 55.23 (OCH_3), 58.97 (CHCOOEt), 60.88 (CH_3CH_2OCO), 61.74 (PhCHN), 77.98 ($OC(Me)_2$), 114.00, 128.28, 128.70, 129.96, 132.84 (aromatic C), 159.12 (NCOO), 171.41 (CO); MS (m/e) 321 [M^+].

6.31.2. Carbonylation of Isoxazolidines (5.2-5.8) using $IrCl_3$ as a Catalyst (General Procedure)

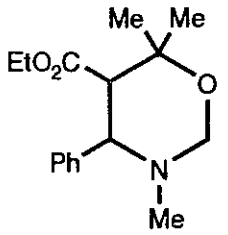
The procedure described for the rhodium catalyzed reaction was used, except for substitution of the rhodium complex by $IrCl_3$ (0.015 g, 0.05 mmol). The use of other iridium catalysts such as $[Ir(CO)_3Cl]_2$ or $[Ir(COD)Cl]_2$ for some reactions (1 mol% each) gave the same product ratios as those of for $IrCl_3$. The purification of the products was effected using preparative thin-layer chromatography with 25% ethyl acetate in hexane as the eluant.

6.31.2.1. 5-Acetoxymethyl-4,6-diphenyl-3-methyltetrahydro-1,3-oxazine (5.14)



45% yield; IR (neat) ν (CO) 1736 cm^{-1}; ^1H NMR δ 1.82 (s, 3H, CH_3CO), 1.92 (s, 3H, NCH_3), 2.15 (m, 1H, $CHCH_2OCO$), 3.29 (d, J = 11 Hz, 1H, PhCHN), 3.40 (m, 2H, CH_2OCO), 3.93 (d, J = 10 Hz, PhCHO), 4.55 (dd, J = 10, 48 Hz, 2H, NCH_2O), 7.25 (m, 10H, aromatic H); ^{13}C NMR δ 21.20 (CH_3CO), 38.16 ($CHCH_2CO$), 47.29 (NCH_3), 62.45 (CH_2OCO), 70.07 (PhCHN), 82.89 (NCH_2O), 88.27 (PhCHO), 127.86, 128.65, 128.91, 129.05, 129.21, 129.33, 140,04 (aromatic C), 170.98 (CO); MS (m/e) 325 [M^+]. Anal. Calcd. for $C_{20}H_{23}NO_3$, C, 73.85; H, 7.08; N, 4.31. Found: C, 74.25; H, 7.12; N, 4.16.

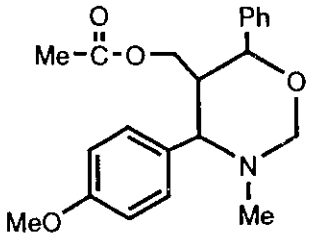
6.31.2.2. 5-Ethoxycarbonyl-4-phenyl-3,6,6-trimethyltetrahydro-1,3-oxazine (5.15)



39% yield; IR (neat) ν (CO) 1734 cm^{-1}; ^1H NMR δ 0.85 (t, J = 7 Hz, 3H, CH_3CH_2), 1.32 (s, 6H,2xCH_3), 1.88 (s, 3H, NCH_3), 2.90 (d, J = 15 Hz, 1H, CHCOOEt), 3.55 (d, J = 15 Hz, 1H, PhCHN), 3.76 (q, J = 7 Hz, 2H, CH_2CH_3),

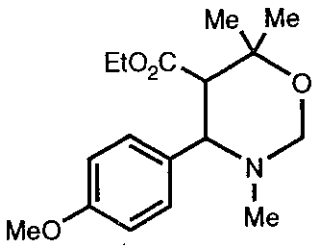
4.18 (dd, J = 11, 45 Hz, 2H, NCH_2O), 7.30 (m, 5H, aromatic H); ^{13}C NMR δ 14.45 ($CH_3$$CH_2$), 20.15 ($CH_3$), 30.79 ($CH_3$), 37.20 ($NCH_3$), 57.61 ($CH$COOEt), 60.74 ($CH_3CH_2$OCO), 65.82 (PhCHN), 73.97 ($OC(Me)_2$), 81.22 (NCH_2O), 128.39, 128.89, 129.14, 140.15 (aromatic C), 171.42 (CO); MS (m/e) 277 [M$^+$].

6.31.2.3. 5-Acetoxymethyl-4-(*p*-methoxyphenyl)-3-methyl-6-phenyltetrahydro-1,3-oxazine (5.16)



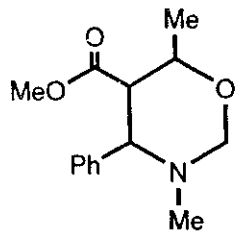
42% yield; IR (neat) ν (CO) 1736 cm^{-1}; ^{1}H NMR δ 1.82 (s, 3H, CH_3CO), 1.90 (s, 3H, NCH_3), 2.10 (m, 1H, $CH$$CH_2$OCO), 3.11 (d, J = 12.8 Hz, 1H, p-OMeC_6H_4CHN), 3.40 (m, 2H, CH_2OCO), 3.80 (s, 3H, OCH_3), 3.91 (d, J = 11.4 Hz, PhCHO), 4.54 (dd, J = 10, 50 Hz, 2H, NCH_2O), 6.68, 7.25 (m, 9H, aromatic H); ^{13}C NMR δ 21.23 (CH_3CO), 38.04 ($CH$$CH_2$CO), 47.35 ($NCH_3$), 55.84 ($OCH_3$), 62.52 ($CH_2$OCO), 69.92 (p-OMe$C_6H_4$CHN), 82.98 ($NCH_2O$), 88.30 (PhCHO), 113.82, 127.74, 127.84, 129.01, 129.20, 129.89, 131.95, 140,07, 159.87 (aromatic C), 171.02 (CO); MS (m/e) 355 [M$^+$].

6.31.2.4. 5-Ethoxycarbonyl-4-(*p*-methoxyphenyl)-3,6,6-trimethyltetrahydro-1,3-oxazine (5.17)



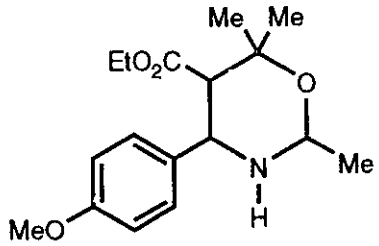
37% yield; IR (neat) ν (CO) 1740 cm^{-1}; ^1H NMR δ 0.95 (t, *J* = 8 Hz, 3H, CH_3CH_2), 1.33 (s, 6H,2xCH_3), 1.90 (s, 3H, NCH_3), 2.92 (d, *J* = 10 Hz, 1H, *CH*COOEt), 3.55 (d, *J* = 10 Hz, 1H, p-$OMeC_6H_4CH$N), 3.75 (s, 3H, OCH_3), 3.85 (q, *J* = 8 Hz, 2H, CH_2CH_3), 4.22 (dd, *J* = 9, 32 Hz, 2H, NCH_2O), 6.82, 7.22 (m, 4H, aromatic H); ^{13}C NMR δ 13.61 (CH_3CH_2), 19.24 (CH_3), 29.90 (CH_3), 36.14 (NCH_3), 54.89 (OCH_3), 56.74 (*CH*COOEt), 59.82 (CH_3CH_2OCO), 64.16 (p-$OMeC_6H_4CHN$), 73.11 ($OC(Me)_2$), 80.35 (NCH_2O), 113.33, 129.28, 131.33, 158.79 (aromatic C), 170.60 (CO); MS (m/e) 307 [M^+]. Anal. Calcd. for $C_{17}H_{25}NO_4$, C, 66.45; H, 8.14; N, 4.56. Found: C, 66.20; H, 8.02; N, 4.28.

6.31.2.5. 5-Methoxycarbonyl-3,6-dimethyl-4-phenyltetrahydro-1,3-oxazine (5.18)



24% yield (Rh), 35% yield (Ir); IR (neat) ν (CO) 1742 cm^{-1}; ^1H NMR δ 1.15 (d, J = 8 Hz, 3H, CH_3CH), 1.90 (s, 3H, NCH_3), 2.61 (t, J = 12 Hz, 1H, $CHCO$), 3.32 (s, 3H, OCH_3), 3.40 (d, J = 12 Hz, 1H, $PhCHN$), 3.72 (m, 1H, CH_3CHO), 3.92, 4.50 (dd, J = 10, 140 Hz, NCH_2O), 7.21 (m, 5H, aromatic H); ^{13}C NMR δ 20.45 (CH_3CH), 37.04 (NCH_3), 52.10 (OCH_3), 55.51 ($CHCOOCH_3$), 69.84 (PhCHN), 75.81 ((O)CMe), 87.61 (NCH_2O), 128.56, 129.14, 139.74 (aromatic C), 172.44 (CO); MS (m/e) 249 [M^+] (see Appendices).

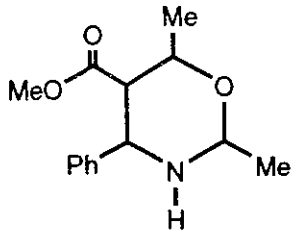
6.31.2.6. 5-Ethoxycarbonyl-4-(p-methoxyphenyl)-2,6,6-trimethyltetrahydro-1,3-oxazine (5.19)



8% yield; IR (neat) ν (CO) 1737 cm^{-1}; ^1H NMR δ 0.97 (t, J = 7 Hz, 3H, CH_3CH_2), 1.20 (d, J = 8 Hz, 3H, CH_3CH), 1.27 (s, 3H,CH_3), 1.30 (s, 3H, CH_3), 1.55 (brs, 1H, NH), 2.75 (d, J = 10 Hz, 1H, $CHCOOEt$), 3.87 (s, 3H, OCH_3), 4.00

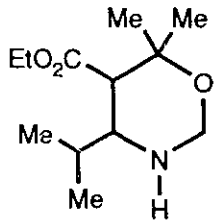
(q, J = 7 Hz, 2H, CH_2CH_3), 4.32 (d, J = 10 Hz, 1H, p-$OMeC_6H_4CHN$), 4.75 (q, J = 8 Hz, 2H, CH_3CH), 6.75, 7.14 (m, 4H, aromatic H); ^{13}C NMR δ 13.96 (CH_3CH_2), 20.47 (CH_3), 22.09 ($CHCH_3$), 30.94 (CH_3), 55.24 (OCH_3), 56.73 (*CH*COOEt), 57.14 (p-$OMeC_6H_4CHN$), 66.10 (CH_3CH_2OCO), 73.24 ($OC(Me)_2$), 77.85 ($NCH(CH_3)O$), 114.01, 128.33, 132.97, 159.12 (aromatic C), 171.81 (CO); MS (m/e) 307 [M^+]. Anal. Calcd. for $C_{17}H_{25}NO_4$, C, 66.45; H, 8.14; N, 4.56. Found: C, 66.24; H, 8.35; N, 4.26.

6.31.2.7. 5-Methoxycarbonyl-2,6-dimethyl-4-phenyltetrahydro-1,3-oxazine (5.20)



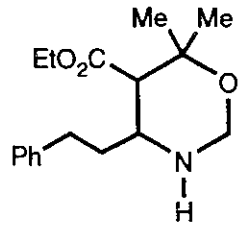
7% yield; IR (neat) ν (CO) 1749 cm^{-1}; ^1H NMR δ 1.13 (d, J = 10 Hz, 3H, CH_3CH), 1.28 (d, J = 7 Hz, 1H, $CH_3CH(O)(N)$), 1.57 (brs, 1H, NH), 2.35 (t, J = 12 Hz, 1H, *CH*CO), 3.37 (s, 3H, OCH_3), 3.82 (dt, J = 2, 10 Hz, 1H, CH_3CHO), 4.05 (d, J = 12 Hz, 1H, Ph*CH*N), 4.40 (q, J = 7Hz, $NCH(CH_3)O$), 7.20 (m, 5H, aromatic H); ^{13}C NMR δ 20.01 (CH_3CH), 22.25 ($(CH_3)CHN(O)$), 52.10 ($NCHPh$), 55.87 (OCH_3), 62.27 ($CHCOOCH_3$),74.84 (CH_3CHO), 85.27 ($NCH(CH_3)O$), 127.45, 128.64, 129.04, 140.64 (aromatic C), 173.20 (CO); MS (m/e) 249 [M^+] (see Appendices). Anal. Calcd. for $C_{14}H_{19}NO_3$, C, 67.47; H, 7.63; N, 5.62. Found: C, 67.41; H, 7.82; N, 5.20.

6.31.2.8. 5-Ethoxycarbonyl-6,6-dimethyl-4-isopropyltetrahydro-1,3-oxazine (5.21)



47% yield; IR (neat) ν (CO) 1733 cm^{-1}; ^1H NMR δ 0.75 (d, *J* = 9.7 Hz, 3H, CH_3CH), 0.92 (d, *J* = 9.7 Hz, 3H,CH_3CH), 1.13 (t, *J* = 10 Hz, 3H, CH_3CH_2), 1.18 (s, 3H, CCH_3), 1.23 (s, 3H, CCH_3), 1.41 (brs, 1H, NH), 1.55 (m, 1H, $CH(CH_3)_2$), 2.30 (d, *J* = 14.4 Hz, 2H, *CH*COOEt), 4.02 (q, *J* = 1- Hz, 2H, CH_2CH_3), 4.33 (dd, *J* = 3.2, 10.3 Hz, 2H, NCH_2O); ^{13}C NMR δ 13.91 (CH_3), 14.54 (CH_3), 19.59 (CH_3CH_2), 20.18 (CH_3), 29.36 (CH_3), 30.51 ($CH(CH_3)_2$), 55.54 (*CH*COOEt), 56.31 (CHN), 59.89 (CH_3CH_2OCO), 72.21 ($OC(Me)_2$), 73.00 (NCH_2O), 172.07 (CO); MS (m/e) 291 [M^+]. Anal. Calcd. for $C_{12}H_{23}NO_3$, C, 62.88; H, 10.04; N, 6.11. Found: C, 62.27; H, 9.68; N, 5.83.

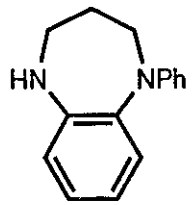
6.31.2.9. 5-Ethoxycarbonyl-6,6-dimethyl-4-phenethyltetrahydro-1,3-oxazine (5.22)



65% yield; IR (neat) ν (CO) 1722 cm^{-1}; ^1H NMR δ 1.12 (t, *J* = 10 Hz, 3H,CH_3CH_2), 1.19 (s, 6H, 2xCH_3), 1.33 (m, 1H, CH_2CH_2Ph), 1.68 (m, 1H,

CH_2CH_2Ph), 2.12 (d, J = 11.4 Hz, 1H, CHCOOEt), 2.58 (m, 1H, CH_2CH_2Ph), 2.82 (m, 1H, CH_2CH_2Ph), 3.10 (m, 1H, CHN), 4.05 (m, 2H, CH_2CH_3), 4.35 (dd, J = 4.3, 10 Hz, 2H, NCH_2O), 7.12 (m, 5H, aromatic protons); ^{13}C NMR δ 14.81 (CH_3CH_2), 20.53 (CH_3), 31.34 (CH_3), 32.34 (CH_2CH_2Ph), 37.56 (CH_2CH_2Ph), 52.61 (CHCOOEt), 59.33 (CH_3CH_2OCO), 60.94 (CHN), 73.06 ($OC(Me)_2$), 73.78 (NCH_2O), 126.44, 128.97, 142.60 (aromatic carbons), 172.80 (CO); MS (m/e) 311 [M$^+$] (see Appendices).

6.32. 1-Phenyl[2,3-*b*]benzo-1,4-diazepin (5.28)



17% yield ^{1}H NMR ($CDCl_3$) δ 1.95 (m, 2H, $CH_2CH_2CH_2$), 3.15 (t, 2H, CH_2NH), 3.75 (br s, 1H, NH), 3.90 (t, 2H, CH_2NPh), 6.70-7.25 (m, 9H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 26.67 ($CH_2CH_2CH_2$), 43.86 (CH_2NH), 47.13 (CH_2NPh), 114.34, 117.44, 119.09, 119.50, 125.64, 129.15, 129.21, 133.70, 146.20, 148.71 (aromatic carbons) (for ^{1}H and ^{13}C NMR spectra see also **Fig. 5.9**, Chapter 5). MS (m/e) 224 [M$^+$].

CLAIMS TO ORIGINAL RESEARCH

1. Carbonylation of two different heteroatoms in heterocyclic compounds.
2. Carbonylation with ketene elimination of thiazolidines. A novel conversion of thiazolidines to thiazolidinones.
3. The completely regioselective conversion of a thiazolidine to a 1,4-thiazin--3-one.
4. The rhodium(I) catalyzed transformation of 1,4-thiazin-3-ones to thiazolidinones.
5. Regiospecific carbonylation of acyclic compounds containng two heteroatoms.
6. Regiospecific carbonylation of heterocyclic compounds containing a heteroatomic side chain.
7. Iridium catalyzed carbonylation/reduction of 3-arylisoxazolidines to tetrahydro-1,3-oxazines.
8. Iridium catalyzed rearrangement of 3-alkylisoxzazolidines to tetrahydro-1,3-oxazines.

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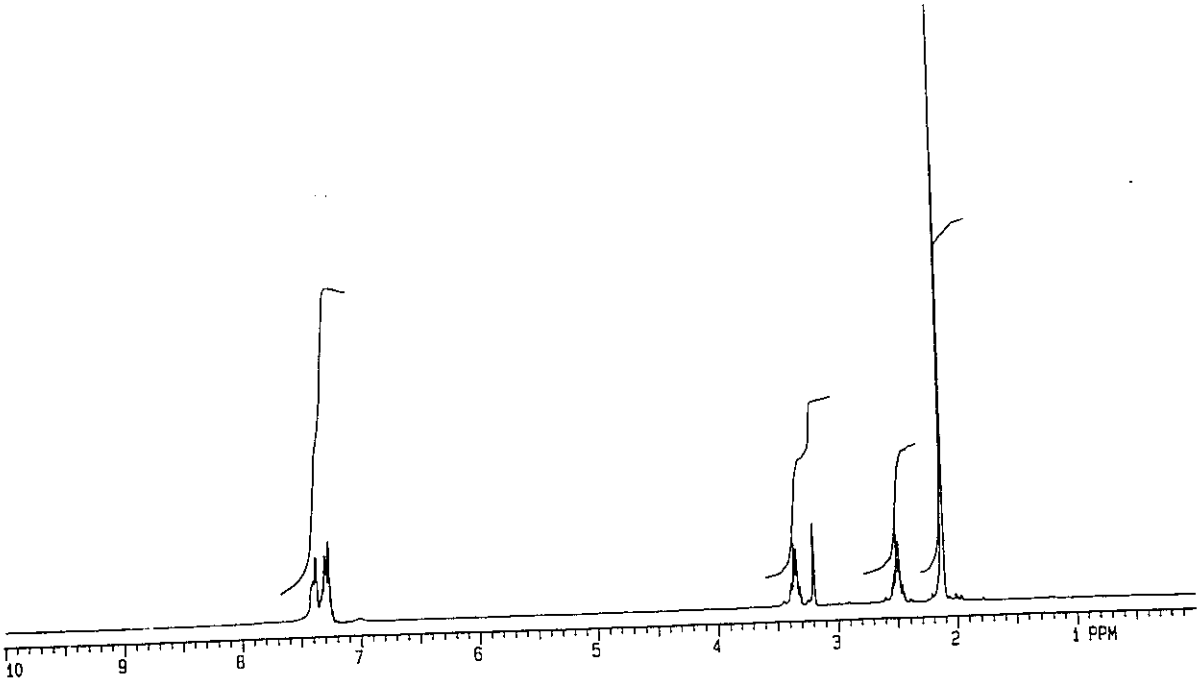
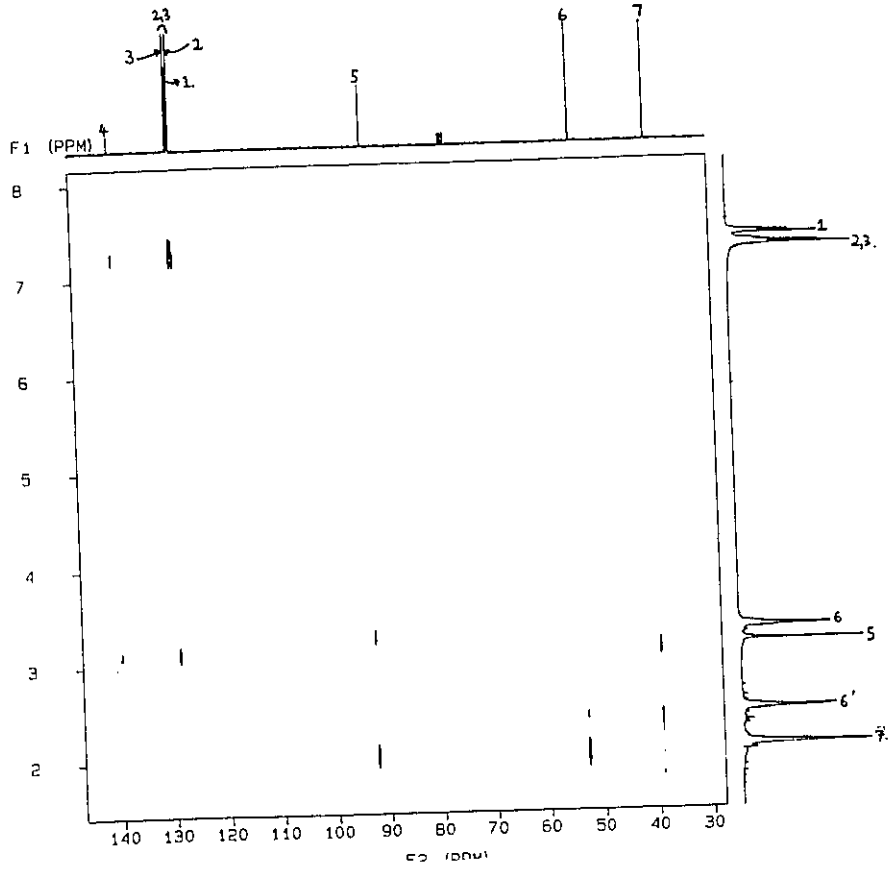
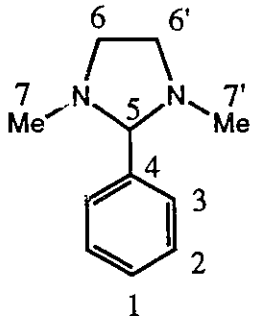
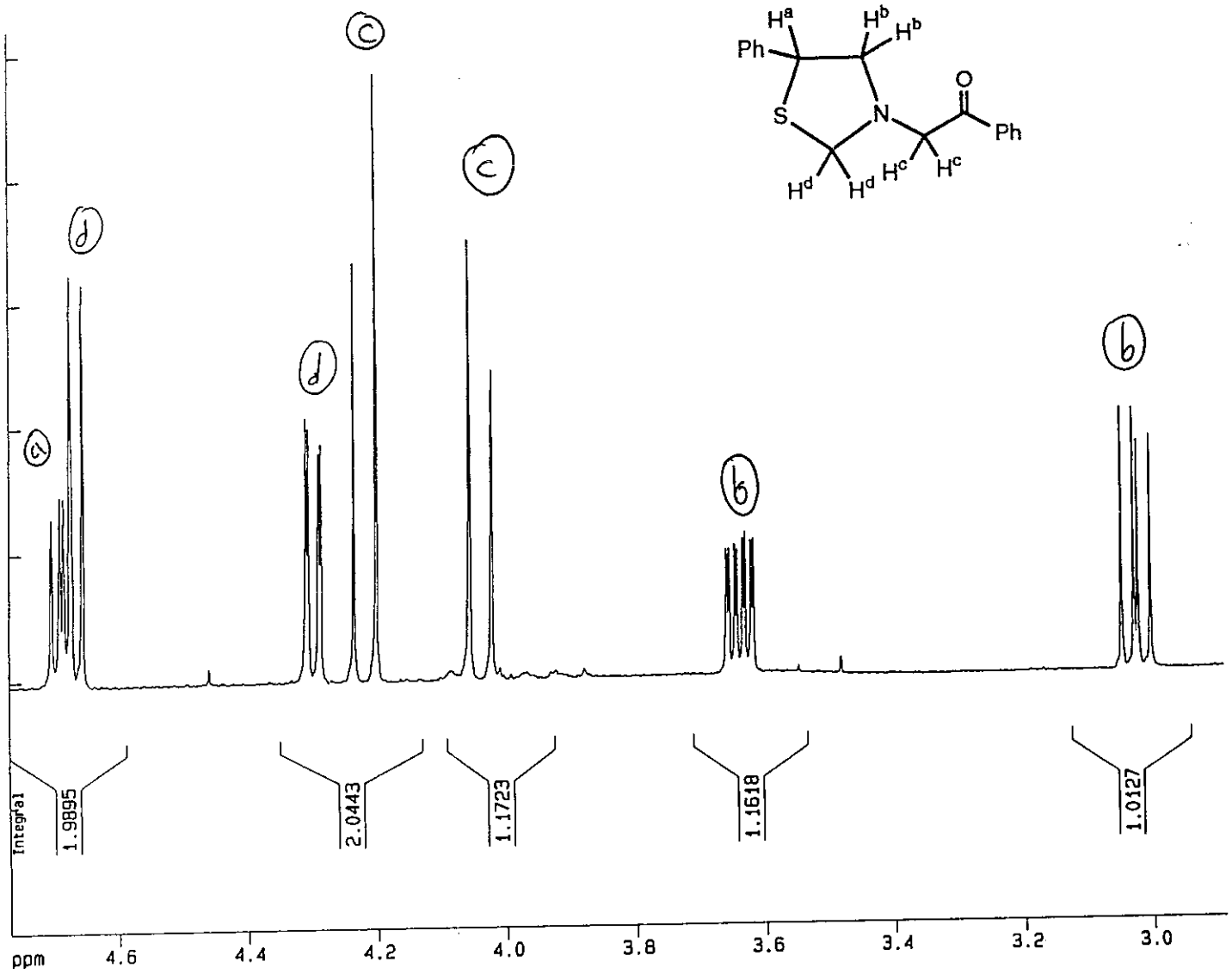
APPENDICES







The three bond coupling spectra of compound **(2.33)**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b
Integral
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2.0443
1.1723
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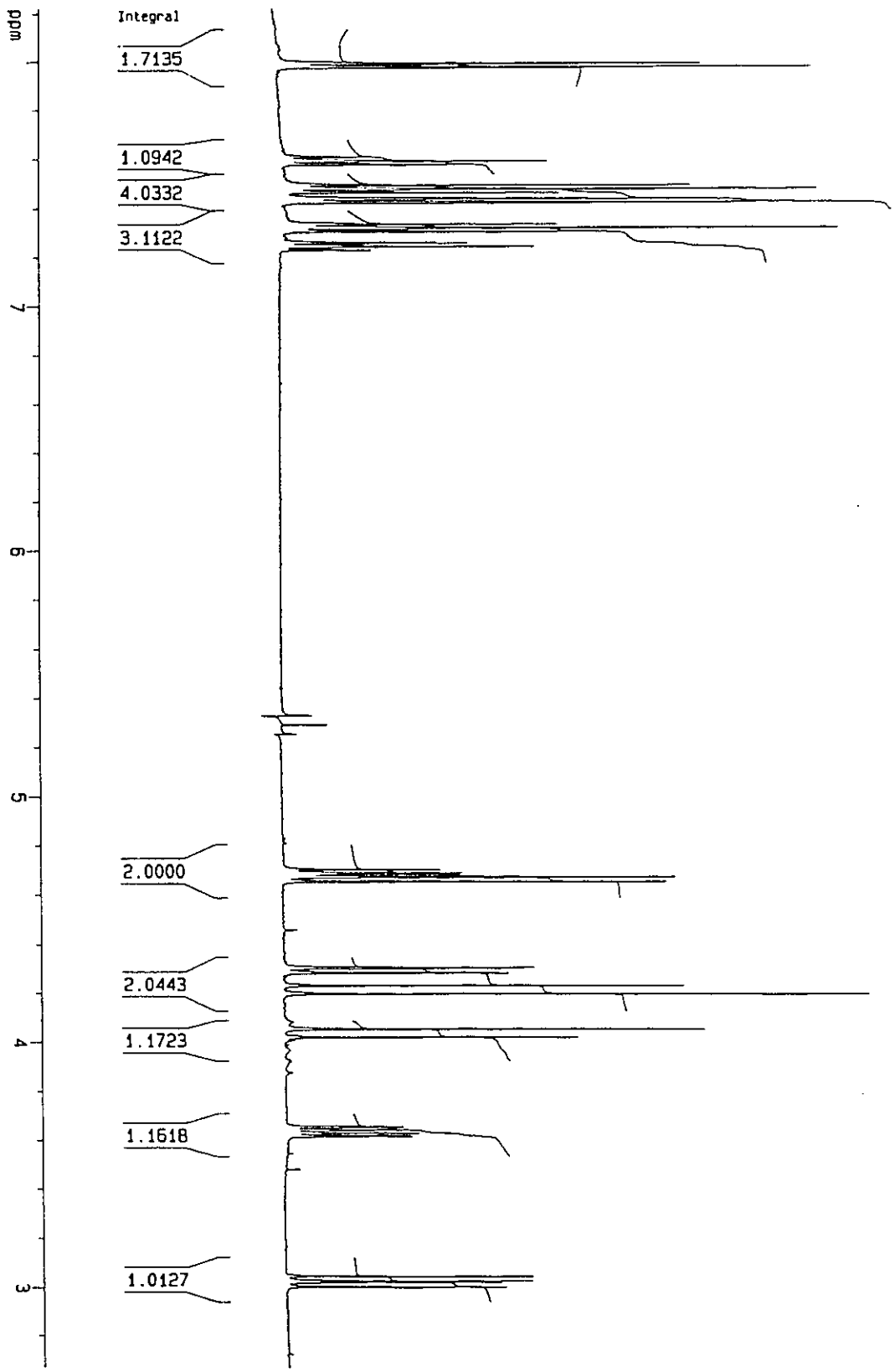
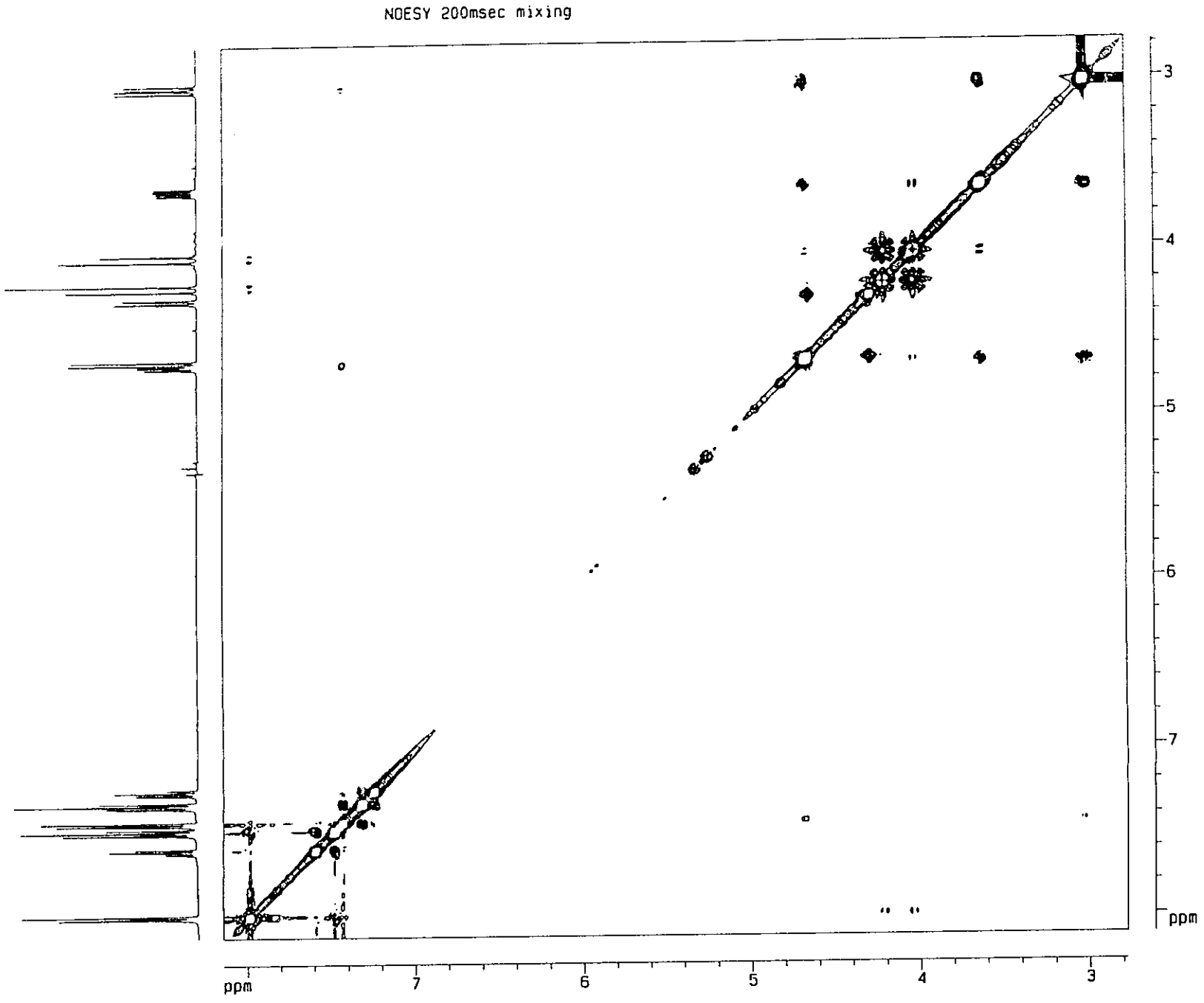


Dang expanded proton spectrum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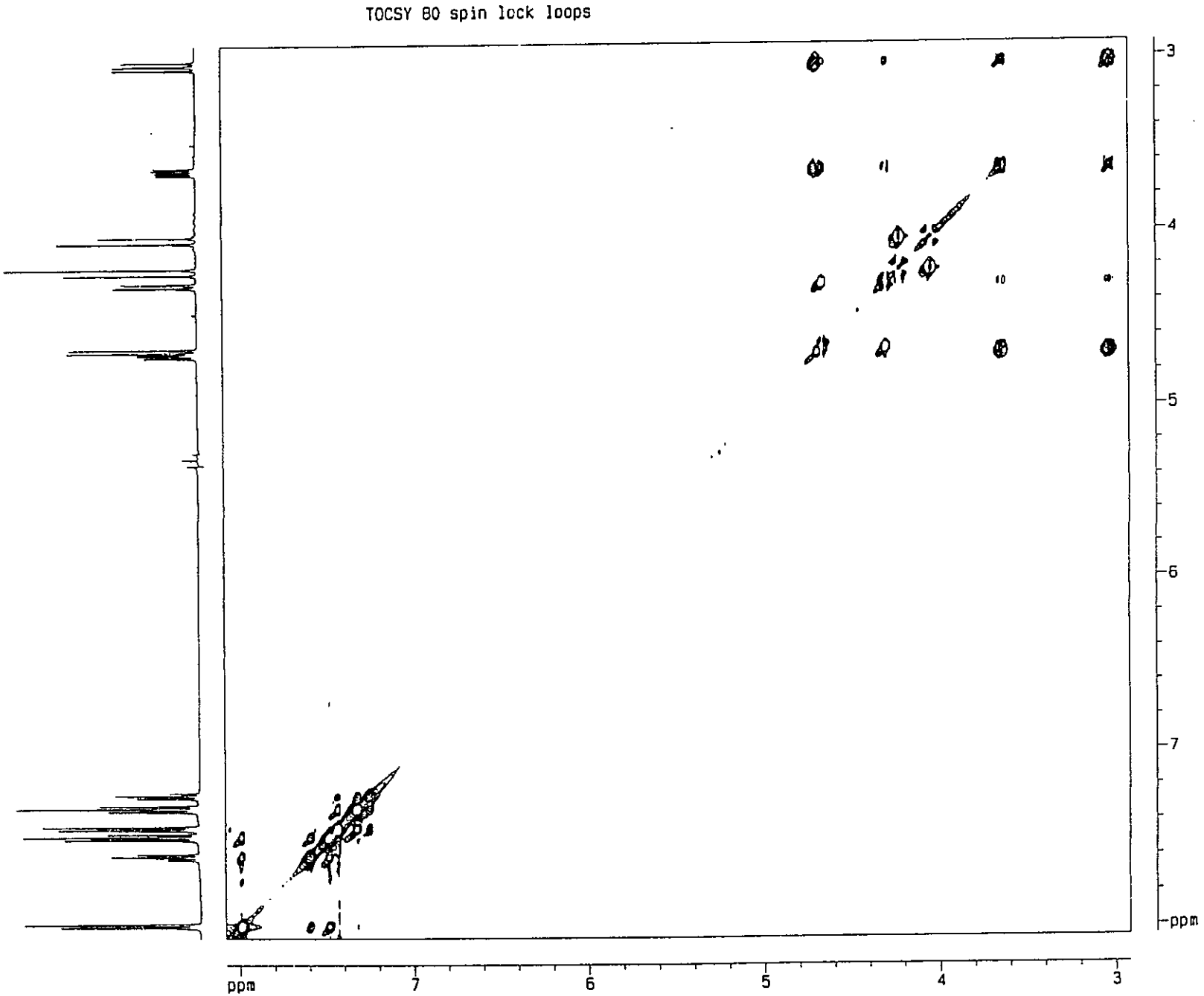
TOCSY 80 spin lock loops
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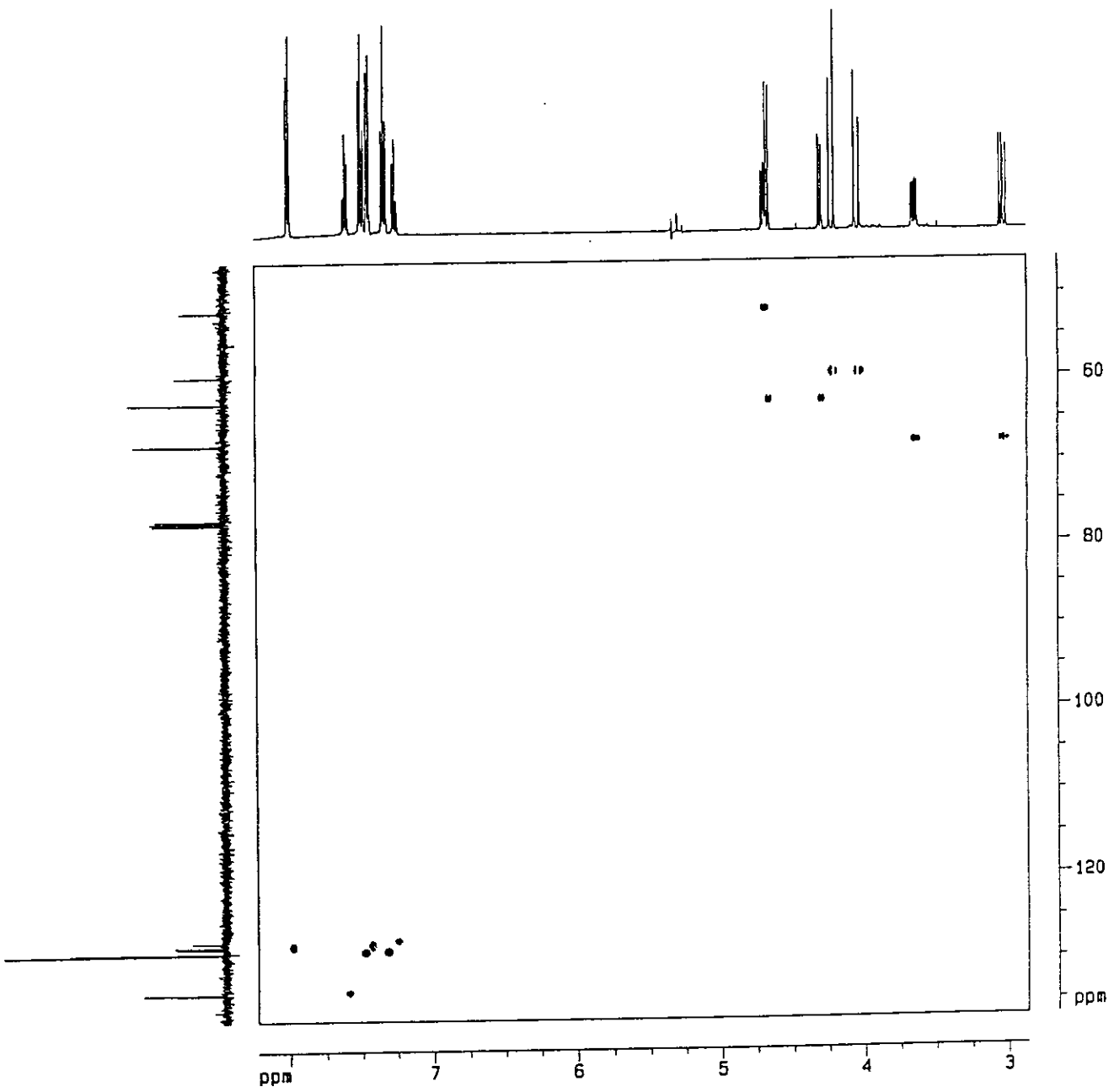
4
3



Current Data Parameters

NAME	dang_1
EXPNO	3
PROCNO	1

F2 - Acquisition Parameters

Date	930629
Time	14.27
PULPROG	invbtp
SOLVENT	CDCl3
AQ	0.1843400 sec
FIDRES	2.712674 Hz
DW	180.0 usec
RG	256
NUCLEUS	1H
NL1	0 dB
D1	2.0000000 sec
P1	6.1 usec
D2	0.0035000 sec
P2	12.6 usec
P4	18.0 usec
SFO2	125.7797595 MHz
D7	0.7000000 sec
P3	9.0 usec
D0	0.0000030 sec
D13	0.0000030 sec
DL0	19.00 dB
DE	225.0 usec
SFO1	500.1815717 MHz
SWH	2777.78 Hz
TD	1024
P31	80.0 usec
NS	8
DS	4
INO	0.0000142 sec

F1 - Acquisition parameters

NDO	4
TD	512
SFO1	125.7758 MHz
FIDRES	34.392902 Hz
SW	140.000 ppm

F2 - Processing parameters

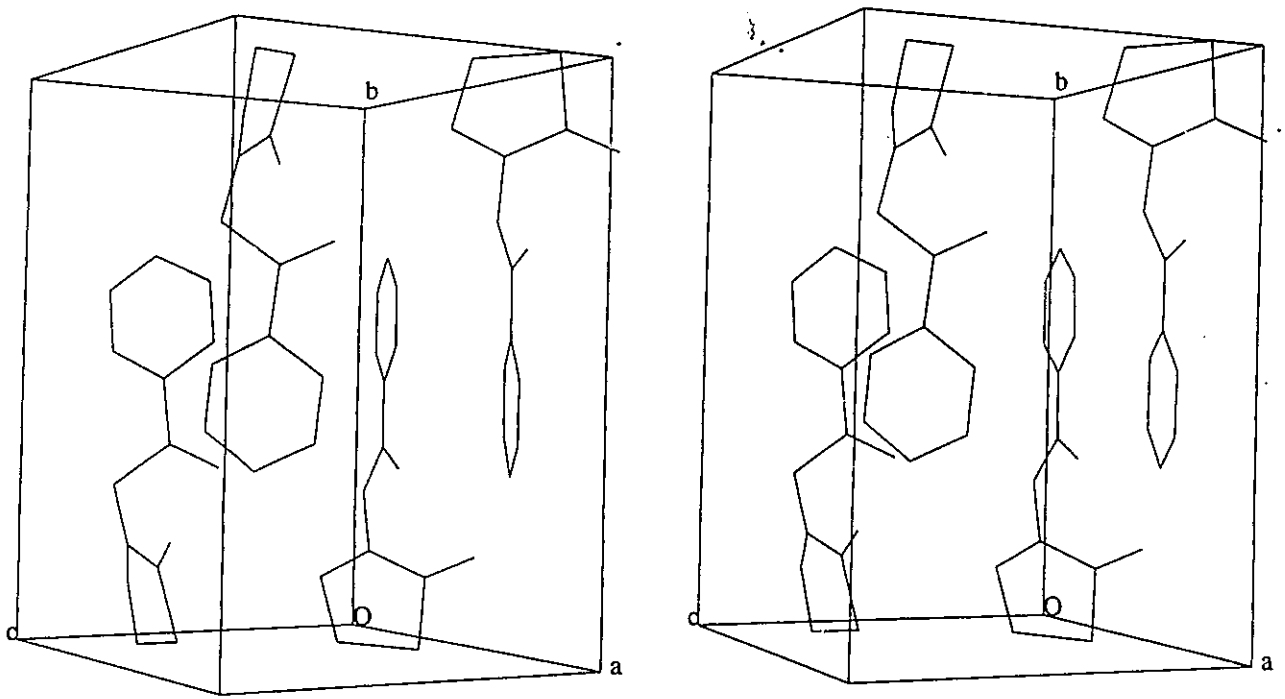
SI	512
SF	500.1788481 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.40

F1 - Processing parameters

SI	512
MC2	TPPI
SF	125.7700759 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	12.29 cm
CX1	12.29 cm
F2PL0	8.222 ppm
F2L0	4112.49 Hz
F2PHI	2.864 ppm
F2HI	1432.37 Hz
F1PL0	136.882 ppm
F1L0	17215.66 Hz
F1PHI	45.820 ppm
F1HI	5762.83 Hz
F2PPMCM	0.40590 ppm/cm
F2HZCM	218.02901 Hz/cm
F1PPMCM	7.46791 ppm/cm
F1HZCM	931.59305 Hz/cm



The Streoview of The Packing Diagram **(2.40)**

Crystal data for 3-(Benzoylmethyl)thiazolidin-2-one **(2.40)**

Formula	$C_{11}H_{11}NO_2S$
FW	221.27
cryst. shape	needle
cryst. size (mm)	0.30 x 0.05 x 0.10
d(calcd), $Mg.m^{-3}$	1.377
cryst. system	orthorhombic
space group	P ca21
a, A	9.866 (10)
b, A	12.614 (11)
c, A	8.579 (10)
Z (molecules / cell)	4
F (000), electrons	464.61
μ, mm^{-1}	0.27
total no. of reflns.	2016
unique reflns.	1873
reflns with Inet > 2.5σ(Inet)	1452
obsd. reflns	1008
no. of variables	135
R(R_w), %	7.8 (4.3)
final GoF	5.09

Atomic Bond Angles in Degrees (2.40)

C1-S1-C2	90.8(5)	C5-C4-H4B	106.8(7)
C1-N1-C3	117.5(7)	H4A-C4-H4B	110.9(8)
C1-N1-C4	120.0(7)	O2-C5-C4	120.2(7)
C3-N1-C4	119.4(7)	O2-C5-C6	121.4(9)
S1-C1-O1	122.8(7)	C4-C5-C6	118.3(8)
S1-C1-N1	110.5(6)	C5-C6-C7	117.8(8)
O1-C1-N1	126.8(7)	C5-C6-C11	123.5(8)
S1-C2-C3	109.3(7)	C7-C6-C11	118.6(7)
S1-C2-H2A	108.2(6)	C6-C7-C8	119.7(9)
S1-C2-H2B	113.4(7)	C6-C7-H7	119.1(6)
C3-C2-H2A	108.8(8)	C8-C7-H7	121.0(8)
C3-C2-H2B	112.1(9)	C7-C8-C9	120.3(8)
H2A-C2-H2B	104.9(7)	C7-C8-H8	119.4(9)
N1-C3-C2	104.9(7)	C9-C8-H8	120.3(7)
N1-C3-H3A	109.1(8)	C8-C9-C10	119.2(7)
N1-C3-H3B	112.8(8)	C8-C9-H9	118.2(9)
C2-C3-H3A	108.8(8)	C10-C9-H9	122.6(10)
C2-C3-H3B	110.5(8)	C9-C10-C11	121.2(9)
H3A-C3-H3B	110.6(8)	C9-C10-H10	119.3(7)
N1-C4-C5	111.7(7)	C11-C10-H10	119.4(8)
N1-C4-H4A	109.7(7)	C6-C11-C10	120.9(8)
N1-C4-H4B	111.7(7)	C6-C11-H11	119.1(9)
C5-C4-H4A	105.9(7)	C10-C11-H11	120.1(9)

Atomic Bond Distances in Angstroms (2.40)

S1-C1	1.797(7)	C4-H4B	1.048(10)
S1-C2	1.796(9)	C5-C6	1.488(10)
O1-C1	1.217(12)	C6-C7	1.436(13)
O2-C5	1.237(13)	C6-C11	1.387(13)
N1-C1	1.363(13)	C7-C8	1.378(10)
N1-C3	1.450(11)	C7-H7	1.088(10)
N1-C4	1.396(10)	C8-C9	1.433(15)
C2-C3	1.524(12)	C8-H8	1.116(9)
C2-H2A	1.161(9)	C9-C10	1.361(14)
C2-H2B	1.063(9)	C9-H9	1.061(8)
C3-H3A	1.108(10)	C10-C11	1.394(12)
C3-H3B	1.037(13)	C10-H10	1.094(9)
C4-C5	1.552(14)	C11-H11	1.071(9)
C4-H4A	1.093(8)		

Atomic Parameters x, y, z and B_{iso} **(2.40)**

	x	y	z	Biso
S1	0.92127(25)	0.01086(18)	0.08769	3.60(11)
O1	1.0677 (6)	-0.1623 (4)	0.0334 (9)	4.4 (4)
O2	0.7795 (6)	-0.3082 (4)	0.0589 (10)	3.9 (4)
N1	0.9164 (7)	-0.1687 (5)	0.2382 (9)	2.9 (4)
C1	0.9809 (8)	-0.1225 (5)	0.1153 (14)	3.2 (5)
C2	0.8169 (9)	0.0007 (8)	0.2586 (11)	4.2 (6)
C3	0.7974 (9)	-0.1158 (5)	0.2997 (15)	4.0 (6)
C4	0.9369 (9)	-0.2760 (6)	0.2704 (12)	2.7 (5)
C5	0.8529 (8)	-0.3480 (6)	0.1601 (15)	3.0 (5)
C6	0.8712 (8)	-0.4649 (5)	0.1718 (14)	2.4 (4)
C7	0.7852 (8)	-0.5311 (5)	0.0782 (14)	3.2 (5)
C8	0.7963 (8)	-0.6397 (6)	0.0887 (15)	3.7 (6)
C9	0.8964 (10)	-0.6866 (6)	0.1883 (16)	4.7 (6)
C10	0.9794 (9)	-0.6226 (6)	0.2730 (13)	3.3 (5)
C11	0.9685 (8)	-0.5125 (8)	0.2650 (11)	2.8 (5)
H2A	0.712	0.038	0.230	4.5
H2B	0.854	0.045	0.355	4.5
H3A	0.706	-0.146	0.238	4.7
H3B	0.787	-0.125	0.419	4.7
H4A	1.043	-0.297	0.250	3.5
H4B	0.908	-0.295	0.385	3.5
H7	0.707	-0.495	0.007	4.0
H8	0.730	-0.691	0.015	4.5
H9	0.903	-0.771	0.192	5.0
H10	1.060	-0.658	0.344	4.3
H11	1.037	-0.464	0.330	3.8

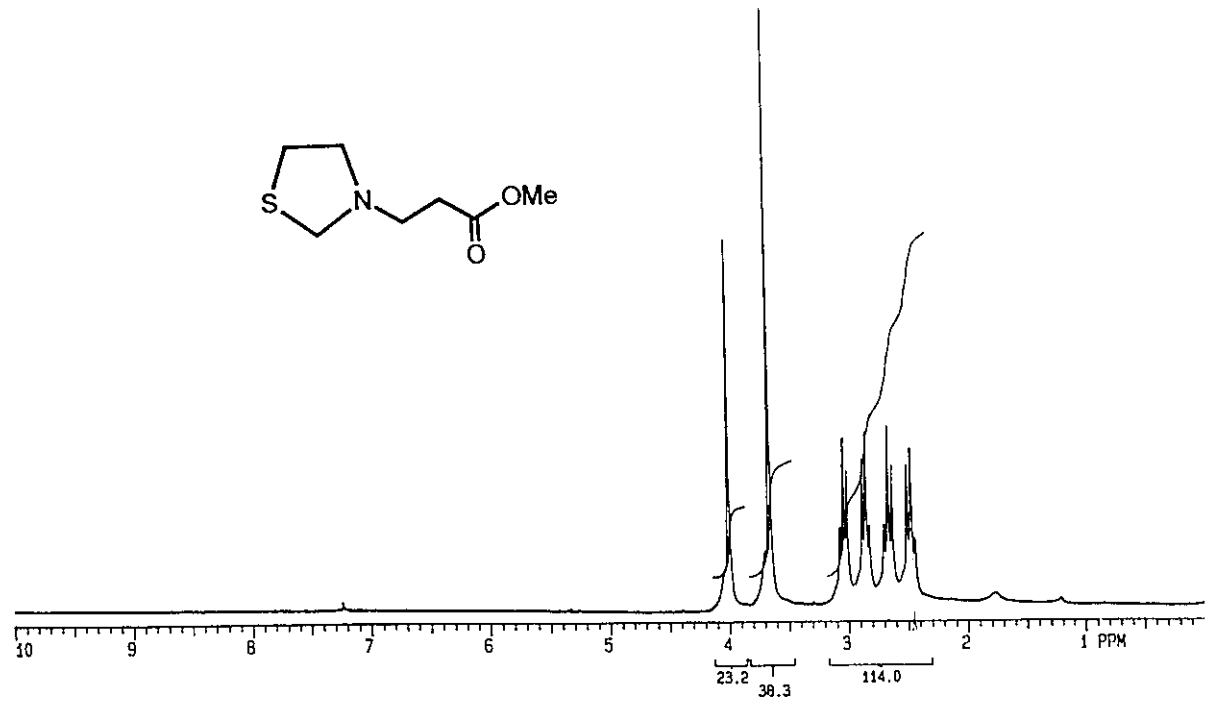
B_{iso} is the Mean of the Principal Axes of the Thermal Ellipsoid

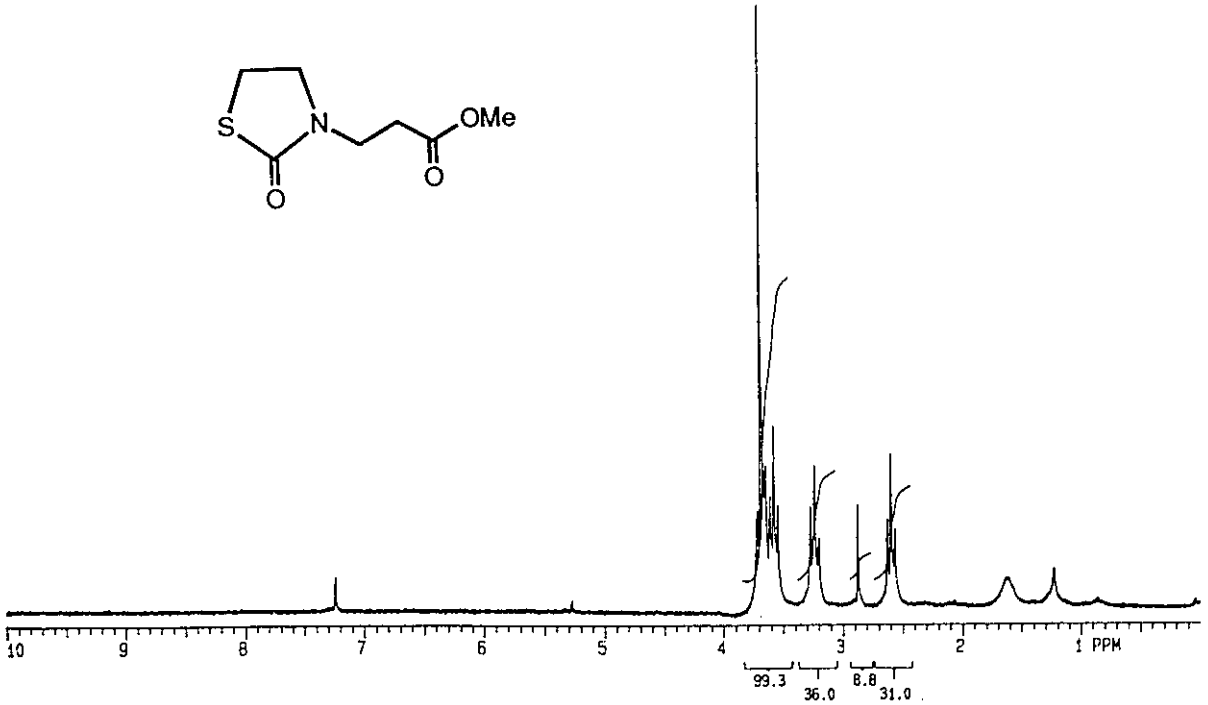
Table of u(i, j) or U values * 100 **(2.40)**

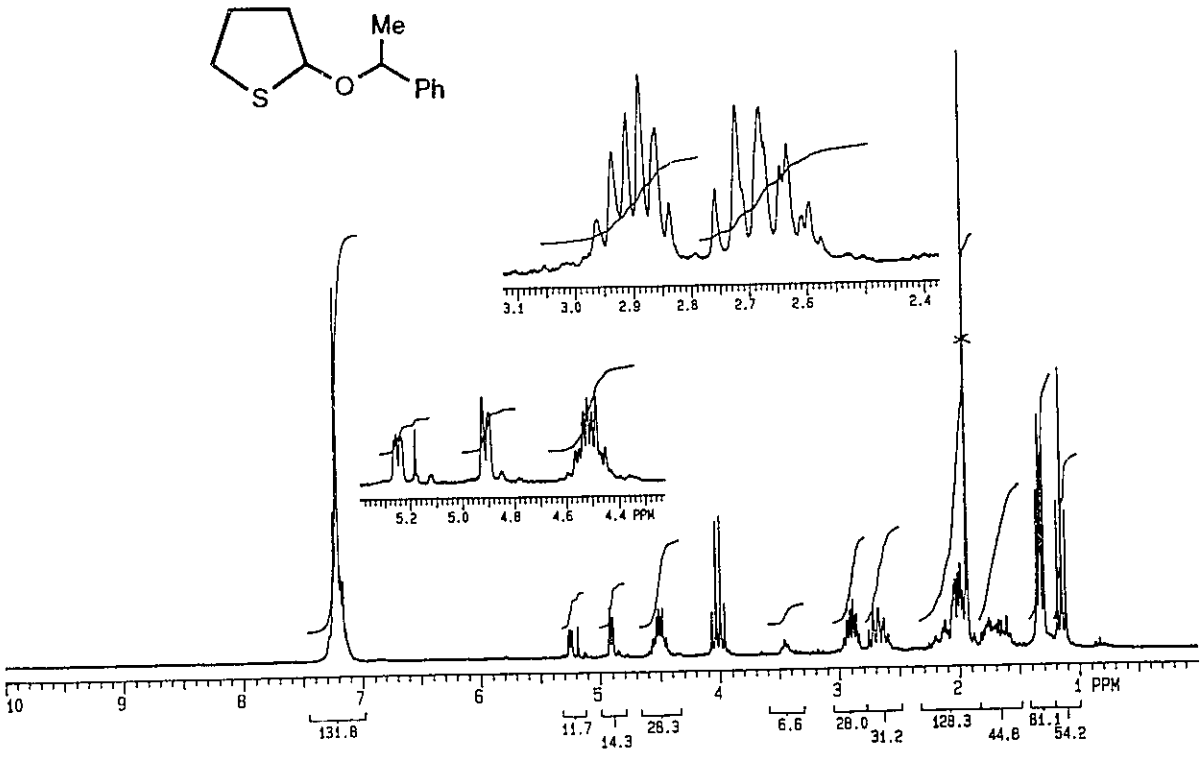
	u11(U)	u22	u33	u12	u13	u23
S1	4.36(14)	3.11(11)	6.18(17)	0.15(15)	0.02(23)	0.26(22)
O1	3.9 (4)	3.7 (3)	9.1 (7)	0.1 (4)	1.4 (6)	0.6 (5)
O2	2.7 (4)	4.1 (3)	8.0 (6)	-0.1 (3)	-0.9 (5)	1.9 (6)
N1	2.8 (4)	2.8 (4)	5.4 (7)	0.5 (4)	0.7 (6)	0.4 (5)
C1	2.9 (5)	2.3 (4)	6.9 (10)	0.0 (4)	-1.7 (7)	-0.3 (7)
C2	6.7 (7)	5.4 (5)	4.0 (7)	2.1 (6)	-1.1 (8)	-1.2 (8)
C3	4.8 (8)	3.1 (5)	7.4 (10)	0.7 (5)	1.2 (9)	0.4 (8)
C4	3.0 (6)	2.9 (5)	4.5 (7)	0.6 (5)	-0.2 (7)	0.6 (6)
C5	2.1 (5)	3.3 (5)	6.1 (8)	0.2 (5)	1.2 (6)	0.2 (6)
C6	2.0 (5)	3.3 (5)	3.9 (6)	-0.3 (5)	0.8 (5)	0.4 (6)
C7	2.9 (6)	4.3 (5)	4.9 (6)	-0.4 (4)	0.2 (8)	-1.1 (8)
C8	4.5 (7)	3.8 (5)	5.9 (8)	-1.7 (5)	0.9 (9)	-1.0 (9)
C9	6.6 (8)	3.8 (5)	7.4 (9)	-0.9 (6)	1.8 (9)	-0.9 (8)
C10	4.4 (6)	3.3 (5)	5.0 (8)	0.8 (5)	0.3 (8)	0.4 (7)
C11	2.8 (6)	3.4 (5)	4.4 (7)	-0.3 (5)	0.6 (6)	-0.5 (7)

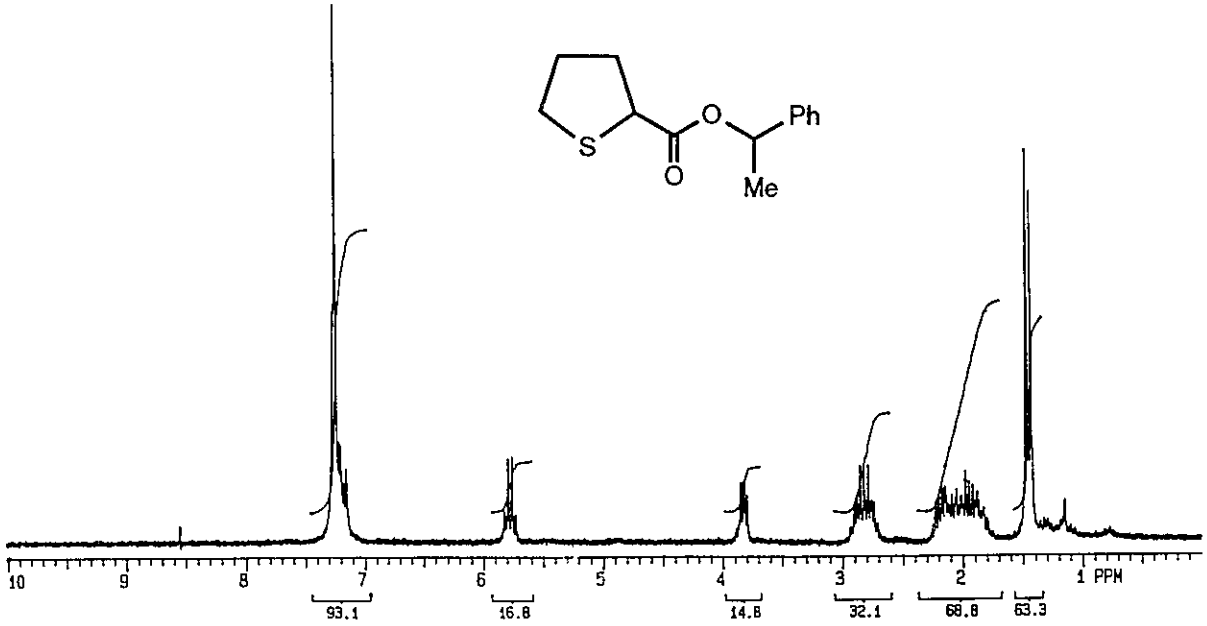
Anisotropic Temperature Factors are of the form

Temp=2*π*π*(h*h*u11*astar*astar+---+2*h*u12*astar*bstar+---)


S
N
OMe
O
10
9
8
7
6
5
4
3
2
1 PPM
23.2
38.3
114.0


S
N
OMe
O
O
10
9
8
7
6
5
4
3
2
1 PPM
99.3
36.0
8.8
31.0


Me
S
O
Ph
3.1 3.0 2.9 2.8 2.7 2.6 2.4
5.2 5.0 4.8 4.6 4.4 PPM
10 9 8 7 6 5 4 3 2 1 PPM
131.8
11.7
14.3
28.3
6.6
28.0
31.2
128.3
44.8
81.1
54.2


S
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O
Ph
Me
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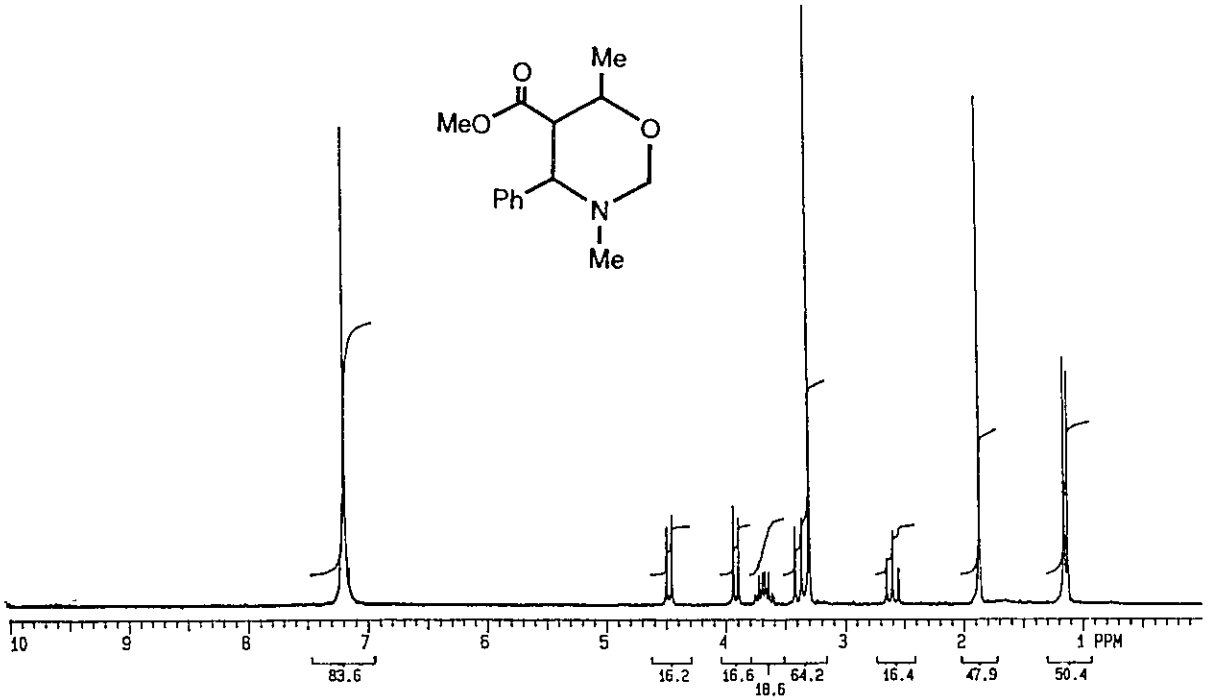
93.1
16.8
14.8
32.1
68.8
63.3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O
MeO
O
Ph
N
Me
10
9
8
7
6
5
4
3
2
1 PPM
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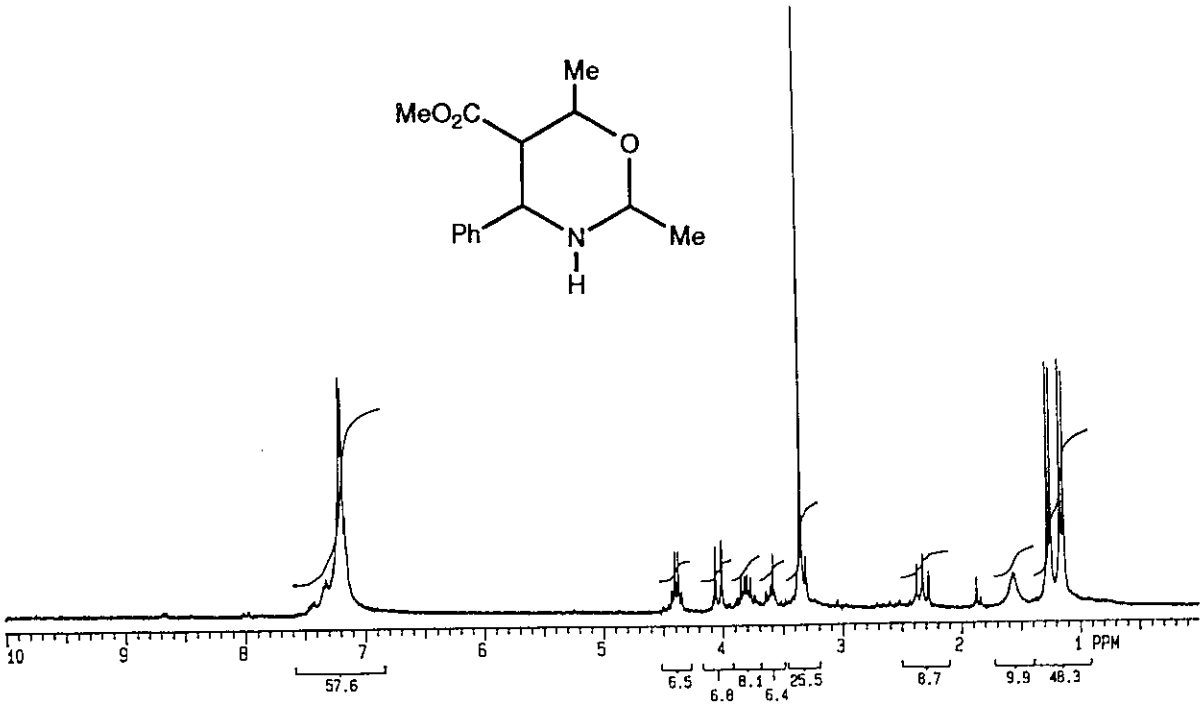
16.2
16.6
64.2
18.6
16.4
47.9
50.4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H
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10
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8
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6
5
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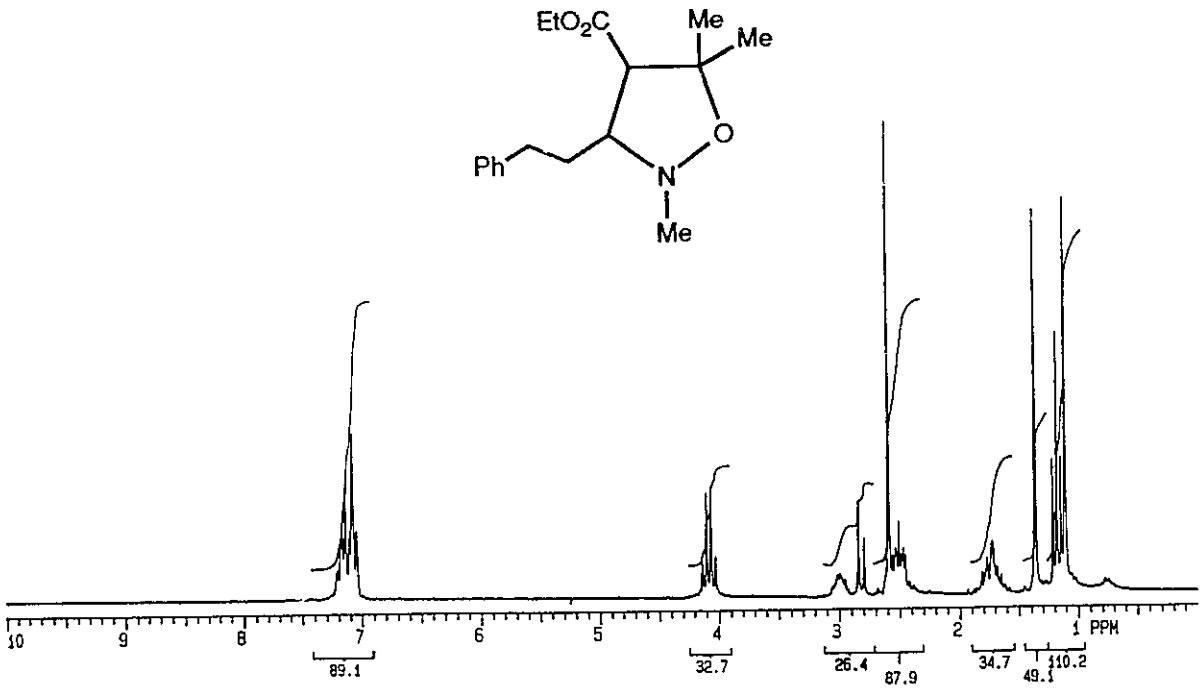
6.5
6.8
8.1
6.4
25.5
8.7
9.9
48.3


EtO2C
Me
Me
Ph
O
N
Me
10
9
8
7
6
5
4
3
2
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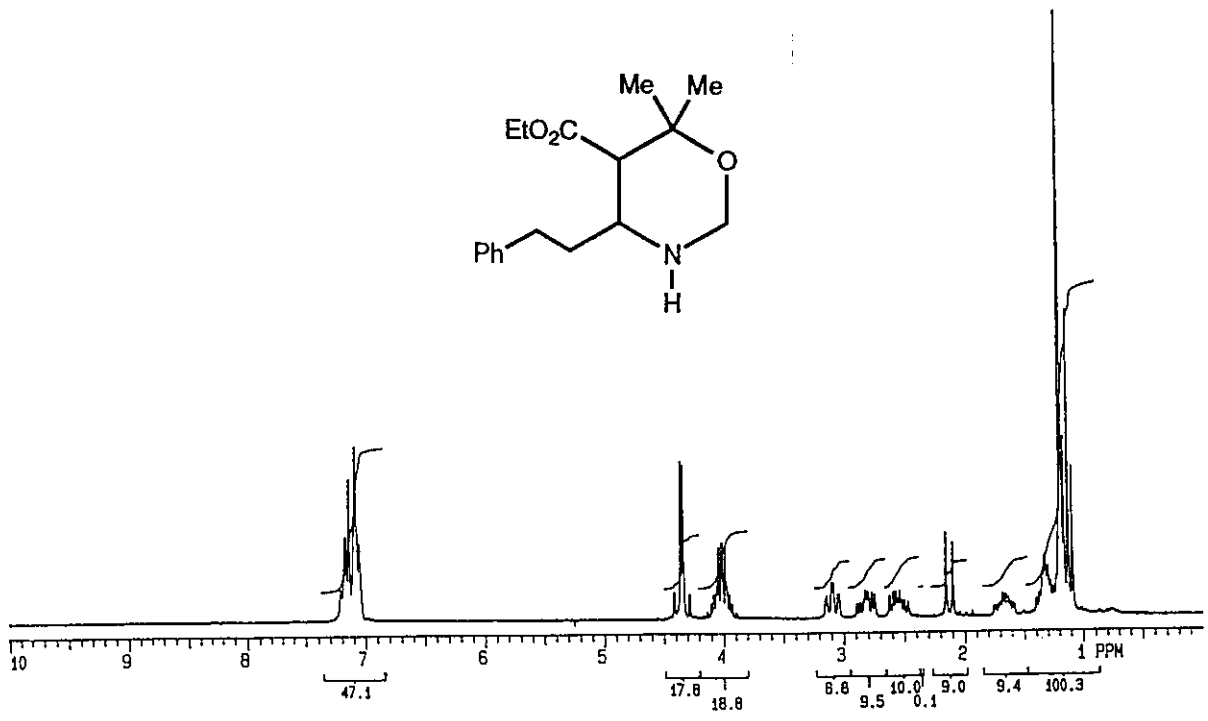
32.7
26.4
87.9
34.7
49.1
110.2


Me
Me
EtO2C
O
Ph
N
H
10
9
8
7
6
5
4
3
2
1 PPM
47.1
17.8
18.8
6.8
9.5
10.0
0.1
9.0
9.4
100.3