NOTICE

The quality of this microform is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us an inferior photocopy.

Reproduction in full or in part of this microform is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30, and subsequent amendments.

AVIS

La qualité de cette microforme dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de qualité inférieure.

La reproduction, même partielle, de cette microforme est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30, et ses amendements subséquents.

ISBN 0-315-56464-4

UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

À MES PARENTS

ET À DANIELE

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to Dr. Howard Alper for his guidance during the course of this work. I greatly appreciated his help, encouragement, patience and kindness.

I wish to thank my colleagues who have been members of our research group, for their friendship.

I acknowledge and thank the University of Ottawa, NSERC and FCAR for scholarships and financial support for this research.

Thanks are owed to Dr. Raj Capoor and Dr. Heather Dettman for recording NMR spectra, and to Dr. Clem Kazakoff for the mass spectral data. Also, I would like to thank Wilma Schmiedel and Christine Pétrin for the typing and drawings of this work.

TABLE OF CONTENTS

Chapter 1

Introduction

In this introduction some important aspects of organometallic chemistry will be briefly reviewed including homogeneous and heterogeneous catalysis, asymmetric induction, and carbonylation reactions. A more detailed analysis will then be made of the carbonylation of linear organonitrogen compounds as well as the carbonylation and cleavage of strained ring compounds by organotransition metal complexes.

1.1 Homogeneous and Heterogeneous Catalysis

Organotransition-metal complexes are compounds which have an organic group bonded to a transition metal via a metal-carbon bond. Such compounds have recently played a prominent part in synthesis, as they are able to catalyze a wide variety of organic reactions. A given organic compound may react differently depending on the metal complex with the nature of the metal and ligands of the complex both being important.

Organotransition-metal catalyzed reactions can be classified as homogeneous and heterogeneous processes. A homogeneous reaction takes place throughout one phase: i.e., all the components of the reaction are present in the same phase. In a heterogeneous reaction one or more of the components are in different phases. Normally the catalyst is a

solid and the reactants are liquids or gases. The reaction takes place at the phase boundary (usually the surface of the catalyst).

Heterogeneous catalysis is the most widely used form in industry. This is because the insoluble heterogeneous catalyst can be separated much more easily from the reaction products than a homogeneous catalyst. Also the heterogeneous catalyst is, in general, thermally more stable. However, homogeneous catalysts are becoming increasingly important[1]. Such catalysts can often be used under mild conditions allowing very high selectivity to the desired product. Moreover, mechanisms are more easily studied for homogeneous catalysts. Infrared and nuclear magnetic resonance spectroscopy can be used in many cases to study the progress of homogeneous reactions.

Nowadays more than twenty industrial processes utilize homogeneous catalysis[2]. Homogeneously catalyzed carbonylation, hydrogenation, isomerization, oligomerization, polymerization, oxidation and metathesis are well known processes. There are many reviews of transition metal homogeneous catalysis in the literature[3,4].

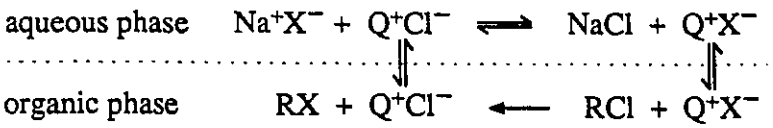
1.2 Phase Transfer Catalysis

In 1976[5], the application of phase transfer catalysis to organometallic chemistry was first described, which has resulted in new organotransition-metal chemistry. It is important to consider some general principles of phase transfer catalysis in organic chemistry. Phase transfer catalysis is related to reactions between salts dissolved in water or present in the solid state, and substances dissolved in organic media[6]. Without a catalyst those reactions are generally slow or do not occur at all. Phase transfer catalysis promotes reactions between ionic compounds and organic, water-insoluble substrates in non-polar solvents.

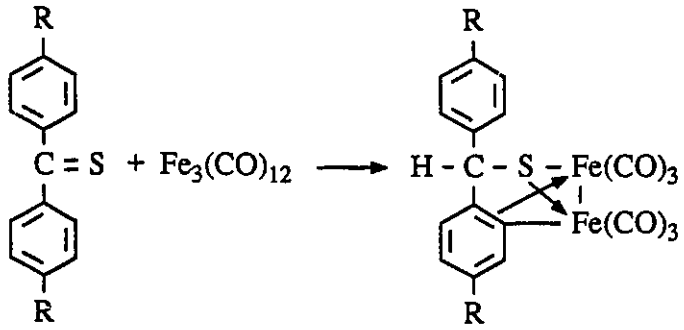
Often used phase transfer agents are lipophilic quaternary salts (ammonium, phosphonium and arsonium salts), crown ethers, cryptands, open chain polyethers (e.g.

polyethylene glycols of various molecular weights), and cyclodextrins. The basic function of the catalyst is to transfer the anions of the reacting salt into the organic medium in the form of ion pairs. In aprotic solvents these anions are unsolvated and consequently are very reactive.

The following mechanism, generalized for the SN_2 displacement of Cl by a nucleophile X^-, catalyzed by a quaternary ammonium salt (Q^+) was proposed by Starks[7]:



The first application of phase transfer to processes involving organometallic complexes[5] involved the synthesis of ortho-metalated complexes from thioketones and triiron dodecacarbonyl.



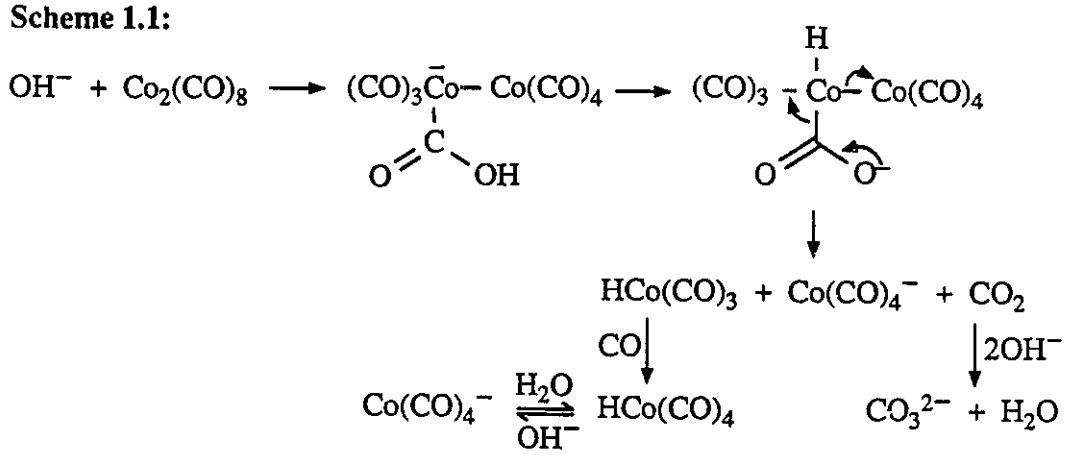
During this reaction, it is possible that $HFe_3(CO)_{11}^-$, generated under the reaction conditions, would undergo nucleophilic attack on the thione group.

Since this discovery, phase transfer catalysis has been established as a simple and cheap method for the generation of anionic metal species from neutral precursors under very gentle conditions[8,9]. The formed anions, being relatively unsolvated in the organic phase, show high reactivity towards appropriate substrates.

A particularly important phase transfer process is the conversion of dicobalt octacarbonyl to the mononuclear cobalt tetracarbonyl anion using aqueous sodium

hydroxide, benzene and benzyltriethylammonium chloride or cetyltrimethylammonium bromide. A possible mechanism for the generation of the cobalt tetracarbonyl anion from dicobalt octacarbonyl is as follows:

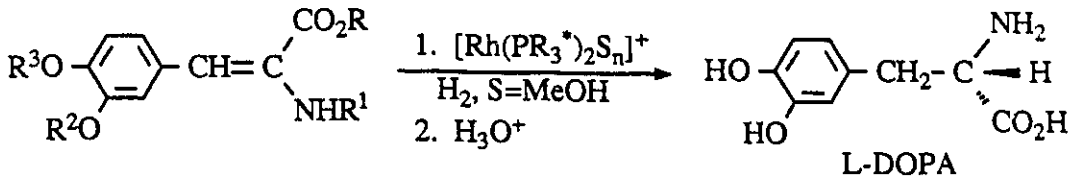
Scheme 1.1:



1.3 Asymmetric Induction

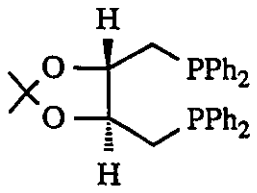
The synthesis of optically active organic compounds from racemic starting materials is perhaps the most elegant application of homogeneous catalysis[2]. Hydrogenation is one good example of asymmetric synthesis. In order to achieve asymmetric hydrogenation it is necessary for the substrate molecule to have prochiral faces, and that the catalyst incorporates a chiral site. A product of high optical purity can be obtained if the prochiral substrate is bound preferentially in one conformation to the vacant site of the catalyst.

Efficient catalytic asymmetric hydrogenations have been obtained using an optically active phosphine complexed to rhodium[10] or ruthenium[11,12,13]. The production of L-Dopa[14], a drug used in the treatment of Parkinson's disease, is a nice example of this method.

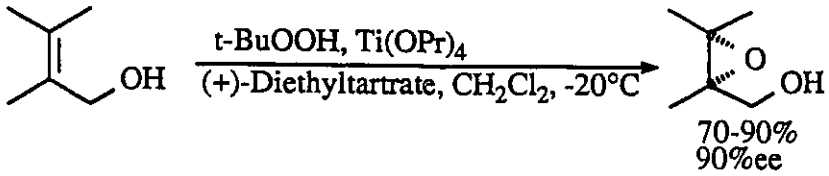


L-DOPA

Several optically active phosphine ligands have been used here including DiOP (2,3-0-isopropylidene-2,3-dihydroxy-1,4-bis (diphenylphosphino) butane):



Epoxidation of allylic alcohols catalyzed by a tartrate titanium complex has been discovered by Sharpless[15]. Chiral epoxides can be obtained in high yield and high optical purity:



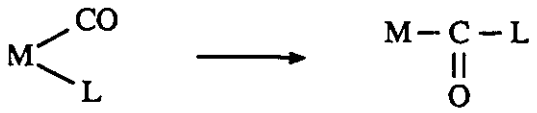
Asymmetric hydroformylation[16] and asymmetric carbonylation[17] have also been achieved.

1.4 Carbonylation Reactions

Carbonylation reactions are a fascinating way for incorporating carbon monoxide in a wide variety of organic substrates. They are one of the most versatile of all the homogeneous catalyzed processes since the carbon monoxide moiety is the most simple synthon for introducing a carbonyl group into an organic compound.

The CO ligand, which is a strongly binding π acid in character, may undergo some

key reactions, the insertion process being one of the most important[18]:



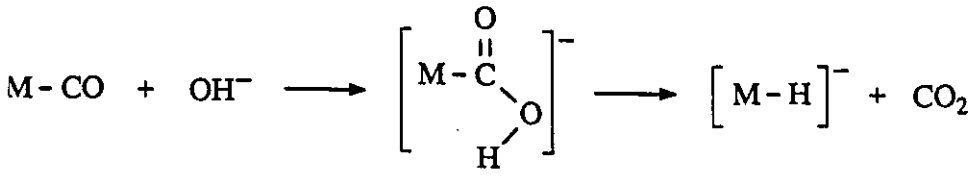
The ease with which alkyl metal carbonyls react with CO to give the corresponding acyl derivatives depends on many factors[19]. Destabilization of the ground state with respect to the M-CO and M-R bonds and stabilization of the transition state for the formation of acyl intermediates increase the rate of reaction. The reactivity depends in part on the strength of the metal-carbon bond. Generally, electron releasing groups enhance the rate whereas electron-withdrawing groups decrease it by strengthening the M-R linkage. For example, insertion of CO into a transition metal-perfluoroalkyl or perfluoroaryl bond has never been reported. The ancillary ligands and the position of the metal within the three transitions series also affect the CO insertion. The first and second-row transition metals undergo this reaction more easily than the third row transition metals of the same subgroup. The 5d metals are less reactive because of the higher strength of the corresponding carbon-metal bond[20].

The insertion reaction for ligands L (L = H, NR_2, OR, SR, Cl, Br, I) depends on the relative thermodynamic stability of M-COL and M-L + CO. When the M-L bonds are stronger than the M-C bonds, the insertion reaction is more difficult to attain[18].

The second key reaction that a carbonyl ligand might undergo is nucleophilic attack by an anionic reagent.

Carbon monoxide is a weak σ-donor ligand. The bonding with the transition metal is reinforced by back-donation from filled d-orbitals to the CO antibonding orbitals of appropriate symmetry. If a partial positive charge exists on the carbon atom, then attack

by a nucleophilic reagent can occur. This addition can be intramolecular or intermolecular depending on whether the species is another ligand or an external nucleophile. The attack of hydroxide ion at a metal carbonyl carbon followed by elimination of carbon dioxide leads to the formation of a hydrido complex:



The susceptibility to nucleophilic attack is higher when there is less back donation from the metal to the carbonyl.

Another useful reaction is electrophilic attack on carbonyl ligands of metal carbonyls. Electrophiles and strong Lewis acids can attack the metal carbonyl complexes at the oxygen atom[21].

The catalytic incorporation of CO into organic compounds has been intensively studied since the early 1940s. Important industrial processes have evolved from this research[1]. Good carbonylation methods allow the synthesis of aldehydes, alcohols, ketones, esters, carboxylic acids from unsaturated and halogenated molecules. The carbonylation of nitrogen compounds has led to the synthesis of amides, ureas, imides, carbamates and lactams.

The carbonylation reactions might be divided into five classes[18]: hydrocarbonylation, azacarbonylation, carbocarbonylation, oxacarbonylation, halocarbonylation. They lead respectively to the formation of a formyl group -C(O)-H, an N-acyl group, -C(O)-N, a ketone, -C(O)-C, an acyloxy moiety, -C(O)-O and a fragment -C(O)-hal.

1.5 Carbonylation of Linear Organonitrogen Compounds

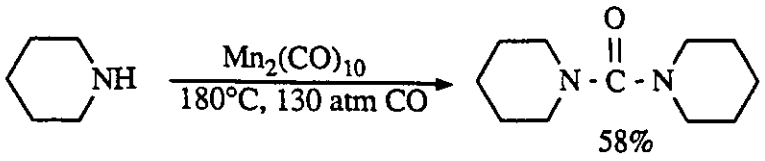
The use of amines as promotors in the cobalt catalyzed hydroformylation of alkenes led to the discovery of insertion of CO into carbon-nitrogen and hydrogen-nitrogen bonds[18]. Azacarbonylation reactions have been reviewed according to starting materials[22,23] and products[18,24,25,26]. The types of compound which can be obtained from carbonylation of nitrogen compounds are amides, ureas, isocyanates, imides, lactams, carbamates and various heterocycles.

Carbon monoxide reacts with amines in the presence of transition metal catalysts to give N-formyl derivatives and substituted ureas:

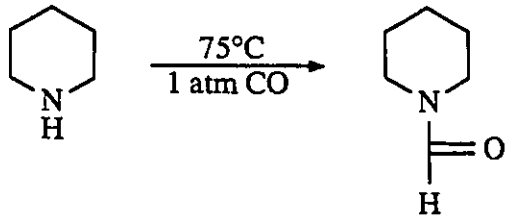
$$R^1R^2NCONR^1R^2 \xleftarrow[ML_n]{CO} R^1R^2NH \xrightarrow[ML_n]{CO} HCONR^1R^2$$

The reaction takes place mainly with primary and secondary amines. However tertiary amines can also be carbonylated[18]. There is a clear distinction in behaviour between aliphatic and aromatic amines: aliphatic amines can be carbonylated to afford principally N-formyl derivatives whereas aromatic amines usually give ureas. This difference in behaviour might be explained by the large difference in basicity of aliphatic and aromatic amines[18]. A careful variation of metal catalysts and ancillary ligands can alter the selectivity. For example, $Co_2(CO)_8$ leads to the formation of substituted formamides from aliphatic amines while $Mn_2(CO)_{10}$ converts primary aliphatic amines to dialkylureas[18].

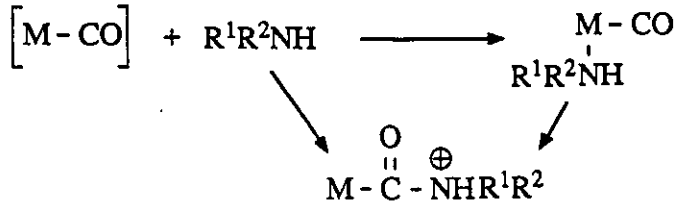
Manganese, cobalt and nickel carbonyl are often used as catalysts for the carbonylation of amines. The reaction conditions are generally severe, with temperatures in the range of 150-270°C and pressures of carbon monoxide between 100 and 300 atm[25,27]. For example, cyclohexylamine can be carbonylated to dicyclohexyl urea by $Mn_2(CO)_{10}$ at 180°C and 130 atm pressure:



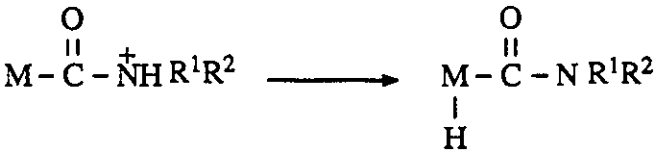
However $[RuOAc(CO)_2]_n$ catalyzes the azacarbonylation of secondary amines under mild conditions[28]:



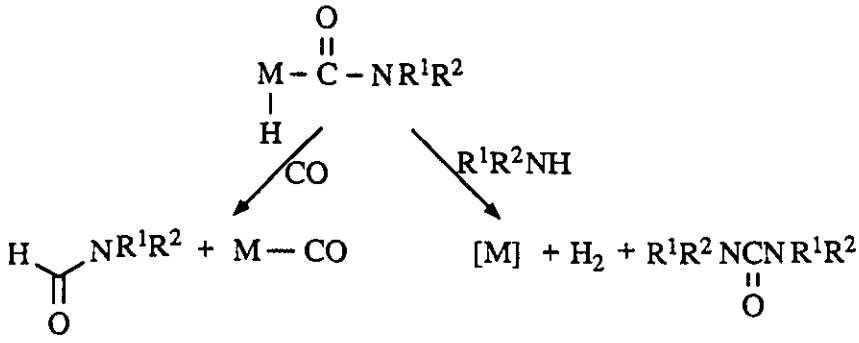
The mechanism of the carbonylation of amines has not been investigated in detail; however, a common intermediate for the formation of formamides and ureas is believed to be a carbamoyl-metal complex. This species could be formed either from an intramolecular 1,2-shift reaction involving coordinated CO and amine or from an intermolecular attack of the amine on a carbonyl ligand[18]:



This carbamoyl species can then undergo a proton shift to the metal center giving a hydridocarbamoyl intermediate:



Reductive elimination of the amide would afford the formamide whereas attack of an additional primary or secondary amine would give urea.



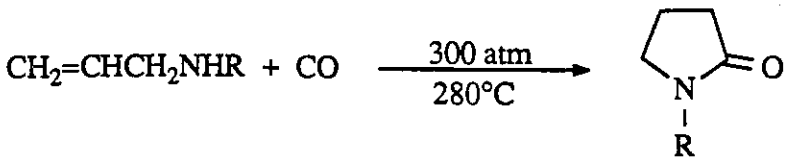
Aromatic amines can be converted to carbamate esters in the presence of $PdCl_2$, carbon monoxide, oxygen, hydrogen chloride and alcohols. $CuCl_2$ acts as reoxidant[29]:

$$RNH_2 + R'OH + CO + O_2 \xrightarrow[\text{R.T., 1 atm}]{PdCl_2/CuCl_2/HCl} RNHCOOR'$$

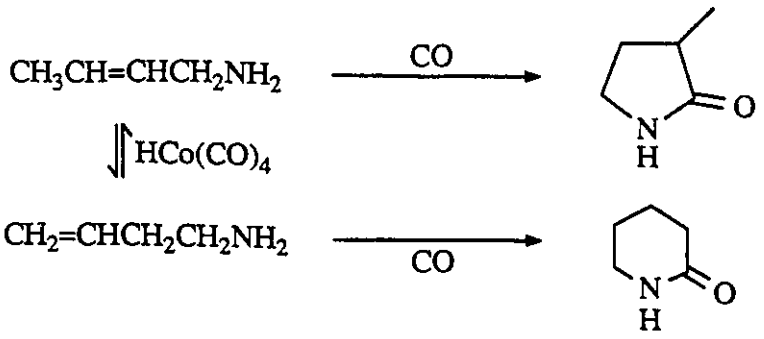
R = aromatic, R' = Me, Et.

Recently[30], di-tert-butyl peroxide was found to be an oxygen substitute in this reaction.

Azacarbonylation of allylamines, in the presence of cobalt, ruthenium and rhodium catalysts, gives γ-lactams. The best catalyst is dicobalt octacarbonyl[22,26,31,32]. For example, carbonylation of allylamine gives 2-pyrrolidone in 60% yield[33].

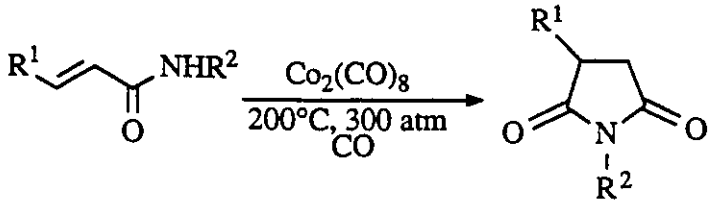


The azacarbonylation of allylic amines sometimes gives γ and δ-lactams. This indicates that initial isomerization occurs to form a γ,δ-unsaturated amine which subsequently cyclizes:

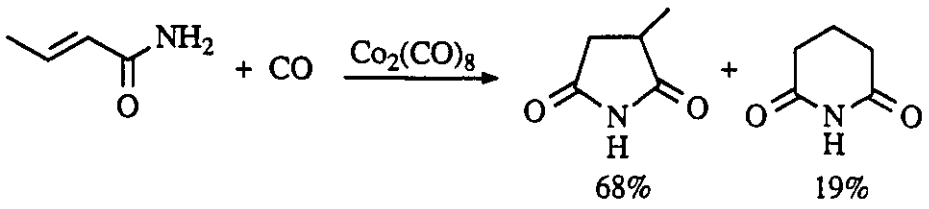


Extension of the azacarbonylation of unsaturated amines to unsaturated amides provides a versatile synthesis of five-and six-membered ring imides[22].

Dicobalt octacarbonyl transforms α,β-unsaturated amides into five-membered ring imides:



Crotonamide yields both 3-methyl-succinimide and glutarimide due to the cobalt-catalyzed isomerization of the starting material[34]:



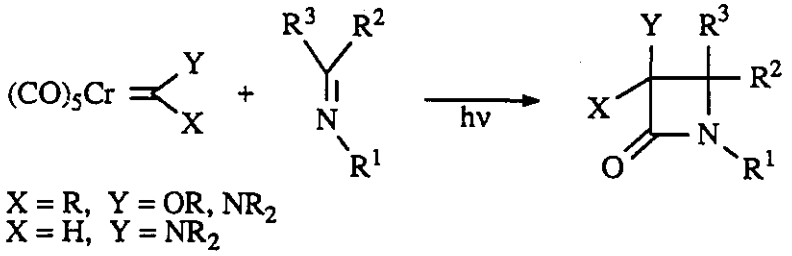
β,γ-Unsaturated amides produce glutarimides[31].

Aromatic nitro compounds can be carbonylated to give the corresponding isocyanates in high yields. The reactions are catalyzed by several transition metals, but

especially by Pd and Rh salts[1]:

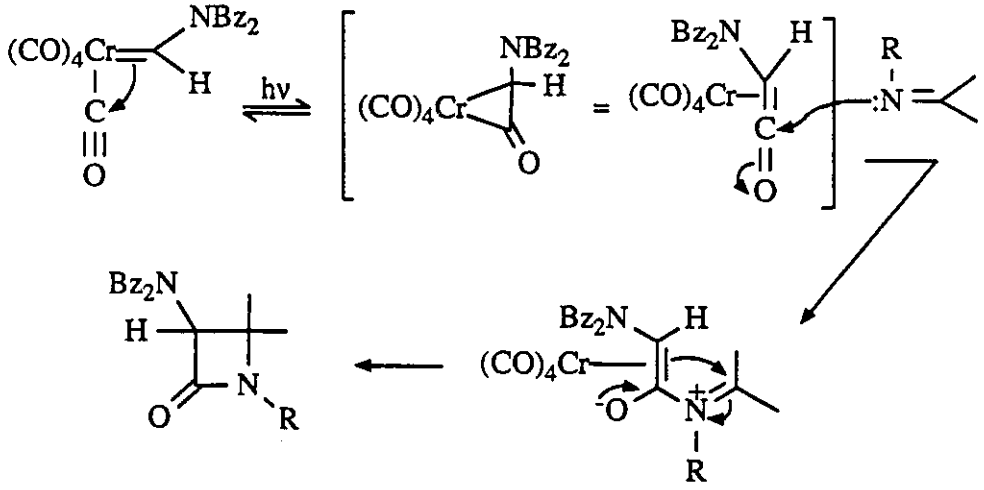
$$ArNO_2 + 3CO \xrightarrow{\text{Pd or Rh salts}} ArNCO + 2CO_2$$

A new approach to β-lactams involving the photolytic reaction of chromium carbene complexes with imine has been developed[35,36].

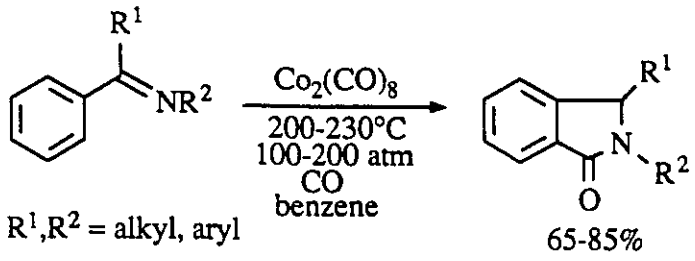


The β-lactam-forming process is thought to involve the reaction of the imine substrate with a photogenerated metal-bound ketene:

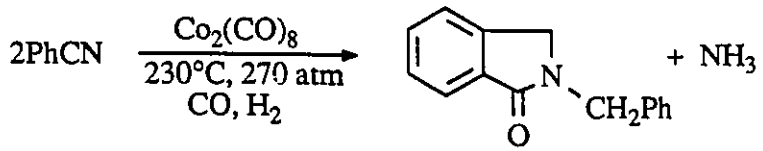
Scheme 1.2

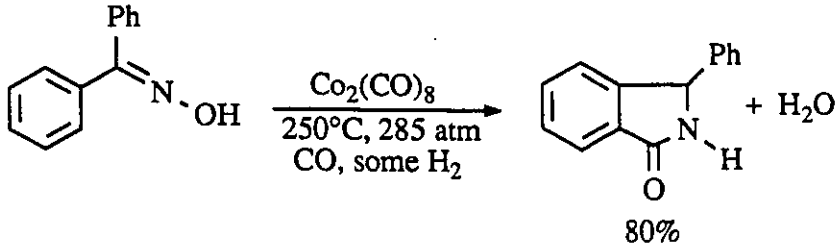


The azacarbonylation of aliphatic and aromatic imines affords a wide variety of phthalimidines[22,25,31]. The best catalyst is $Co_2(CO)_8$.

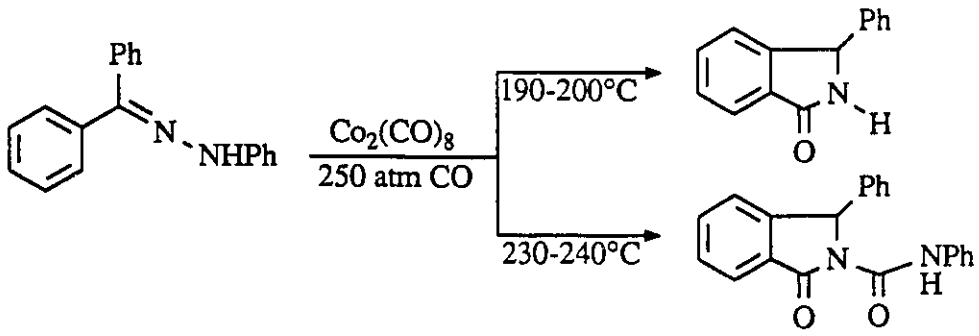


Aromatic nitriles and ketoximes have also been carbonylated to produce phthalimidines. Those azacarbonylations proceed under CO pressure and varying amounts of hydrogen. For example[22]:



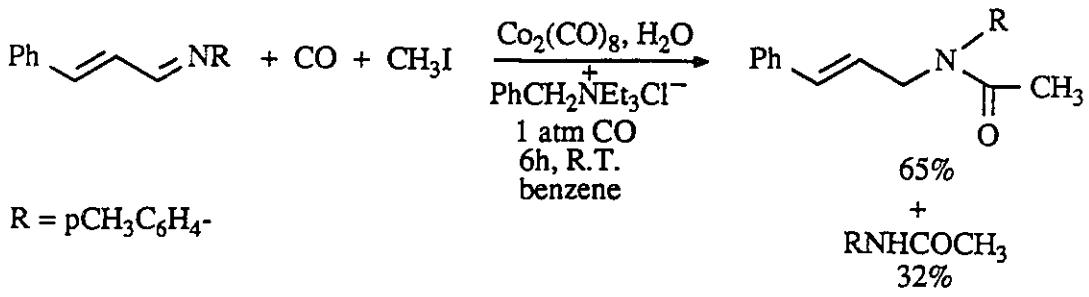


Phthalimidines can also be obtained from phenylhydrazones, semicarbazones and azines[22,31]. For example:



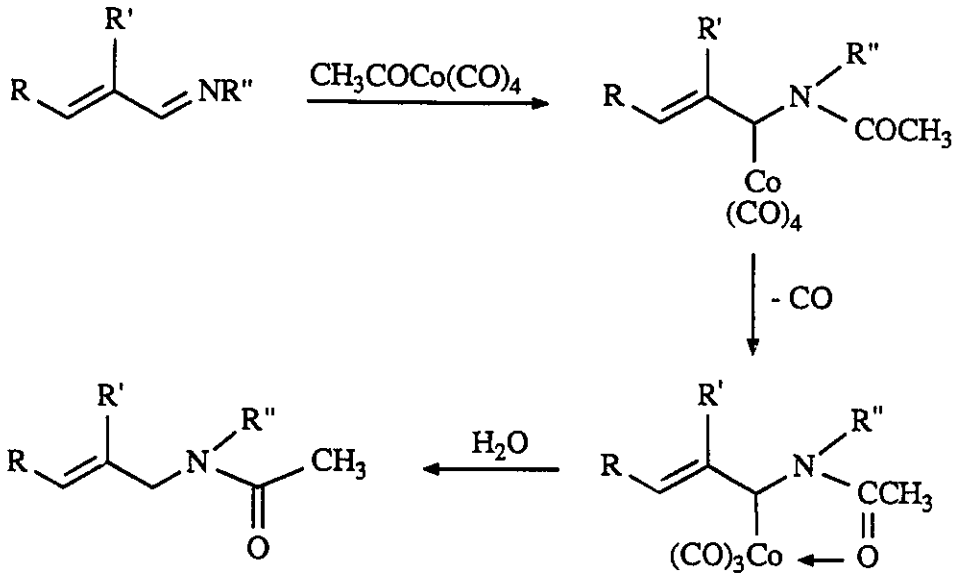
Azadienes react with a stoichiometric amount of dicobalt octacarbonyl under phase

transfer catalysis conditions, in presence of carbon monoxide and methyl iodide, to give allylic amides[37]. For example:

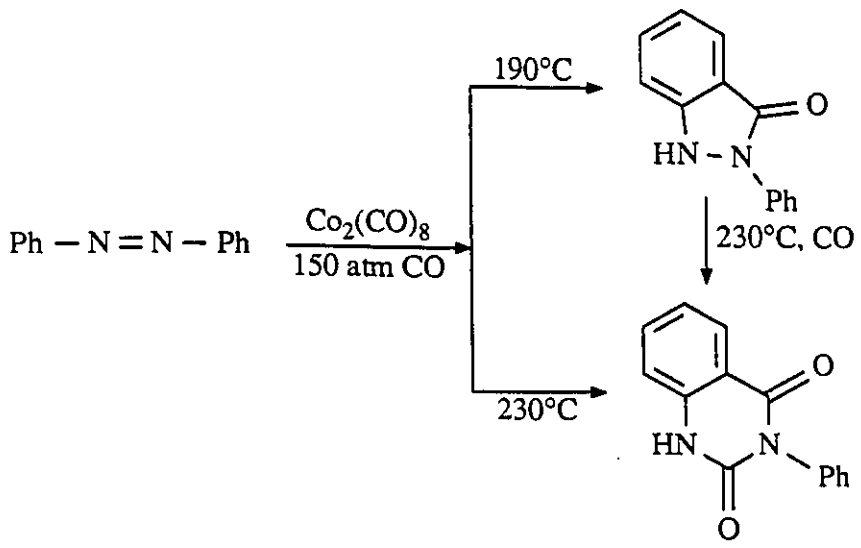


A possible mechanism for allyl amide formation would be as follows[37]:

Scheme 1.3



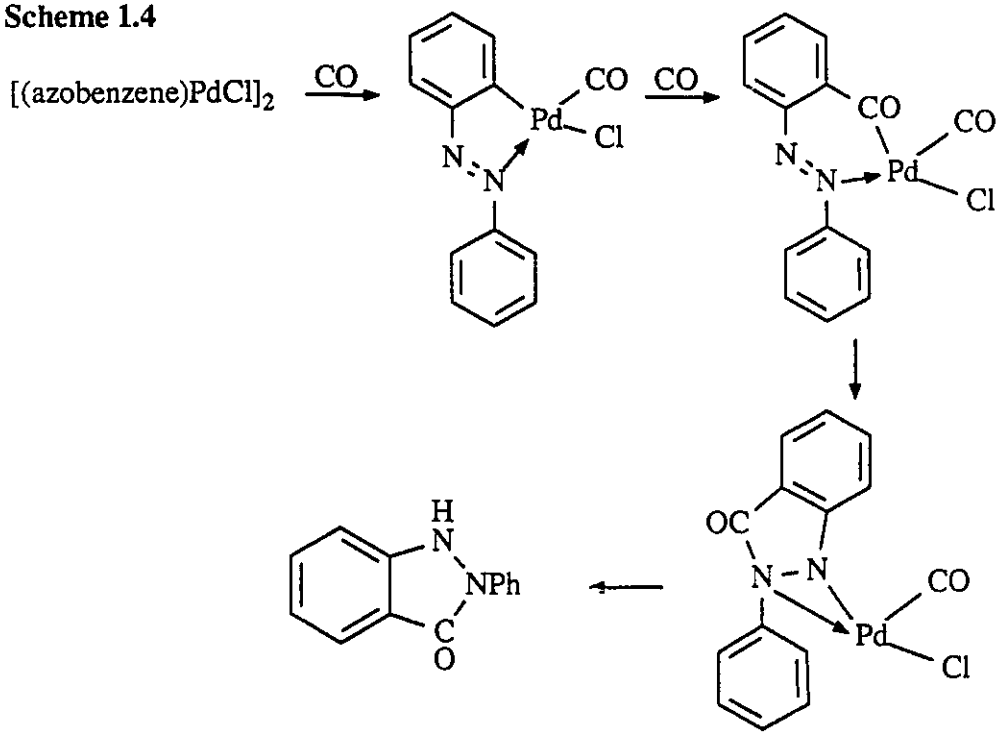
In the presence of CO and dicobalt octacarbonyl, aromatic azo compounds afford different heterocycles. The nature of the products depends on the reaction temperature. At 180-190°C, indazolones are obtained, using hydrocarbon solvents. Above this temperature there is CO insertion into the nitrogen-nitrogen bond forming 2,4-dioxo-1,2,3,4-tetrahydroquinazolines[18,38,39]:



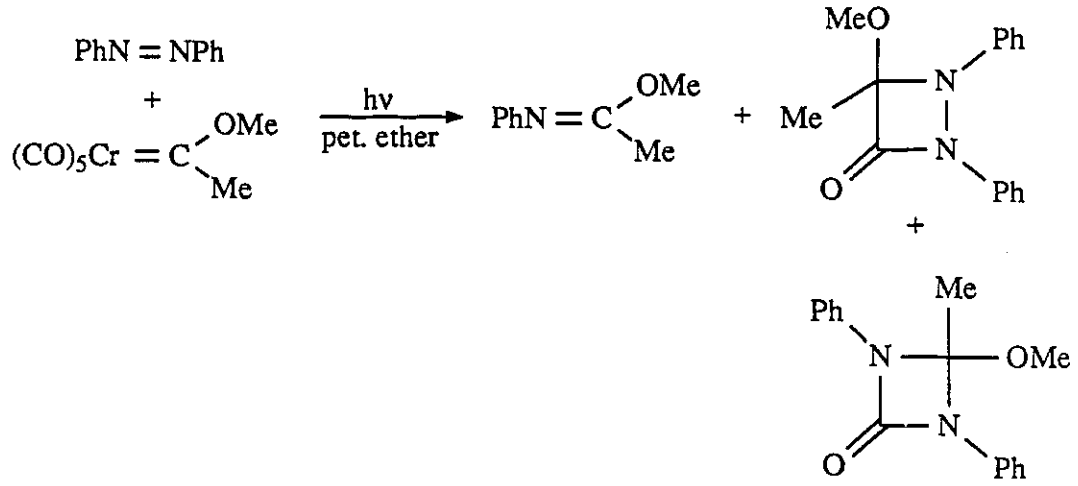
With substituted azobenzenes there is ring closure at the ring containing an electron-releasing substituent.

In ethanol, $PdCl_2$ catalyzes the formation of indazolones from azobenzene under somewhat milder conditions (50°C, 100 atm)[40]. A possible mechanism for this carbonylation was proposed.

Scheme 1.4



Sunlight irradiation of a solution of azobenzene and (methylmethoxycarbene) pentacarbonylchromium(0) at 30°C gives 10% of a 1:1 mixture of 1,2-diazetidinone and 1,3-diazetidinone. The major product (65%) doesn't come from carbonylation: it is the imino ether[41]

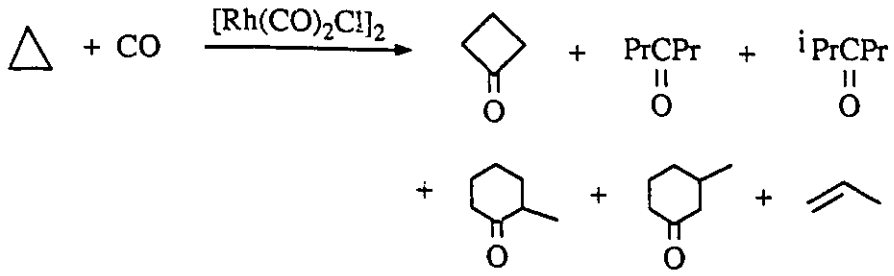


1.6 Carbonylation and Cleavage of Strained Ring Compounds by Organotransition-metal Complexes

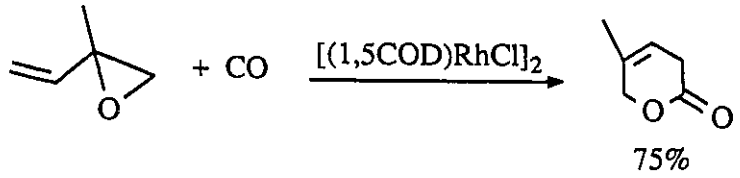
In recent years it has been shown that organotransition-metal complexes can induce the opening of strained ring compounds (e.g. three-membered ring substances)[42].

The organotransition-metal chemistry of cyclopropanes, epoxides, episulfides, azirines, aziridines, aziridinones is really fascinating. Carbonylation with cleavage of three-membered ring compounds by organotransition-metal complexes is the basis of new methods to prepare all kinds of heterocyclic and acyclic compounds including β,γ and δ-lactones, β-lactams, 2,4-azetidinediones and vinylisocyanates.

Under carbon monoxide pressure, very low yields of cyclic and acyclic ketones result from the carbonylation of cyclopropane in the presence of chlorodicarbonylrhodium(I) dimer[43]:

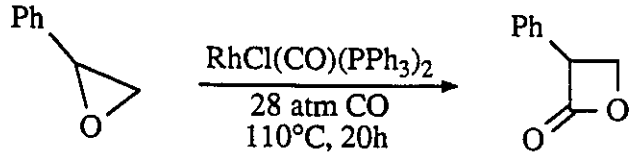


Unsaturated δ-lactones might be obtained from epoxides using a catalytic quantity of chloro(1,5-cyclooctadiene)rhodium dimer[44]:



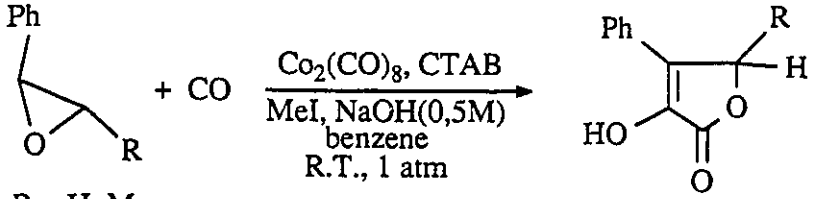
75%

$RhCl(CO)(PPh_3)_2$ reacts with styrene oxide to give a β-lactone[45]:



67%

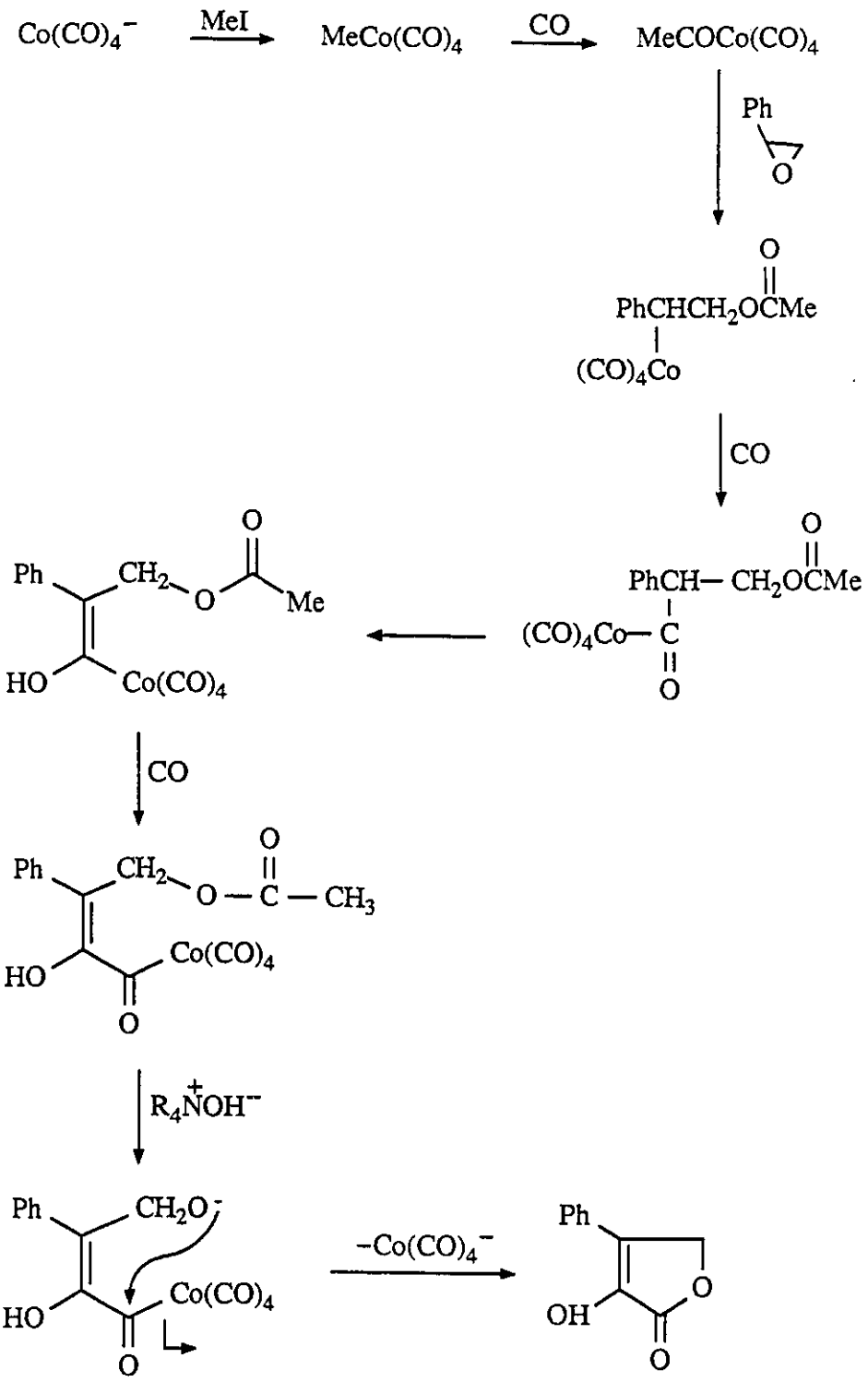
A fascinating double carbonylation of styrene oxides occurs on treatment of the heterocycle with $Co_2(CO)_8$, carbon monoxide, methyl iodide, NaOH, and cetyltrimethylammonium bromide[46]:



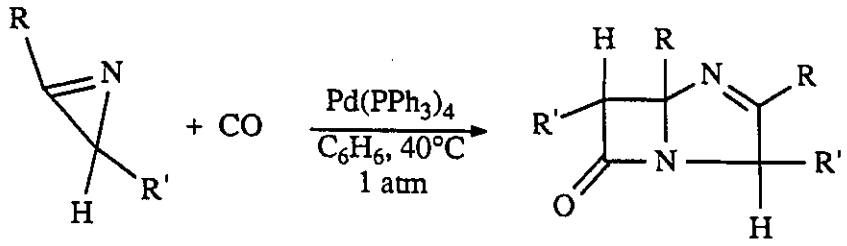
R = H, Me

A possible mechanism for this novel transformation follows[46]:

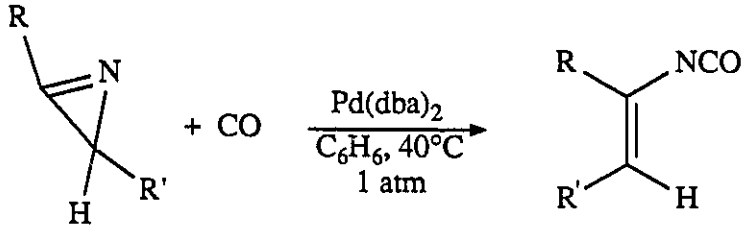
Scheme 1.5


Co(CO)4−
MeI
MeCo(CO)4
CO
MeCOCo(CO)4
Ph
O
PhCHCH2OCMe
(CO)4Co
CO
PhCH— CH2OCMe
(CO)4Co— C
Ph
CH2
O
Me
HO
Co(CO)4
CO
CH3
R4N+OH−
CH2O−
−Co(CO)4−
OH

Recently the azacarbonylation of reactive nitrogen heterocycles has become important in organic synthesis. Tetrakis(triphenylphosphine)palladium(0) transforms azirines into β-lactams[47]. It is a remarkable method to synthesize an important class of antibiotics.

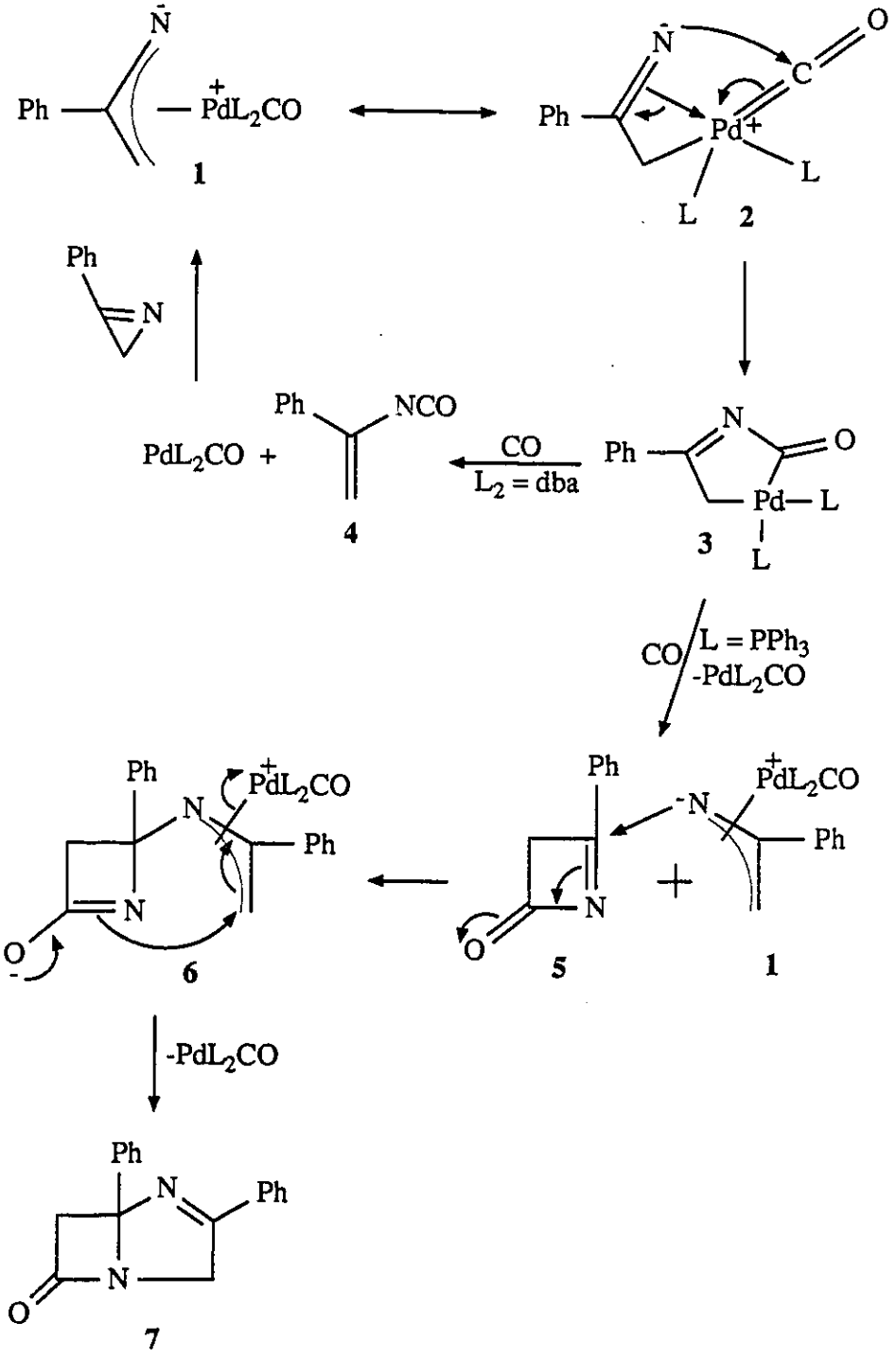


If bis(dibenzylideneacetone)palladium (0) is used as catalyst, vinylisocyanates are obtained[47]:



A possible mechanism for the formation of these products is illustrated in the following scheme:

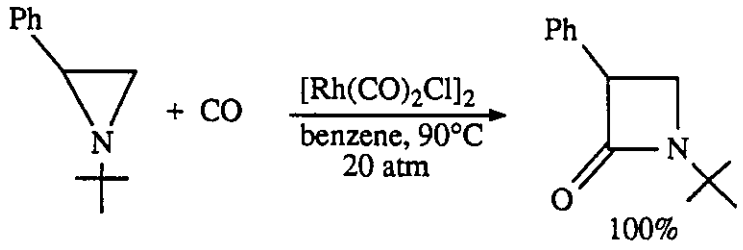
Scheme 1.6


Ph
PdL2CO
1
Ph
Pd
L
L
2
Ph
N
PdL2CO +
Ph
NCO
4
CO
L2 = dba
Ph
N
O
Pd
L
L
3
CO
L = PPh3
-PdL2CO
Ph
PdL2CO
N
Ph
N
O
6
Ph
N
PdL2CO
Ph
N
O
5
1
-PdL2CO
Ph
N
Ph
N
O
7

The intramolecular cyclization of **2** would give **3** which may be a common intermediate of both reactions. When L_2 = dba, vinylisocyanate (**4**) would be obtained by elimination of Pd(dba)CO in the presence of carbon monoxide. When L = PPh_3, there would be elimination to give the azetinone (**5**) and $Pd(PPh_3)_2CO$; the latter would then react with another azirine molecule to give (**1**). Compound **6** could be obtained by nucleophilic addition of **1** to **5**. The elimination of $Pd(PPh_3)_2CO$ would give the β-lactam(**7**).

The chlorodicarbonylrhodium(I) dimer, in the presence of carbon monoxide, also induces vinyl isocyanate formation from azirines[48]. Unfortunately a stoichiometric quantity of the rhodium complex has to be used in this case.

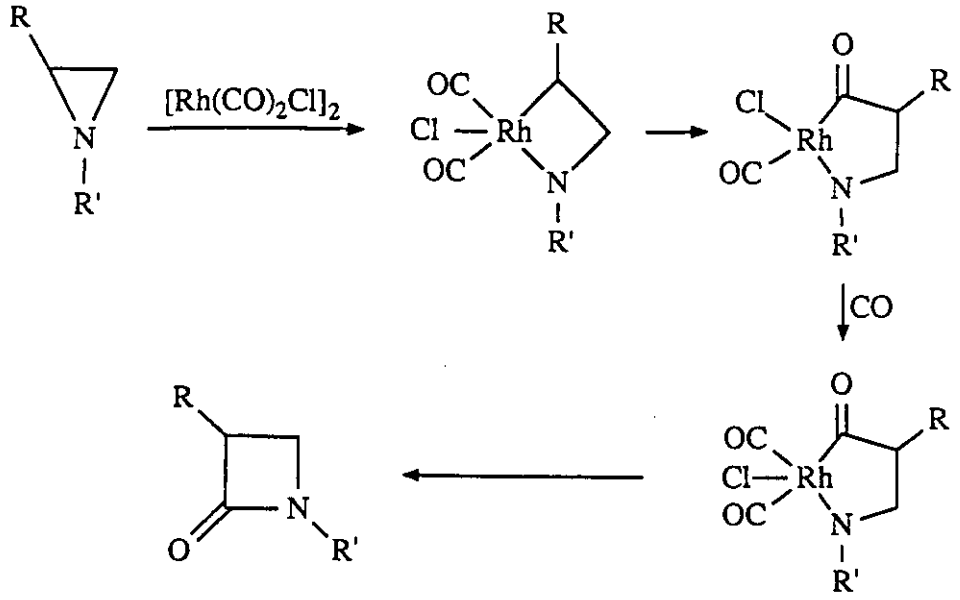
Several years ago a novel ring expansion was developed by carbon monoxide incorporation into an aziridine[49]. β-Lactams can be obtained in the presence of a catalytic quantity of chlorodicarbonylrhodium dimer. The reaction is regiospecific. Excellent yields are obtained when the reaction is effected at 90°C, under 20 atm of carbon monoxide, in benzene.



Chloro(1,5-cyclooctadiene)rhodium(I) also induces the conversion of aziridines to β-lactams. However the chloro(1,5-hexadiene)rhodium(I) dimer and rhodium acetate are unable to catalyze this reaction.

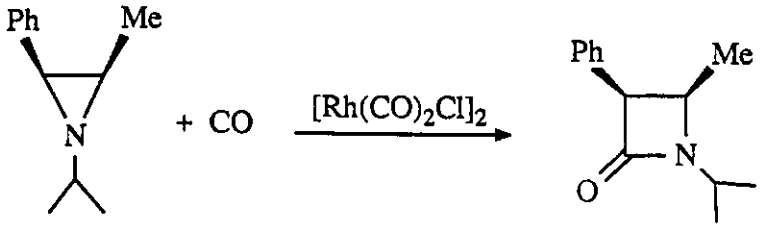
A possible mechanism[49] (scheme 1.7) involves initial oxidative addition at the most substituted C-N bond of the heterocycle to give a Rh(III) complex. Subsequent insertion of CO followed by reductive elimination would give the β-lactam.

Scheme 1.7



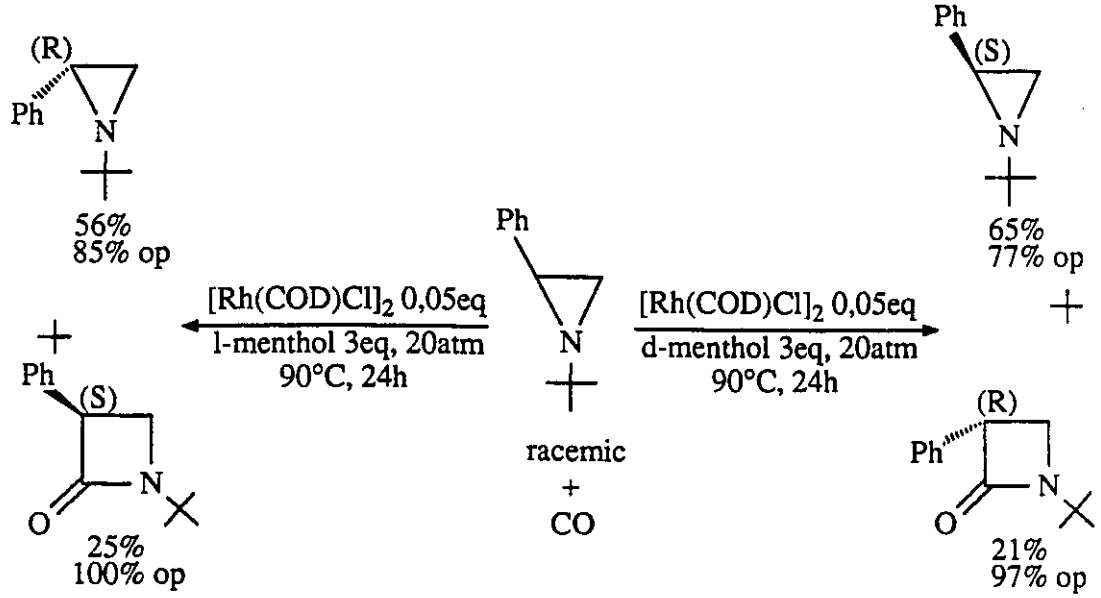
The 2-azarhodacyclobutane which might be involved as intermediate in this metal-catalyzed conversion of aziridines to β-lactams has, as yet, not been isolated. However an azairidocyclobutane has recently been isolated and characterized[50].

Recently the azacarbonylation of aziridines, catalyzed by Rh(I), has been found to be stereospecific[17]



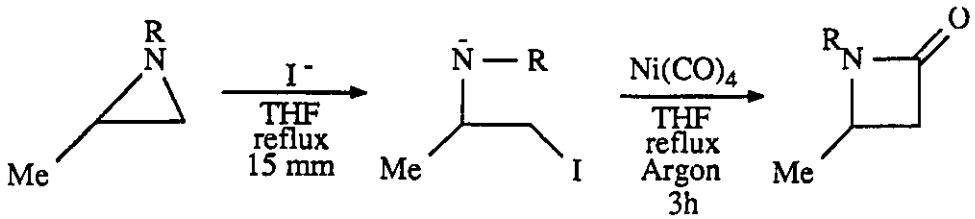
and enantiospecific.

Furthermore, in the presence of menthol, a remarkable high degree of asymmetric induction is observed[17]:



It was found that the R enantiomer reacts more rapidly in the presence of d-menthol than in the presence of l-menthol. The opposite was observed with the S enantiomer[17].

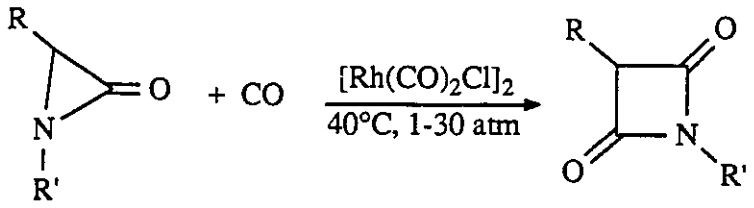
The conversion of an aziridine to a β-lactam can also be achieved using an excess of nickel tetracarbonyl[51]. The less substituted C-N bond of the aziridine is carbonylated.



R = CH_2Ph, SO_2Me

For R=CH_2Ph and SO_2Me the yields of β-lactams are respectively 51% and 18%.

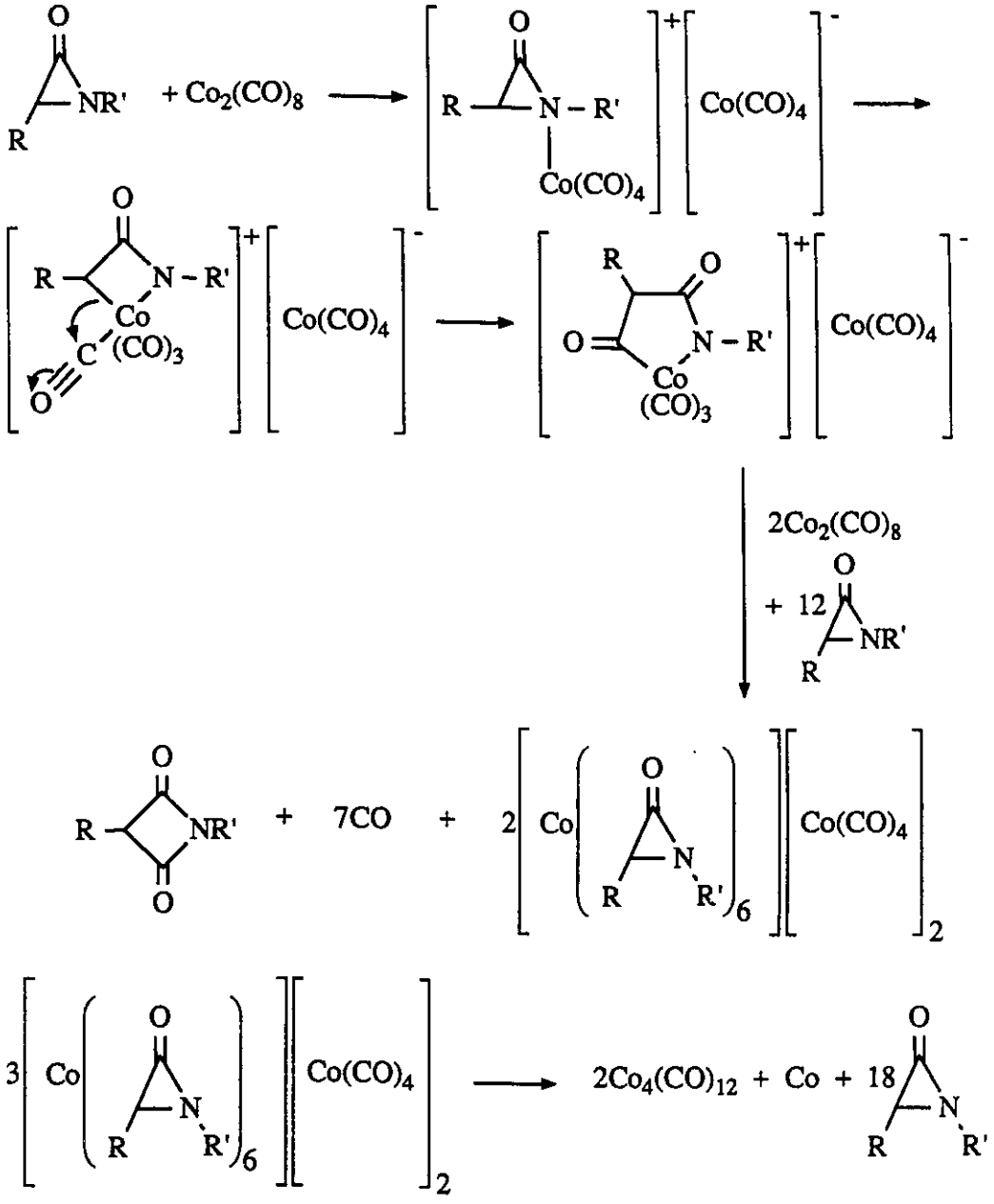
Aziridinones (α-lactams) are also carbonylated regiospecifically by the $[Rh(CO)_2Cl]_2$ catalyst to give 2,4-azetidinediones[52].



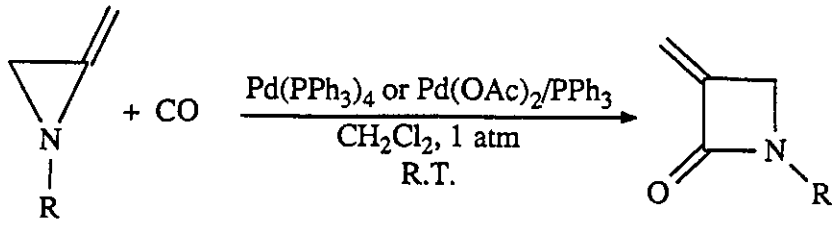
R = $(CH_3)_3C$, 1-adamantyl
R' = $(CH_3)_3C$, 1-adamantyl

Other good catalysts include $[RhCl(1,5HD)]_2$ and $[RhCl(1,5COD)]_2$, and $Co_2(CO)_8$ induces this carbonylation at 65°C under nitrogen. The use of a carbon monoxide instead of a nitrogen atmosphere inhibits the cobalt reaction, making this process non-catalytic with respect to cobalt. A possible pathway for the dicobalt octacarbonyl reaction is outlined in scheme 1.8[52]:

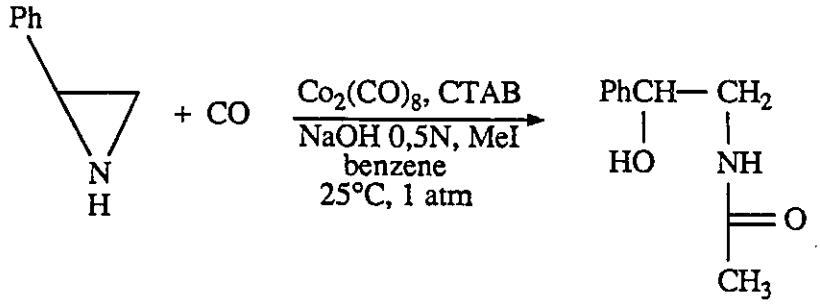
Scheme 1.8



The regiospecific synthesis of α-methylene β-lactams by carbonylation of methyleneaziridines was described in 1987[53]:

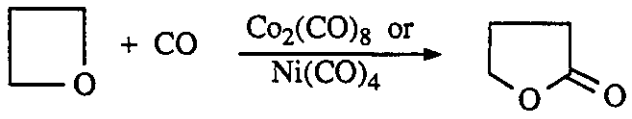


The acylation of 2-phenylaziridine under phase transfer catalysis has also been observed[54]:

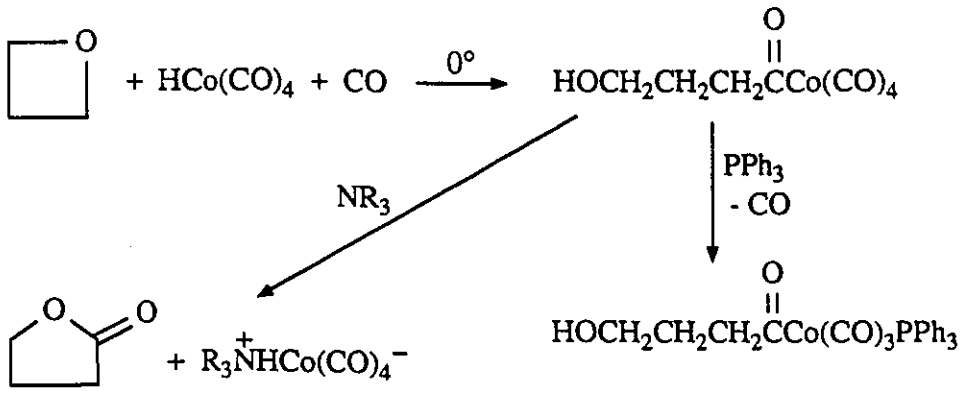


Although four-membered ring compounds are less strained than the three-membered ring analogs, carbonylation with cleavage of four-membered rings is also known.

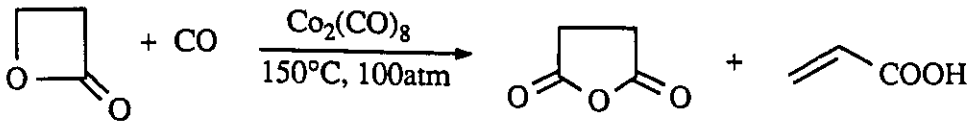
In the presence of cobalt and nickel carbonyls, oxetanes react to give the corresponding γ-butyrolactones. The reaction occurs under milder conditions with $Ni(CO)_4$ (250°C, 60 atm) than with $Co_2(CO)_8$ (200°C, 200-250 atm)[18,32].



With $CoH(CO)_4$ a stoichiometric reaction occurs but the γ-lactone is only obtained in the presence of dicyclohexylethylamine[55,56].



β-Lactones can also be carbonylated in the presence of $Co_2(CO)_8$, albeit in moderate yields[18,24]:



1.7 Aims of Research

Fascinated by the remarkable carbonylation and ring expansion reaction of aziridines, methyleneaziridines and aziridinones, we asked ourselves what would happen to a diaziridine if it was treated with carbon monoxide and an organotransition-metal complex. Would it react and if so, would it undergo carbonylation with ring expansion? In that event, where would CO insert, i.e. between the two nitrogens or between the carbon and one of the nitrogen atoms? The aim of the first part of this thesis will be to answer those questions.

Oxetanes and β-lactones can be carbonylated with ring expansion. By analogy would it be possible to carbonylate azetidines? The second part of this thesis will consider this matter.

Five-membered ring compounds are not strained. Nevertheless, they can

conceivably experience carbonylation and ring expansion to give the six-membered ring heterocycles. The third section of this thesis describes an investigation of metal catalyzed chemistry of pyrrolidines.

Chapter 2
Carbonylation of Diaziridines

2.1 Introduction

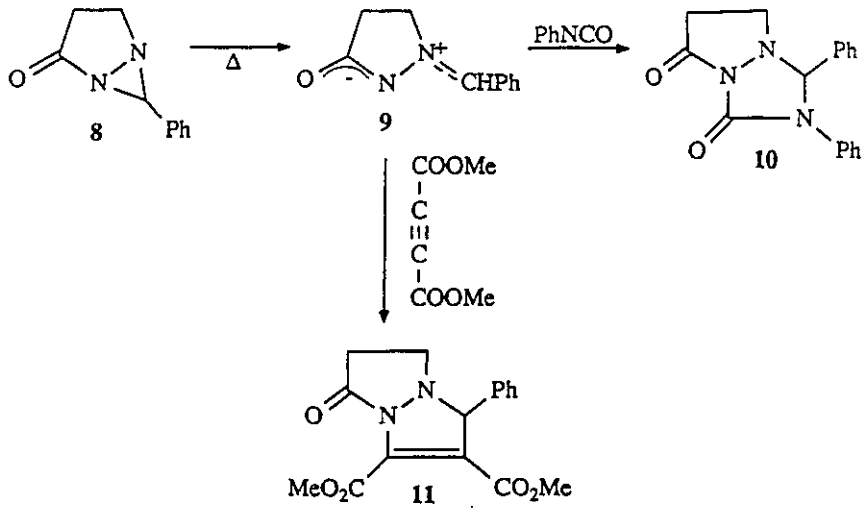
Several reviews have appeared in the literature since the first[57-59] reported synthesis of diaziridines in 1959[60-64]. The ring opening reactions of diaziridines can be divided into two classes: those proceeding with retention of the N-N bond and those involving N-N cleavage. Many of the ring opening reactions lead to ring expansion.

2.1.1 Organic Chemistry of Diaziridines

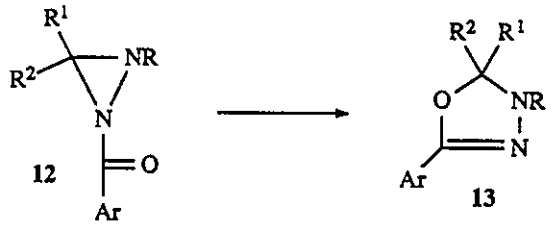
2.1.1.1 Reactions of Diaziridines Proceeding with Retention of the N-N Bond

Diaziridines having electron-withdrawing substituents at one or both nitrogens frequently rearrange upon heating. They also react with ynamines, isocyanates, dimethylacetylene dicarboxylate, and enamines to give five-membered ring heterocycles. These transformations are explained by the formation of an azomethine imine derivative which then rearranges or undergoes cycloaddition.

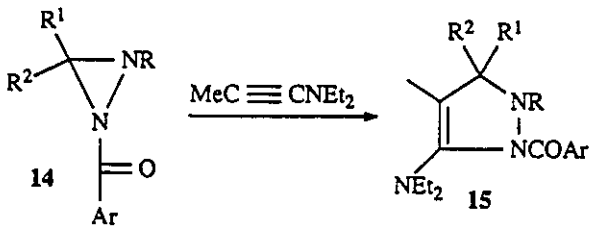
For example, heating diaziridine **8** gives the isolable azomethine imide **9** [65] which undergoes cycloaddition with phenyl isocyanate and dimethylacetylene dicarboxylate to give **10** and **11**, respectively[66].



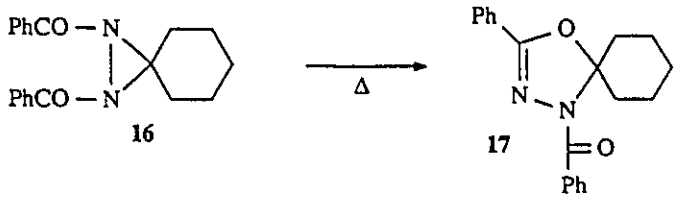
The thermal isomerization of 1-aroyl-2,3,3-trialkyldiaziridines (12) affords 4,5,5-trialkyl-Δ^2-1,3,4-oxadiazolines (13) [67].



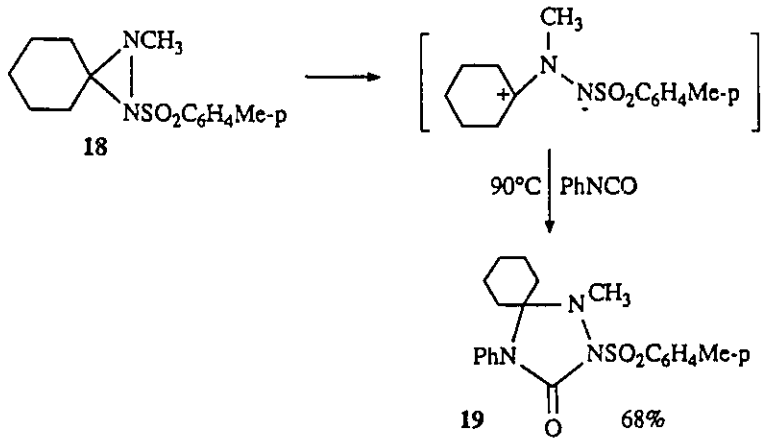
If heated in the presence of an ynamine, the diaziridine undergoes cycloaddition to form 15 [67].



Thermolysis of the dibenzoyldiaziridine **16** gives 2,3-dihydro-1,3,4-oxadiazole **17** [68].

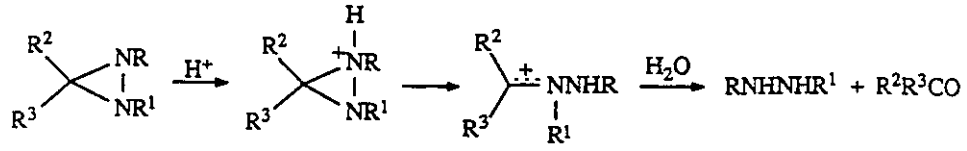


When heated in the presence of arylisocyanates, 1-p-toluenesulfonyl-2-alkyl-3,3-pentamethylenediaziridines (e.g. **18**) form triazolidin-3-one derivatives (e.g. 19) [69].



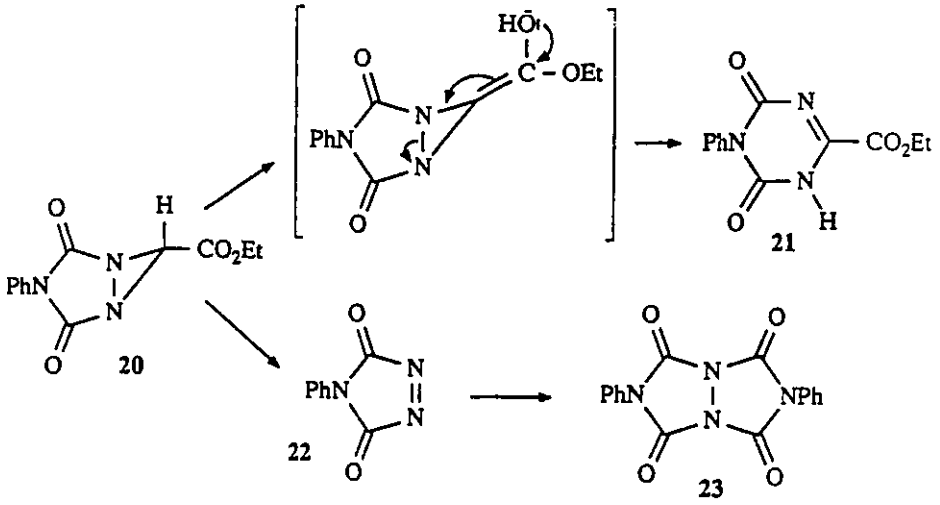
In contrast to **18**, 1-(p-toluenesulfonyl)-2-cyclohexyl-3-methyldiaziridine failed to react when heated with phenyl isocyanate . This lack of reactivity is consistent with the observation that the formation of azomethine imines from diaziridines usually requires two stabilizing substituents at the diaziridinyl carbon as well as electron-withdrawing groups at the 1- or 1,2-positions[69].

In acid media, the hydrolysis of diaziridines gives carbonyl derivatives and substituted hydrazines. This reaction occurs regardless of the nature of the C- or N- substituents[63].



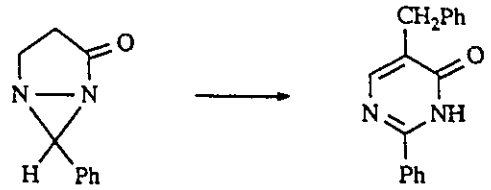
2.1.1.2 Reactions of Diaziridines Involving Nitrogen-Nitrogen Bond Cleavage

Pyrolysis of diaziridine 20 affords 21 (76%) and 23 (17%)[70]:



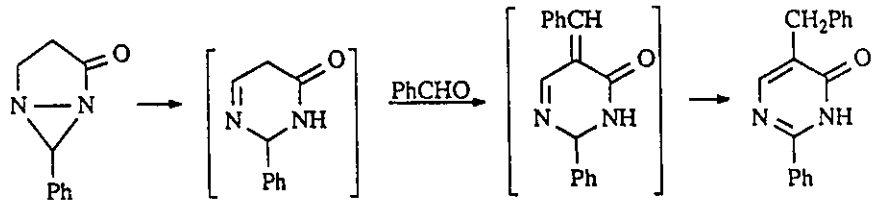
23 would be formed by elimination of a carbethoxy carbene from 20 to give 22 [70].

At room temperature, in the presence of an equimolar quantity of potassium-t-butoxide, 8 undergoes nitrogen-nitrogen bond cleavage to form 24 in 52% yield[71].



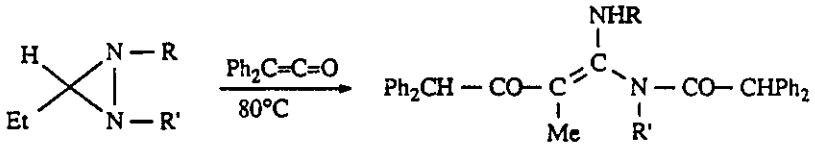
8 24

It has been suggested that **8** ring opens to give **25.** The latter could then condense with benzaldehyde (somehow produced in a side reaction) to give **24** [71]:



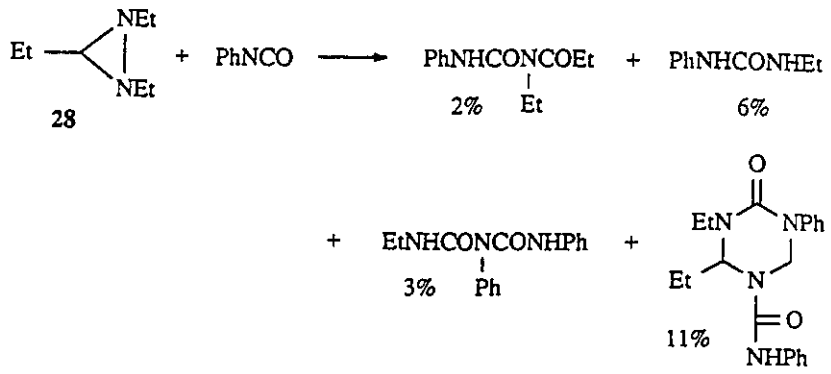
25 24

1,2,3-trialkyldiaziridines (e.g. **26**) react with diphenylketene to form acyclic 1:2 adducts (e.g. **27**) [72-73].

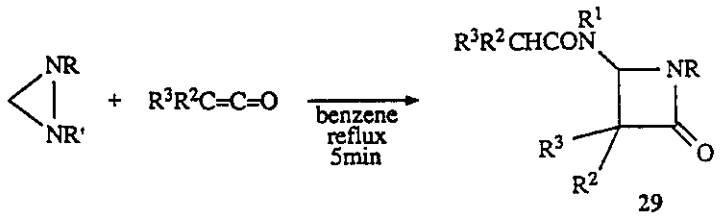


26 27

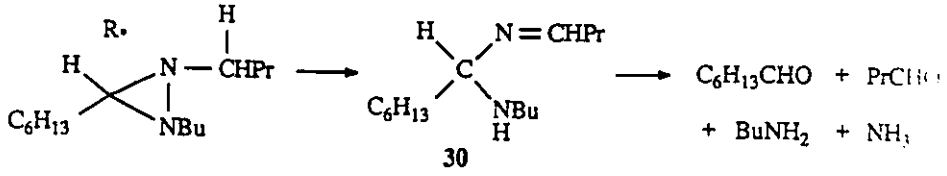
Reaction of phenyl isocyanate with 1,2,3-triethyldiaziridine (**28**) gives a mixture of products, all in low yield[73].



1,2-Dialkyldiaziridines react with ketene affording azetidinones **29** in 25% yield[74].

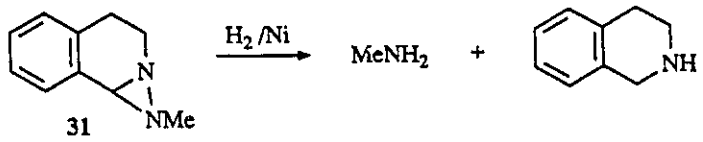


Finally, 1,2-dialkyldiaziridines undergo thermal decomposition, even at room temperature. For example, 1,2-dibutyl-3-hexyldiaziridine undergoes 70% decomposition when kept at 0°C for 9 months[64]. Heptanal, butyraldehyde, butylamine and ammonia are obtained, possibly by a radical chain reaction (**30** generated by attack of a radical on an N-methylene group involving N-N cleavage)[64].



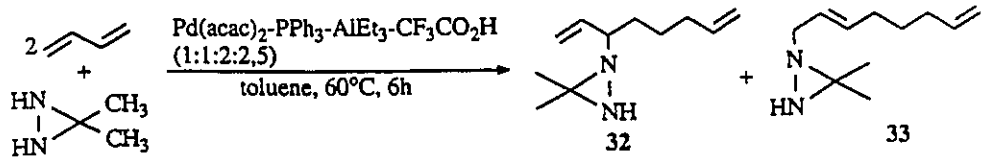
2.1.2 Organometallic Chemistry of Diaziridines

Few reports have appeared in the literature on the chemistry of diaziridines with metal containing systems. Catalytic hydrogenation of 1-cyclohexyl-3-ethyldiaziridine over Raney nickel forms n-propylamine and cyclohexylamine[75]. Under the same conditions, diaziridines **31** gives methylamine and tetrahydroisoquinoline[63].



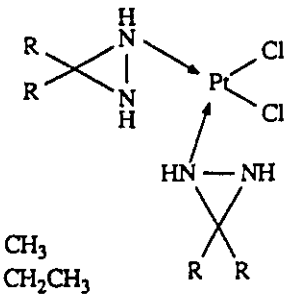
31

Telomerization of 3,3-dimethyldiaziridine with butadiene catalyzed by Pd complexes affords **32** and **33** [64].



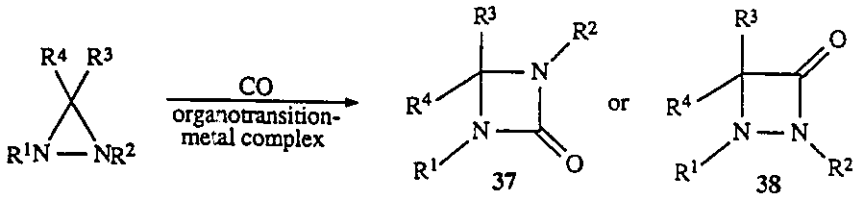
32 33

Recently, good antitumor activity against leukemia in mice was obtained with platinum complexes of diaziridines **(34, 35, 36)** [76].



34: R = CH_3
35: R = CH_2CH_3
36: R,R = $-(CH_2)_5-$

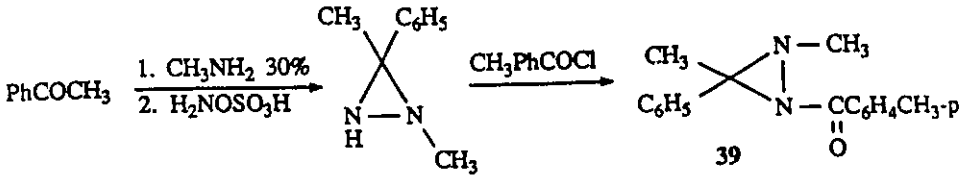
The reaction of diaziridines with metal carbonyls has not been investigated. We thought it would be really interesting to see if appropriately substituted diaziridines might undergo carbonylation with ring expansion on treatment with an organotransition-metal complex in the presence of carbon monoxide. We were also curious to know the regioselectivity of the reaction: i.e., would insertion of carbon monoxide occur between the two nitrogen atoms to give a 1,3-diazetidinone (**37**) or between the carbon atom and a nitrogen atom to afford a 1,2-diazetidinone (**38**).



2.2 Results and Discussion

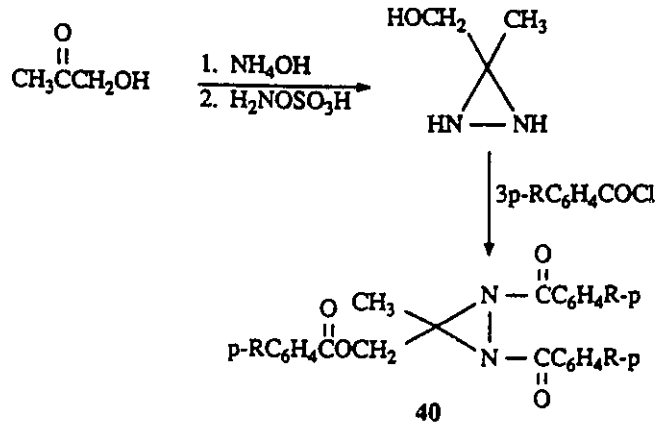
In order to study the organometallic chemistry of diaziridines we prepared three representative classes of these heterocycles: 1,3-dimethyl-2-p-toluoyl-3-phenyldiaziridine (**39**), 1,2-diaroyldiaziridinyl aroates (**40**), and 1-methyl-2-butyl-3,3-butamethylenediaziridine (**41**).

1,3-Dimethyl-2-p-toluoyl-3-phenyldiaziridine (**39**) was synthesized by reaction of 1,3-dimethyl-3-phenyldiaziridine[77] with p-toluoylchloride[78]:



39

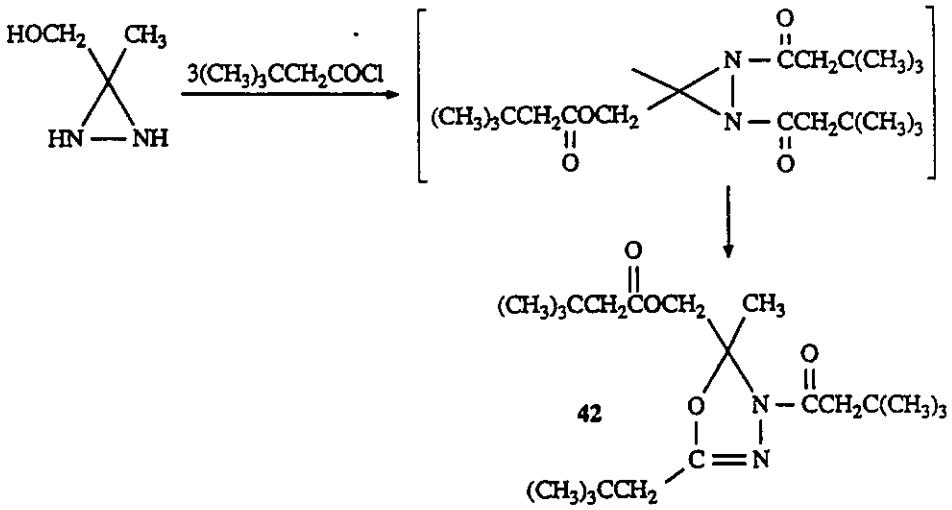
Three 1,2-diaroyldiaziridinyl aroates (aroyl=p-toluoyl, p-methoxybenzoyl, p-chlorobenzoyl) were prepared in a similar way[78-79]:



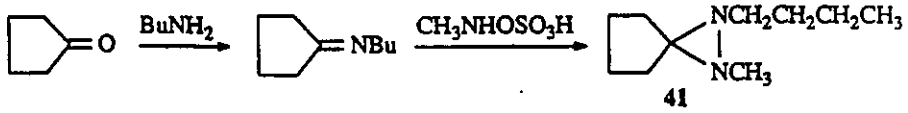
40

Attempts were also made to prepare 1,2-di-t-butylacetyldiaziridinyl-t-butylacetate but this protected diaziridine could not be isolated. It

rearranged to 1,3,4-oxadiazoline (**42**) under the reaction conditions:



1-Methyl-2-butyl-3,3-butamethylenediaziridine (**41**) was prepared by reaction of the N-butylcyclopentanimine[80] with methylhydroxylamine-o-sulfonic acid[81-82]:



The behaviour of 1,3-dimethyl-2-p-toluoyl-3-phenyldiaziridine (**39**) was studied using different metal complexes: $RuCl_2(PPh_3)_3$, $Co_2(CO)_8$, $[Rh(CO)_2Cl]_2$, $IrCl(CO)(PPh_3)_2$, $[Ir(COD)Cl]_2$, $Ni(CO)_2(PPh_3)_2$ and $Pd(PPh_3)_4$. The results are listed in Table 1.

When 1,3-dimethyl-2-p-toluoyl-3-phenyldiaziridine was exposed to carbon monoxide and a catalytic amount of $RuCl_2(PPh_3)_3$ in benzene at 65°C, no reaction was observed. Under the same reaction conditions $IrCl(CO)(PPh_3)_2$ and $Ni(CO)_2(PPh_3)_2$ were also used, but to no avail.

Table 1 Reaction of 1,3-Dimethyl-2-p-toluoyl-3-phenyldiaziridine (39) with Metal Complexes

Metal Complex	Diaziridine / Metal Complex (mmol/mmol)	Solvent	T °C	Gas	P Atm	Time Days	Recovered Diaziridine %[a]	Acetophenone %[a]
$RuCl_2(PPh_3)_3$	5/1	benzene	65	CO	1	4	100	0
$Co_2(CO)_8$	1/1	benzene	65	N_2	1	2	100	0
$[Rh(CO)_2Cl]_2$	4/1	benzene	65	CO	1	1or2	80	20
$[Rh(CO)_2Cl]_2$	2/1	benzene	65	CO	1	1	45[b]	37[b]
$[Rh(CO)_2Cl]_2$	5/1	benzene	22	CO	30	1	81	19
$[Rh(CO)_2Cl]_2$	5/1	4-methyl-2-pentanone	22	CO	1	1	46[b]	26[b]
$IrCl(CO)(PPh_3)_2$	5/1	benzene	65	CO	1	3	100	0
$IrCl(CO)(PPh_3)_2$	5/1	benzene	65	CO	30	1	100	0
$[Ir(COD)Cl]_2$	6/1	benzene	65	CO	1	1or2	76	24
$Ni(CO)_2(PPh_3)_2$	5/1	benzene	65	CO	1	2	100	0
$Pd(PPh_3)_4$	5/1	benzene	65	CO	30	1	92	8
$Pd(PPh_3)_4$	2/1	benzene	65	CO	1	1or4	64	36

a) % calculated by ^1H NMR

b) % isolated by thin layer chromatography (silica)

Furthermore, the diaziridine remained unchanged when stirred with a stoichiometric amount of dicobalt octacarbonyl under nitrogen.

When a benzene or a 4-methyl-2-pentanone solution of the diaziridine was stirred with chlorodicarbonylrhodium dimer, acetophenone was obtained. This was observed at 22°C as well as at 65°C. This reaction occurred with CO bubbling (1 atm) and under 30 atm of CO. It could be seen by infrared spectroscopy that, during the reaction, the carbonyl bands of $[Rh(CO)_2Cl]_2$ decreased considerably. In order to obtain a fair yield of acetophenone (20-26%) it was necessary to use a considerable amount of $[Rh(CO)_2Cl]_2$ (4 or 5/1 ratio of diaziridine to rhodium complex).

A reaction was run, in benzene, using two equivalents of diaziridine for one equivalent of $[Rh(CO)_2Cl]_2$. After one day of stirring, at 65°C under CO, an orange precipitate was formed which was filtered. Purification of the filtrate, by column chromatography, afforded 37% of acetophenone and 45% of diaziridine. The orange precipitate was a rhodium complex. Its infrared spectrum, taken in chloroform, showed carbonyl bands at 2018 and 2085 cm^{-1}. These frequencies are different from those of $[Rh(CO)_2Cl]_2$ (2040 and 2100 cm^{-1}). The ^1H NMR of the complex ($CDCl_3$) suggests the presence of the $CH_3C_6H_4CONNCH_3$ ligand:

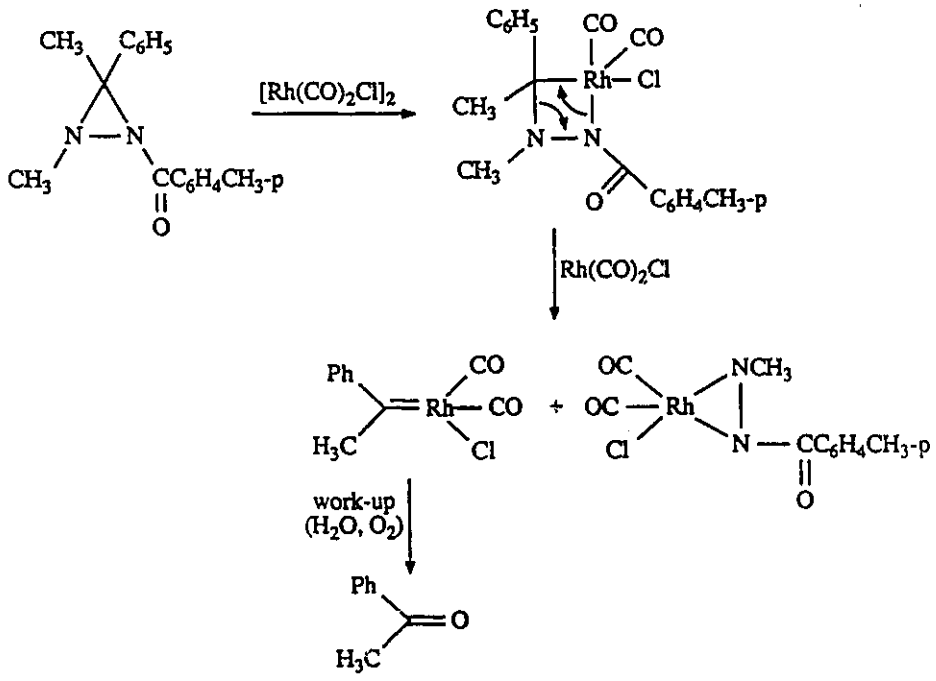
δ 2,35 (s; 3H, $\underline{CH_3}C_6H_4$); 3,60 (s; 3H, CH_3N); 7,03-7,53 (AA'BB' pattern; 4H, C_6H_4).

1,3-Dimethyl-2-p-toluoyl-3-phenyldiaziridine was also converted to acetophenone by $[Ir(COD)Cl]_2$ and $Pd(PPh_3)_4$.

How can one account for the formation of acetophenone from 1,3-dimethyl-2-p-toluoyl-3-phenyldiaziridine in the presence of $[Rh(CO)_2Cl]_2$, $[Ir(COD)Cl]_2$ and $Pd(PPh_3)_4$? Initially there may be oxidative addition of the metal to one C-N bond of the ring to give a four-membered ring metallacycle followed by

ring opening to form a transition metal carbene complex. This carbene comlex may afford acetophenone during the work-up of the reaction, the azo part of the metallacycle would link to another metal species affording a diazene complex. This proposed mechanism is illustrated for $[Rh(CO)_2Cl]_2$ in Scheme 2.1.

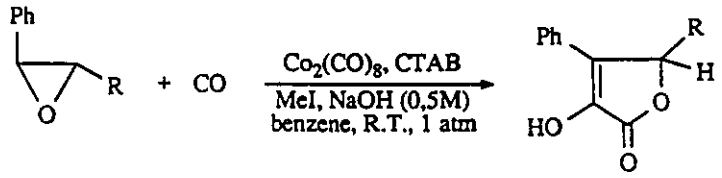
Scheme 2.1



The spectral data for the rhodium complex that was observed at the end of the reaction is in accord with a diazene rhodium complex having two carbonyl ligands.

The production of acetophenone from diaziridine is uninteresting from a practical point of view!

Recently[46] it has been discovered that double carbonylation of styrene oxides occurs on treatment of the heterocycle with $Co_2(CO)_8$, carbon monoxide, methyl iodide, NaOH and cetyltrimethylammonium bromide:



It seemed conceivable that 1,3-dimethyl-2-p-toluoyl-3-phenyldiaziridine would also undergo carbonylation under phase transfer catalysis. In order to determine whether such a process can occur, the behaviour of the diaziridine in the presence of $Co_2(CO)_8$, $Ni(CN)_2.4H_2O$ and $Pd(PPh_3)_4$ was investigated under phase transfer catalysis. The results are listed in Table 2. All except one of the attempts at carbonylating the diaziridine were unsuccessful.

When a mixture of 1,3-dimethyl-2-p-toluoyl-3-phenyldiaziridine (0,75 mmol), cetyltrimethylammonium bromide (0,19 mmol), $Co_2(CO)_8$ (0,19 mmol), methyl iodide (21 mmol), benzene (12 ml) and NaOH 0,5N (12 ml) was stirred under 30 atm of CO (at 60°C), some reaction did occur. Purification of the crude product on silica plates afforded 55% of 1-acetyl-2-methyl-1-p-toluoylhydrazine (**43**) and traces of 1,1-dimethyl-2-p-toluoylhydrazine (**44**) or 1,2-dimethyl-1-p-toluoylhydrazine (**45**). Acetophenone and 15% of recovered diaziridine were also isolated.

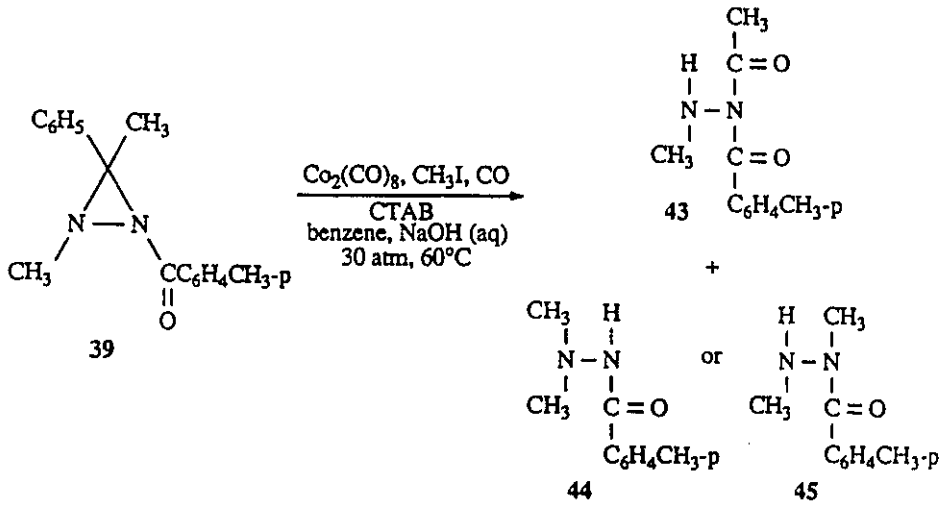


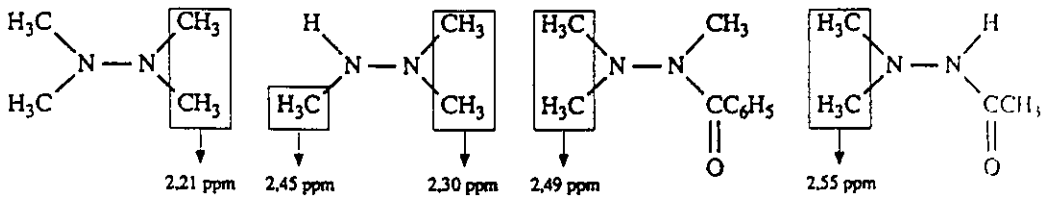
Table 2 Reaction of 1,3-Dimethyl-2-p-toluoyl-3-phenyldiaziridine (39) with Metal Complexes under Phase Transfer Catalysis Conditions

Metal Complex "MC"	Phase Transfer Catalyst[a] "PTC"	Diaziridine/MC/ PTC/CH_3I mmol/ mmol/mmol/mmol	NaOH N	T °C	Pco Atm	Time Days	Reaction
nil	CTAB	4/0/1/0	0,5	60	1	1	No
$Co_2(CO)_8$	TEBAC	3/3/1/0	5	60	1	1	No
$Co_2(CO)_8$	CTAB	4/1/1/0	0,5	60	30	1	No
$Co_2(CO)_8$	CTAB	4/1/1/111	0,5	22	1	1	No
$Co_2(CO)_8$	CTAB	4/1/1/111	0,5	22	30	1	No
$Co_2(CO)_8$	CTAB	4/1/1/111	0,5	35	30	1	No
$Co_2(CO)_8$	CTAB	4/1/1/111	0,5	60	30	2	yes[b]
$Ni(CN)_2.4H_2O$	TBAHS	17/2/1/0	5	60	1	1	No
$Pd(PPh_3)_4$	CTAB	4/1/1/111	0,5	22	1	1	No

a) TBAHS = tetrabutylammonium hydrogen sulfate
TEBAC = benzyltriethylammonium chloride
CTAB = cetyltrimethylammonium bromide

b) 15% of diaziridine, acetophenone, 55% of 43, and traces of 44 or 45 were isolated.

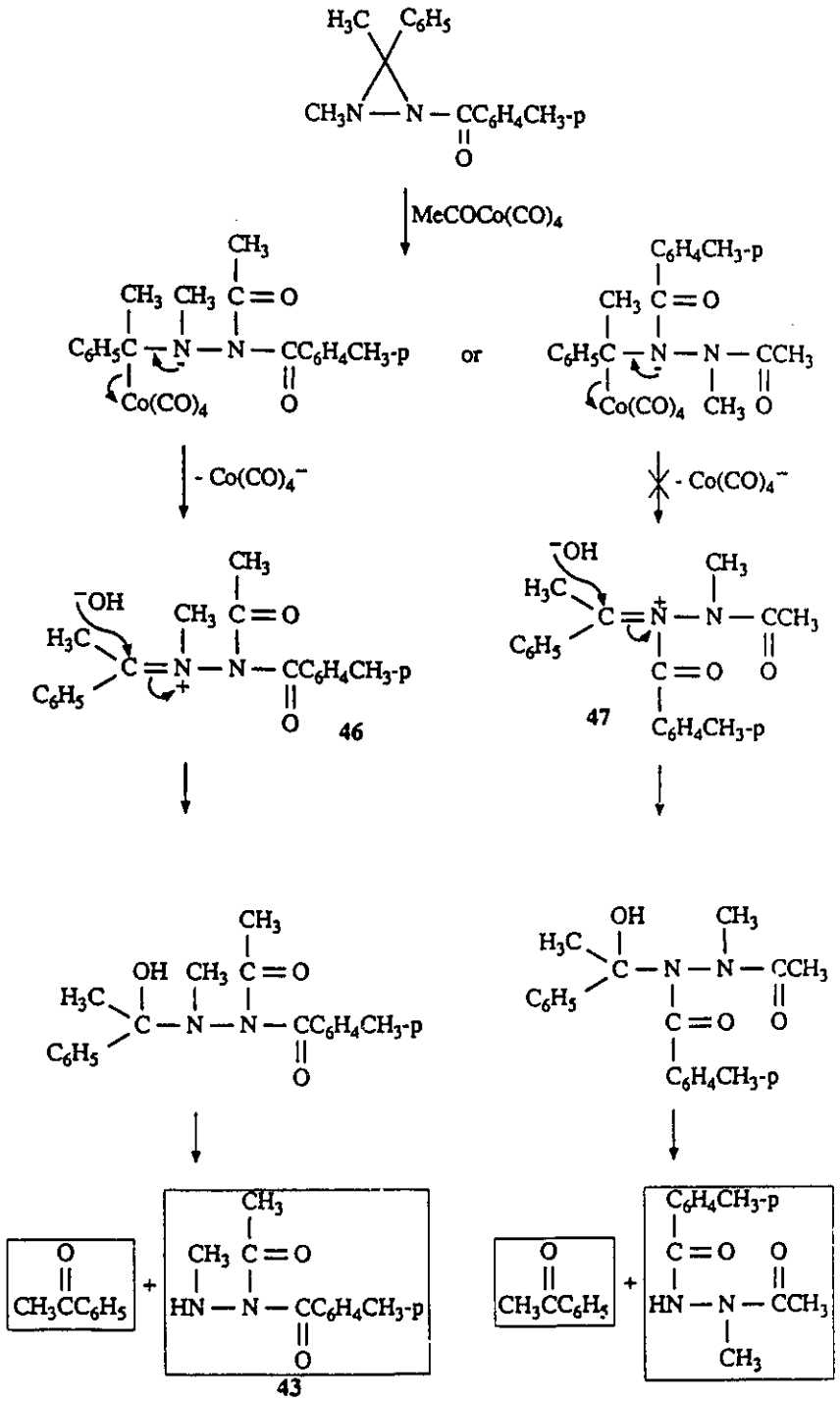
The fact that **43** is the major product, and not 1-acetyl-1-methyl-2-p-toluoylhydrazine, is supported by spectral data. Indeed, the infrared spectrum (ν CO($CHCl_3$) = 1710 cm^{-1} and 1655 cm^{-1}) is quite different from the one reported for 1-acetyl-1-methyl-2-benzoylhydrazine (ν max ($CHCl_3$) = 1675 cm^{-1} and 1620 cm^{-1})[83]. The substitution of the toluoyl group for a benzoyl group would not be expected to lead to a significant change in the infrared spectrum. On the other hand, the chemical shift for the protons of CH_3N (δ =3,13 ppm) is too high to correspond to CH_3NCOCH_3. Indeed, CH_3NCO of 1-acetyl-1,2,2-trimethylhydrazine is at δ3,94 ppm[84]. Unfortunately, no ^{1}H-NMR spectrum of a 1-methyl-2,2-diacetyl or dibenzoylhydrazine could be found in the literature. However, considering the deshielding effect of substituents on various hydrazines, δ 3,13 ppm is a reasonable value for the CH_3N of **43**. Indeed, in tetramethylhydrazine the methyls are at 2,21 ppm[85]. The substitution of one CH_3 of a $N(CH_3)_2$ by H causes deshielding of the remaining CH_3 by 0,24 ppm[85]. Likewise substitution of one CH_3 by a benzoyl or an acetyl group also causes deshielding of the CH_3 on the adjacent nitrogen by 0,28 or 0,25 ppm[84]. A rough estimate of the chemical shift for the NCH_3 of **43** would be 2,21 + 0,24 + 0,28 + 0,25 = 2,98 ppm, which is close to 3,13 ppm.



Since 1-acetyl-2-methyl-1-p-toluoylhydrazine and not 1-acetyl-1-methyl-2-p-toluoylhydrazine is formed, it is probable that the minor product is 1,2-dimethyl-1-p-toluoylhydrazine.

Under the reaction conditions, $Co(CO)_4^-$ is generated from dicobalt octacarbonyl. Conversion of the anion to $MeCo(CO)_4$ and $MeCOCo(CO)_4$ occurs in the presence of methyl iodide and carbon monoxide. Then there may be addition of either $MeCo(CO)_4$ or $MeCOCo(CO)_4$ to one of the carbon-nitrogen bonds of the diaziridine. The addition of $MeCo(CO)_4$ would afford the product obtained in low yield (probably **45**) while the addition of $MeCOCo(CO)_4$ would give the major product. A possible pathway leading to the major product is illustrated in scheme 2.2. It may explain why **43** and not 1-acetyl-1-methyl-2-p-toluoylhydrazine is the major product. Indeed, compound **47** should be less stable then **46** since it has a positive charge α to a carbonyl group.

Scheme 2.2



The results with 1,3-dimethyl-2-p-toluoyl-3-phenyldiaziridine were disappointing inasmuch that carbonylation did not occur with ring expansion. Perhaps the absence of a phenyl group on the carbon atom of the heterocycle would avoid cleavage of the two carbon-nitrogen bonds to form the ketone. For these reasons another class of diaziridines, the 1,2-diarcyldiaziridinyl aroates (**40**), were prepared for study.

When equimolar quantities of a 1,2-diaroyldiaziridinyl aroate and dicobalt octacarbonyl in dry benzene were stirred overnight under nitrogen at 65-70°C, dihydrooxazoles (oxazolines, **48**) were obtained. After chromatographic work-up, 1,2-di-p-toluoyldiaziridinyl p-toluoate, 1,2-di-p-methoxybenzoyldiaziridinyl p-methoxybenzoate and 1,2-di-p-chlorobenzoyldiaziridinyl p-chlorobenzoate afforded the oxazolines in yields of 51%, 59% and 79% respectively (see Table 3 for data). During the reaction carboxylic acid (**50**) was also formed. For instance, p-chlorobenzoic acid was obtained in 70% yield with 1,2-di-p-chlorobenzoyldiaziridinyl p-chlorobenzoate as the substrate. The analytical and spectral data support the proposed structures of the products.

Table 3 Reaction of 1,2 Diaroyldiaziridinyl Aroates (40) with Metal Complexes, in Benzene

Aryl group	Metal Complex	Diaziridine / Metal Complex mmol/mmol	T °C	Gas	P atm	Time days	Dihydro oxazole (48) %[a]	1,2,4-Oxadiazoline (51) %[a]
$CH_3C_6H_4$	nil	--	65-70	N_2	1	1	0	0
$CH_3C_6H_4$	$Co_2(CO)_8$	1/1	65-70	N_2	1	1	51	0
$CH_3OC_6H_4$	$Co_2(CO)_8$	1/1	65-70	N_2	1	1	59	0
ClC_6H_4	$Co_2(CO)_8$	1/1	65-70	N_2	1	1	79	0
$CH_3C_6H_4$	$Co_2(CO)_8$	1/1	65-70	CO	1	1	79	0
$CH_3C_6H_4$	$Co_2(CO)_8$	3/1	RT	N_2	1	3	18	14[b]
$CH_3C_6H_4$	$Co_2(CO)_8$	5/1	35	CO	1	2	0	29[c]
$CH_3C_6H_4$	$Co_4(CO)_{12}$	5/1	RT	CO	1	2	0	9[b]
$CH_3C_6H_4$	$Co(O_2CPh)_2$	1/1	65-70	CO	1	1	0	0
$CH_3C_6H_4$	$[Rh(CO)_2Cl]_2$	10/1	60	CO	1	1	0	0
$CH_3C_6H_4$	$[Rh(CO)_2Cl]_2$	10/1	60	CO	40	2	0	0
$CH_3C_6H_4$	$Pd(PPh_3)_4$	9/1	54	CO	1	1	0	22
$CH_3OC_6H_4$	$Pd(PPh_3)_4$	3/1	54	CO	1	1	0	63
ClC_6H_4	$Pd(PPh_3)_4$	3/1	54	CO	1	1	0	77
$CH_3C_6H_4$	$Pd(PPh_3)_4$	10/1	RT	CO	1	3	0	0
$CH_3C_6H_4$	$Pd(dba)_2$	10/1	RT	CO	1	3	0	0

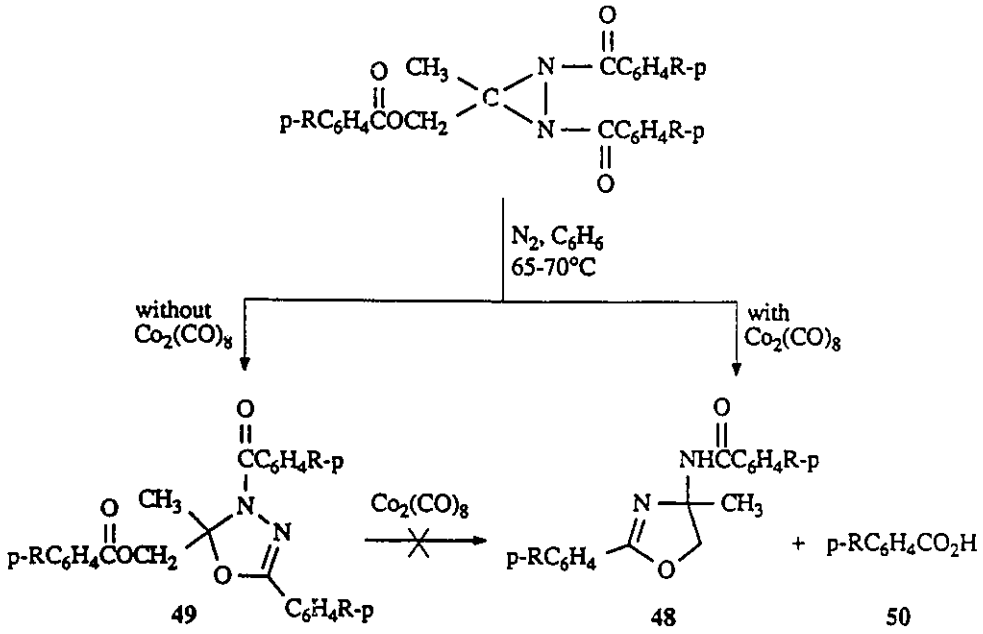
a) Isolated yields

b) Yield determined by NMR spectroscopy

c) THF as solvent

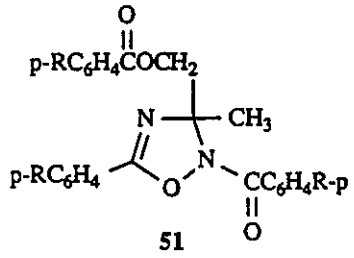
Use of a carbon monoxide instead of a nitrogen atmosphere also afforded the oxazolines. For example, 1,2-di-p-toluoyldiaziridinyl p-toluoate gave the oxazoline in 79% yield.

When the diaziridine was heated at 65-70°C, in the absence of $Co_2(CO)_8$, quantitative thermal rearrangement occurred yielding 1,3,4-oxadiazoline **(49)**. The oxazoline does not arise from 1,3,4-oxadiazoline since no reaction occurred by exposure of the latter to $Co_2(CO)_8$ in benzene at 65-70°C.



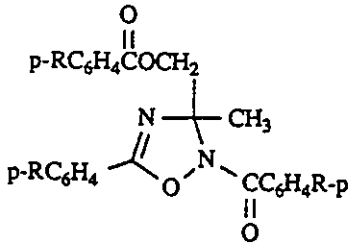
When a catalytic amount of dicobalt octacarbonyl [10:1 ratio of diaziridine to $Co_2(CO)_8$] was used, under CO bubbling at 65°C, the diaziridine was converted to the 1,3,4-oxadiazoline. This result shows that the thermal rearrangement was fast compared with any catalytic reaction with $Co_2(CO)_8$.

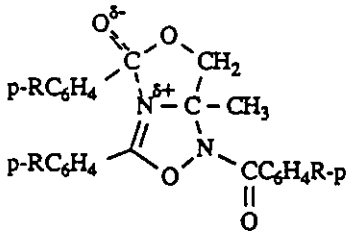
When a benzene solution of 1,2-di-p-toluoyldiaziridinyl p-toluoate (0,45 mmol) and dicobalt octacarbonyl (0,15 mmol) was stirred under nitrogen at room temperature for three days, 18% of the oxazoline was obtained along with recovered diaziridine and 14% of another product. Its analytical and spectral data show that this new product is an isomer of 1,3,4-oxadiazoline, possibly the 1,2,4-oxadiazoline (**51**). Unsuccessful attempts were made to grow a crystal of the compound for x-ray analysis, in order to unequivocally establish the structure of this product.



51

The infrared spectrum of this compound showed two carbonyl bands (1700-1705 cm^{-1} and 1722 cm^{-1}-1726 cm^{-1}) for the ester group. The one at the lower frequency might be explained by the interaction of the iminyl nitrogen with the carbonyl group:





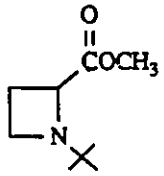
ν CO of ester(benzene):

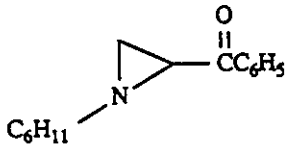
1722 cm^{-1}-1726 cm^{-1}

ν CO of ester(benzene):

1700 cm^{-1}-1705 cm^{-1}

In the literature, other monocarbonyl compounds have been reported to show two absorptions in the infrared carbonyl region. For example, azetidinyl esters[86] and 2-aroylaziridines[87]:





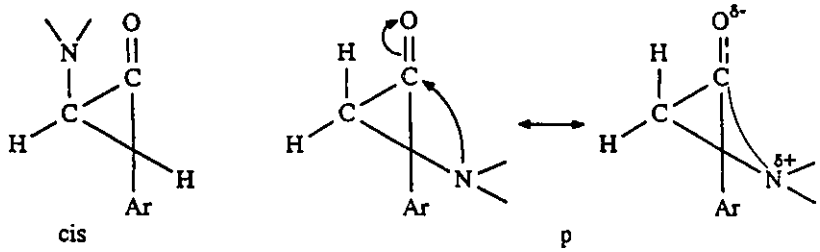
ν CO(CCl_4):

1753 cm^{-1} and 1725 cm^{-1}

ν CO(2,2,4-trimethylpentane):

1695 cm^{-1} and 1673 cm^{-1}

The presence of two carbonyl absorptions was attributed to conformational isomerism. α-Piperidinoacetophenone also shows split carbonyl bands in CCl_4 solution, at 1701 cm^{-1} and 1685 cm^{-1}.[87] Since acetophenone shows a single carbonyl frequency at 1692 cm^{-1} it was suggested that the band at higher frequency should be assigned to a conformation with the C=O and C-N bonds in an eclipsed cis arrangement. The lower frequency band (1685 cm^{-1}) was assigned to a gauche conformation "P" in which a small polarization of the carbonyl group might be expected from an intramolecular three-membered ring interaction of the amino nitrogen with the carbonyl carbon[87]:



In tetrahydrofuran, using a 5:1 ratio of diaziridine to dicobalt octacarbonyl at 35°C and under CO, the 1,2,4-oxadiazoline was obtained in 29% yield after two days. The rest of the crude product was unreacted diaziridine. In benzene, a catalytic amount of $Co_4(CO)_{12}$ (5:1 ratio of diaziridine to tetracobalt dodecacarbonyl) also afforded 1,2,4-oxadiazoline in low yield (9% after two days), at room temperature with the remaining being unreacted diaziridine.

When dicobalt octacarbonyl was replaced by a stoichiometric amount of cobalt benzoate or a catalytic amount of $[Rh(CO)_2Cl]_2$, under CO at 65-70°C, the thermal product was obtained in high yield. The rhodium complex was inert even under 40 atm of carbon monoxide.

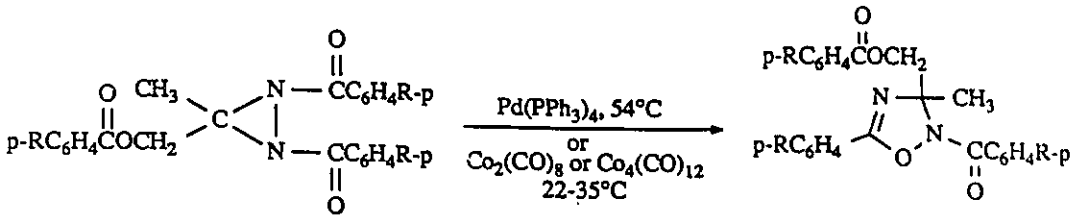
The thermal isomerization observed here (1,2-diaroyldiaziridines ——→ 1,3,4-oxadiazolines) was previously found with monoaryldiaziridines[67], the latter heterocycles rearranging at ambient temperature in chloroform, acetonitrile, or methylene chloride. It was originally reported[88] that thermal rearrangement of spirocyclic 1,2-diaroyldiaziridines does not afford oxadiazolines, but β,β-diaroylhydrazones. However, recently Somogyi[68] demonstrated that the thermal rearrangement of 1',2' - dibenzoylspiro[cyclohexane-1,3'-diaziridine] (**16**) leads to 1,3,4-oxadiazoline (**17**) instead of the claimed isomeric dibenzoylhydrazone. Our results support the findings of Somogyi.

When 1,2-diaroyldiaziridinyl aroates (1,23 mmol) and $Pd(PPh_3)_4$ (0,408 mmol) in dry benzene (36 ml) were stirred under CO, at 54°C, 1,2,4-oxadiazolines were obtained. After purification on silica gel, 1,2-di-p-methoxybenzoyldiaziridinyl p-methoxybenzoate and 1,2-di-p-chlorobenzoyldiaziridinyl p-chlorobenzoate afforded 63% and 77%, respectively, of the 1,2,4-oxadiazoline. A small amount of 1,3,4-oxadiazoline was obtained as a by-product (9% and 4%).

The reaction with 1,2-di-p-toluoyldiaziridinyl p-toluoate was done with three times less $Pd(PPh_3)_4$ (9:1 ratio of diaziridine to Pd). However, only 22% of the corresponding 1,2,4-oxadiazoline was isolated along with 50% of 1,3,4-oxadiazoline.

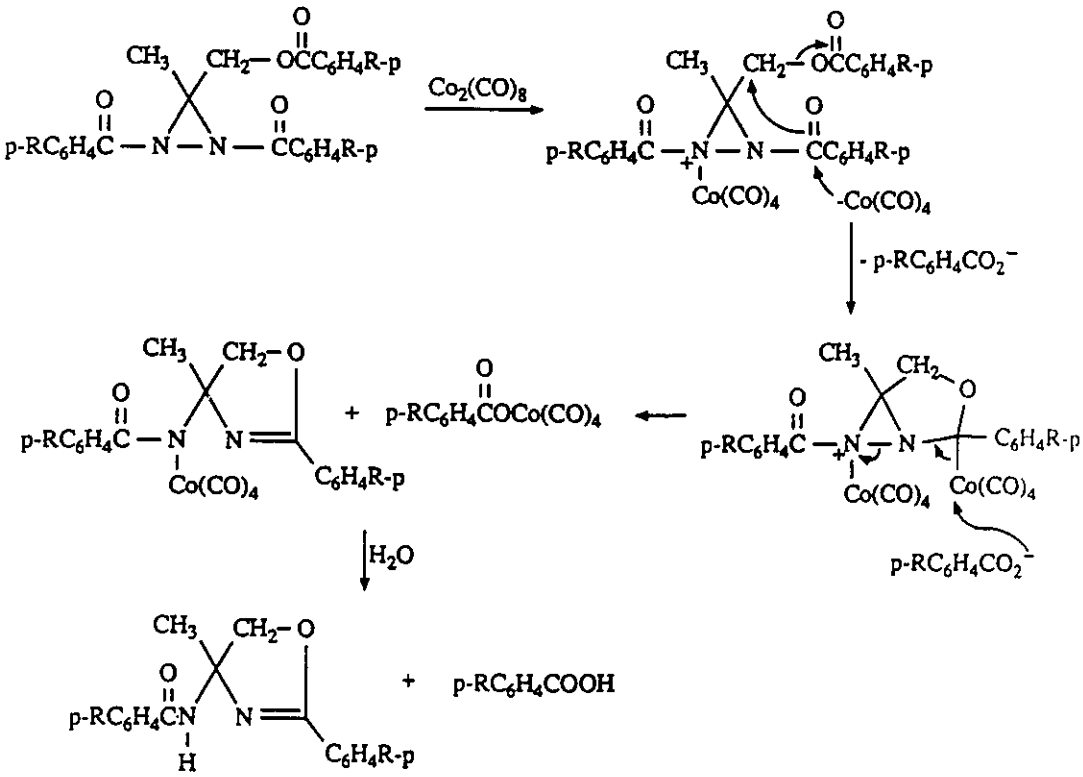
These results show that it is necessary to use a considerable quantity of $Pd(PPh_3)_4$ in order to avoid thermal rearrangement. The tetrakistriphenylphosphine palladium induced conversion of 1,2-diaroyldiaziridinyl aroates into 1,2,4-oxadiazolines is catalytic in nature. Indeed, more than 33% of 1,2,4-oxadiazoline was obtained using a 3:1 ratio of diaziridine to palladium.

At room temperature, a catalytic amount (10:1 ratio of diaziridine to Pd) of $Pd(PPh_3)_4$ and $Pd(dba)_2$ failed to give the 1,2,4-oxadiazoline on attempted carbonylation. After three days, the diaziridine was recovered unchanged.



A possible mechanism for the dicobalt octacarbonyl induced conversion of 1,2 - diaroyldiaziridines into oxazolines is as follows:

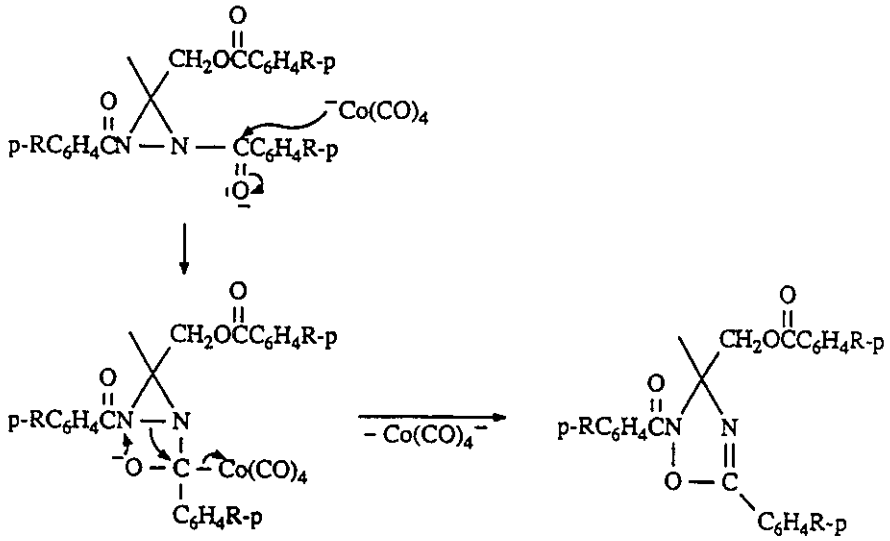
Scheme 2.3



In the proposed mechanism, the diaziridine can function as a Lewis base, inducing disproportionation of dicobalt octacarbonyl. Such reactions have been observed previously for a variety of Lewis bases including the amide, N,N-dimethylformamide[89].

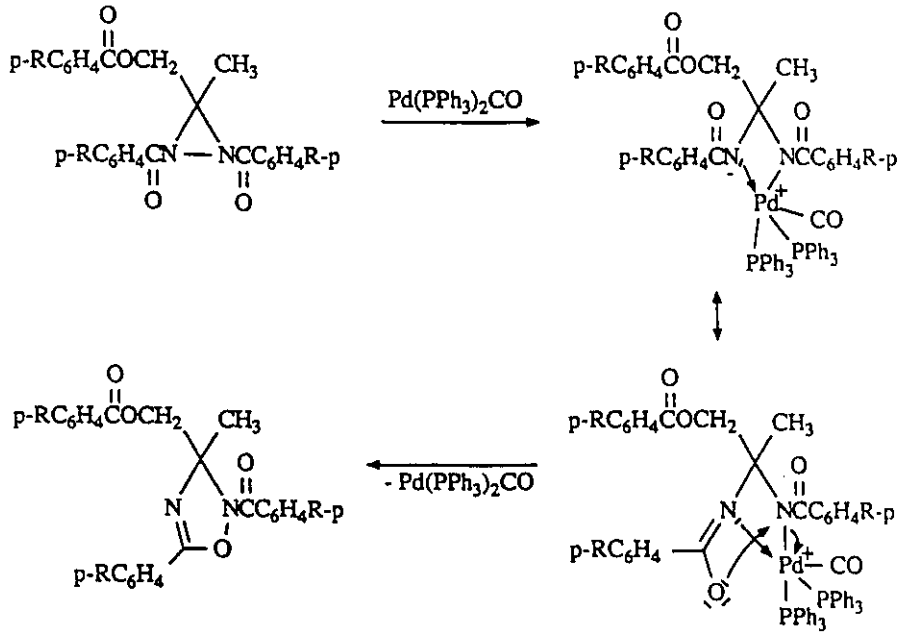
The formation of 1,2,4-oxadiazolines, in the presence of $Co_2(CO)_8$ at room temperature, may result by attack of $Co(CO)_4^-$ on a molecule of the diaziridine (Scheme 2.4):

Scheme 2.4



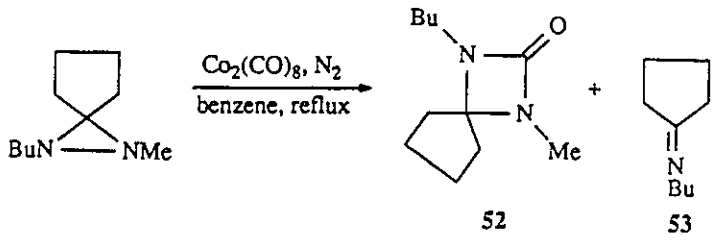
A metallacyclic intermediate may be responsible for the conversion of diaziridines to 1,2,4-oxadiazolines induced by $Pd(PPh_3)_4$ under a CO atmosphere (Scheme 2.5).

Scheme 2.5



While the use of cobalt and palladium complexes to induce conversion of 1,2-diaroyldiaziridinyl aroates into oxazolines or 1,2,4-oxadiazolines is interesting, our goal to carbonylate diaziridines with ring expansion was not realized. Since both oxazolines and 1,2,4-oxadiazolines were obtained due to the presence of the aroyl substituents, we thought it might be interesting to study the behaviour of simple 1,2-dialkyldiaziridines. Consequently, we synthesized 1-methyl-2-butyl-3,3-butamethylenediaziridine for study.

When 1-methyl-2-butyl-3,3-butamethylenediaziridine was refluxed in benzene with half the equimolar quantity of dicobalt octacarbonyl (N_2 atmosphere), the 1,3-diazetidinone (**52**) was obtained along with N-butylcyclopentanimine (**53**).

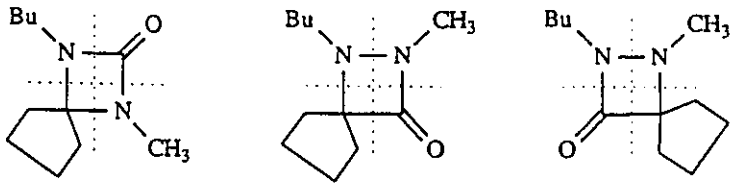


52 53

The reaction was monitored by infrared spectroscopy. After ten minutes, the carbonyl bands of $Co_2(CO)_8$ [1848 cm^{-1}(m), 2020 cm^{-1}(S), 2040 cm^{-1} (S), 2070 cm^{-1}(S)] disappeared and were replaced by a broad carbonyl band at 1890 cm^{-1}. A carbonyl peak at 1775 cm^{-1} confirmed the presence of some diazetidinone. Another peak at 1680 cm^{-1} showed that some N-butylcyclopentanimine had been formed: it was confirmed by GC-mass spectroscopy. After 5 hours the peak at 1890 cm^{-1} had almost disappeared. The peak at 1775 cm^{-1} was about the same intensity while the peak at 1680 cm^{-1} increased. These observations indicate that the diazetidinone is principally formed in the first minutes of the reaction. Accumulation of the imine occurs at a later stage of the reaction. The fact that there is no more $Co_2(CO)_8$ after 10 minutes indicates that $Co_2(CO)_8$ is responsible for the formation of the diazetidinone. The cobalt complex with a broad carbonyl band at 1890 cm^{-1} ($Co(CO)_4^-$?) cannot effect this carbonylation with ring expansion.

The yield of N-butylcyclopentanimine was 41% as determined by gas chromatography using decane as internal standard. Some traces of N-methylcyclopentanimine were detected by GC-mass spectroscopy. Purification on alumina plates afforded the 1,3 -diazetidinone in 11% yield.

The structure of the 1,3-diazetidinone was assigned from its analytical and spectral data. The fact that the 1,3-diazetidinone is formed and not the 1,2-diazetidin-3-one is supported by the fragmentation pattern in the mass spectrum. Indeed, in addition to the molecular ion peak, the mass spectrum shows one peak at m/e 139 and one at m/e 97 which correspond, respectively, to the loss of CH_3NCO and BuNCO from the molecular ion. It would be impossible to have these two fragments generated from either 1,2-diazetidin-3-one isomer.

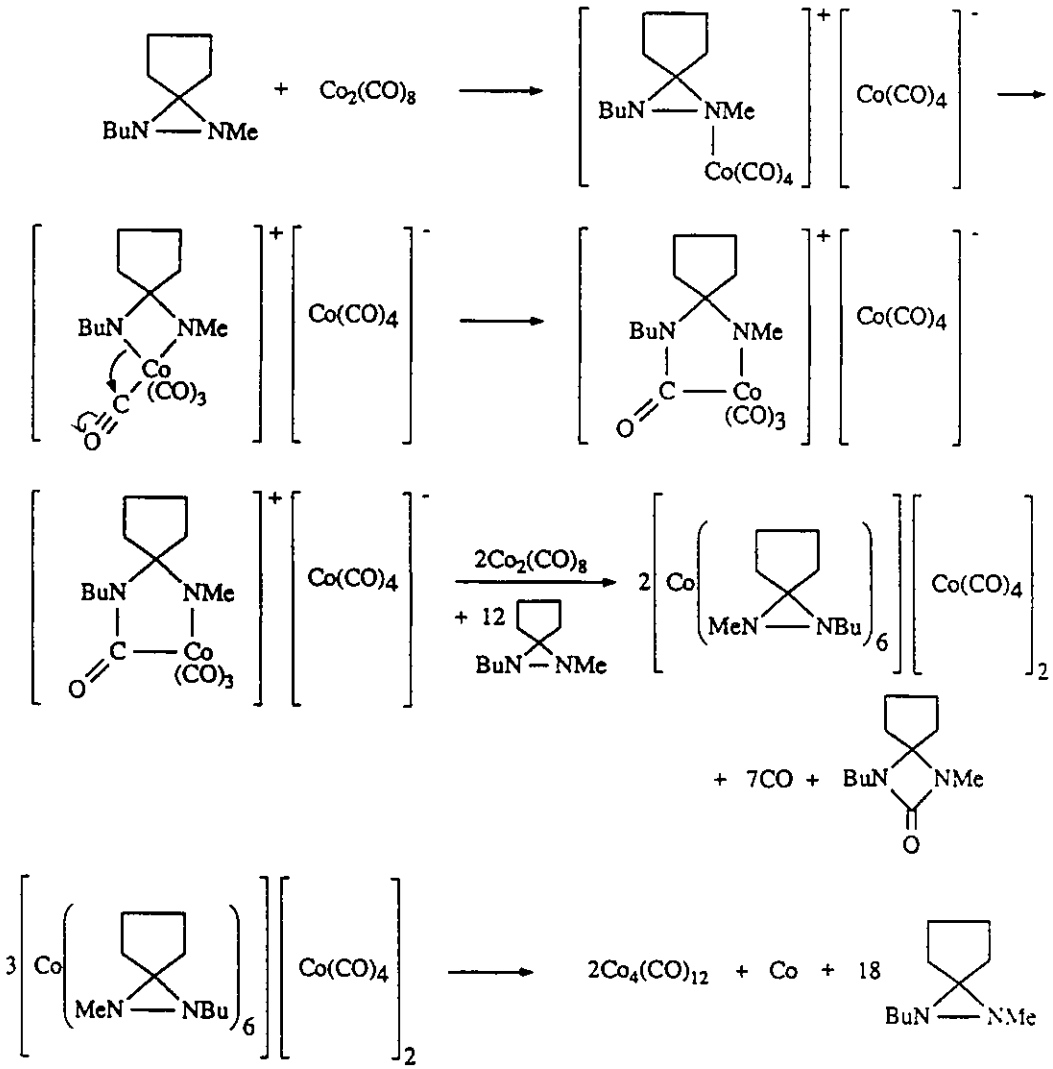


Furthermore, the mass spectrum of the product does not show a signal at m/e 100 which would correspond to $CH_3N{=}NBu$ of the 1,2-diazetidin-3-one. The formation of the azo derivative is the major peak in the mass spectrum of 1,2-diazetidinones[41].

Recently[90], 1,2-dimethyl-3,3-pentamethylenediaziridine had been prepared in our laboratories and reacted with $Co_2(CO)_8$ under the same experimental conditions. A diazetidinone was obtained, whose ^{13}C-NMR spectrum showed only one signal for CH_3N, indicating that the product was the 1,3-diazetidinone. (The 1,2-diazetidin-3-one should have 2 different NCH_3 signals). These results also support the structure assigned to the diazetidinone obtained in the present work.

The dicobalt octacarbonyl reaction affording 1,3-diazetidinone can be accounted for by a pathway similar to the one which has been proposed for the cobalt carbonyl induced formation of azetidine -2,4-diones from α-lactams[52] (Scheme 2.6).

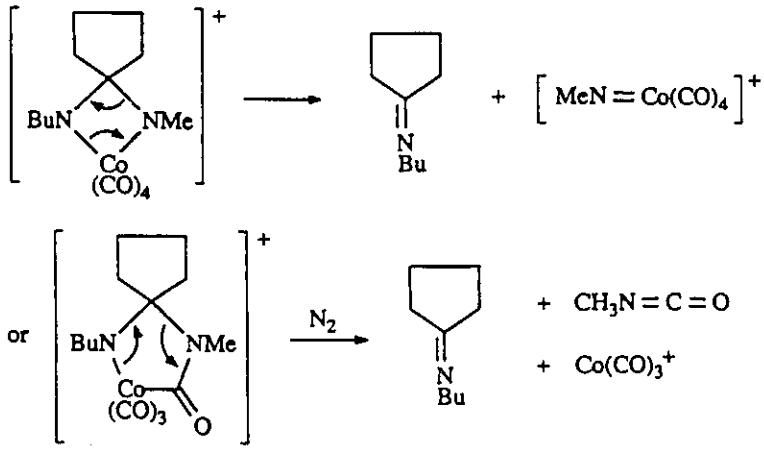
Scheme 2.6



The formation of N-butylcyclopentanimine in 41% yield and only traces of N-methylcyclopentanimine is not easy to rationalize. It is conceivable that N-methylcyclopentanimine is actually formed in quantities similar to that of N-butylcyclopentanimine but that only traces of this product were observed probably because of its high volatility.

The imines may arise by the cleavage of a metallacyclic intermediate, as described in sheme 2.7.

Scheme 2.7



At the beginning of this study we wanted to determine whether diaziridines could undergo carbonylation with ring expansion on treatment with an organotransition-metal complex. Such a process is possible in the case of selected diaziridines with regiospecific insertion affording the 1,3-diazetidinone. It is probable that 1,2,3,3-tetraalkyldiaziridines in general will give 1,3-diazetidinones on exposure with dicobalt octacarbonyl in refluxing benzene.

This study has shown that 1,2-diaroyldiaziridines possess a rich organometallic chemistry. For example, diaziridines can function as a source of 1,2,4-oxadiazolines and of oxazolines.

Finally it was found that, in the presence of dicobalt octacarbonyl and under phase transfer catalysis, 1,3-dimethyl-2-p-toluoyl-3-phenyldiaziridine afforded an acetylated diazene in good yield. It would be interesting to see if azo compounds themselves are acetylated under phase transfer catalysis conditions.

2.3 Experimental Data

2.3.1 General Comments

Infrared spectra were recorded using a Perkin-Elmer 783 spectrometer, and were calibrated with a polystyrene standard. Sodium chloride cells were used for running the spectra. Proton magnetic resonance spectra were recorded on a Varian T60, EM 360A, or XL 300 spectrometer whereas carbon magnetic resonance spectra were obtained with a Varian FT 80 or an XL 300 spectrometer. Mass spectra were recorded with a VG Micromass 7070E spectrometer. Gas chromatography-mass spectra were obtained with a Varian 3300 chromatograph, fitted with a Megabore DB5 capillary column in tandem with the VG Micromass 7070E spectrometer.

Gas chromatography was carried out with a Varian Vista 6000 or Varian 3400 gas chromatograph equipped with a flame ionization detector and a Varian 4270 integrator. Glass columns packed with 3% OV-101 or 3% OV-17 on chromosorb W, 80-100 mesh were utilized.

A Fisher-Johns apparatus was used to obtain the melting points.

Elemental analyses were carried out by M.H.W. Laboratories in Phoenix, Arizona or Guelph Chemical Laboratories, Guelph, Ontario.

The organic chemicals used were purchased from Aldrich Chemical Co, Pfaltz and Bauer, or Fluka, or were prepared according to literature methods. Organometallic complexes were purchased from Strem Chemicals Company or Pressure Chemical Co.

Gases were obtained from Air Products Company. Solvents were purified and dried by standard methods.

High pressure reactions were conducted in 45 ml-series 4700 stainless steel, screw-cap, autoclaves manufactured by Parr Instruments.

Thin layer chromatographic plates, silica gel or neutral (type E) alumina oxide 60 F_{254} were purchased from Terochem Co. as were the silica gel and aluminium oxide used for column chromatography.

2.3.2 Synthesis of Diaziridines

2.3.2.1 Synthesis of 1,3-Dimethyl-3-phenyldiaziridine

1,3-Dimethyl-3-phenyldiaziridine was synthesised according to the literature procedure[77] except that 30% methylamine in water was used instead of methylamine gas. The diaziridine was obtained as a white solid in 23% yield.

b.p. = 60°C (0,8 mm Hg) [lit[77] b.p. = 65°C (0,8 mm Hg)

^{1}H NMR($CDCl_3$): δ 2,00 (S; 3H, CH_3C), 3,02(S;3H, CH_3N); 4,72 (S; 1H, NH), 7,10-7,65 (m; 5H, C_6H_5).

Mass spec.: m/e 148 [M]+

2.3.2.2 Synthesis of 1,3-Dimethyl-2-p-toluoyl-3-phenyldiaziridine (39)

1,3-Dimethyl-3-phenyldiaziridine was reacted with p-toluoyl chloride according to known methodology[78]. To a two-necked round bottomed flask equipped with a condenser, a drying tube and a dropping funnel was added the diaziridine (0,90g; 6,1 mmol) dissolved in dry

benzene (8 ml) and freshly distilled pyridine (9 ml). Freshly distilled p-toluoyl chloride (0,945g; 6,7 mmol) in benzene (9 ml) was added dropwise, at 60°C. The reaction mixture was stirred for 30 minutes, cooled to room temperature, and then poured into 200 ml of water. The layers were separated, the aqueous layer was washed with 25 ml of benzene, and the organic extracts were combined, washed with water (50 ml) and then with 5% sodium carbonate solution (50 ml). After drying over $MgSO_4$, benzene was removed using a rotary evaporator to give a yellow solid (1,59g). The latter was washed with ether and filtered, affording 78% of pure diaziridine (1,27g; 4,8 mmol) as a white solid.

m.p. = 119-121°C

IR (benzene): ν CO: 1650 cm^{-1}.

'H NMR ($CDCl_3$): δ 2,20 (S; 3H, CH_3C); 2,30 (S; 3H, $\underline{CH_3}C_6H_4$); 3,33 (S;3H, NCH_3); 6,95 - 7,80 (m; 9H, C_6H_5 and C_6H_4)

Mass spec: m/e 266 [M]+

2.3.2.3 Synthesis of 3-Hydroxymethyl-3-methyldiaziridine

3-Hydroxymethyl-3-methyldiaziridine was readily synthesized following the literature procudure[79]. Distillation of the crude product under reduced pressure gave 25% of pure 3-hydroxymethyl-3-methyldiaziridine.

b.p. = 60-64°C (0,5 mm Hg) [lit[79] b.p. = 62-63 (0,5 mm Hg)]

'H NMR ($CDCl_3$): δ 1,40 (S; 3H, CH_3); 3,03 (broad S; 3H, 2NH and OH); 3,62 (S; 2H,CH_2).

2.3.2.4 Synthesis of 1,2-Diaroyldiaziridinyl Aroates **(40)**

1,2-Diaroyldiaziridinyl aroates were synthesized by reaction of 3-hydroxymethyl-3-methyldiaziridine with aroyl chlorides in pyridine[78]. The procedure is analogous to the one described for the synthesis of 1,3-dimethyl-2-toluoyl-3-phenyldiaziridine except that 3 equivalents of aroyl chloride were used for 1 equivalent of diaziridine. The 1,2-diaroyldiaziridinyl aroates were purified by silica gel chromatography using 7:3 hexane/ethyl acetate as eluant.

1,2-di-p-toluoyldiaziridinyl p-toluoate

yield: 43%

IR (benzene): νCO: 1710 cm^{-1} (O=CN) and 1730 cm^{-1} (OC=O)

'H NMR ($CDCl_3$): δ 1,56(S; 3H, CH_3C); 2,36 (S; 9H, $3\underline{CH_3}Ph$); 4,50 (S;2H, CH_2O); 6,96 - 8,06 (m; 12H, $3C_6H_4$)

Mass spec.: m/e 442 [M]+; 293 [M-$CH_2O_2CPhCH_3$]+; 119 [CH_3PhCO]+

1,2-di-p-methoxybenzoyldiaziridinyl p-methoxybenzoate

yield: 35%

IR (benzene): ν CO 1710 cm^{-1} (O=CN) and 1730 cm^{-1} (OC=O)

'H NMR ($CDCl_3$): δ 1,60 (S; 3H, CH_3C); 3,80 (S,9H, $3CH_3O$); 4,53 (S;2H, CH_2O); 6,66-8,16 (m; 12H, $3C_6H_4$)

Mass spec.: m/e 490 [M]+; 325 [M-$CH_2O_2CPhOCH_3$]+; 135 [CH_3OPhCO]+

1,2-di-p-chlorobenzoyldiaziridinyl p-chlorobenzoate

yield: 48%

IR (benzene): ν CO 1710 cm^{-1} (O=CN) and 1730 cm^{-1} (O=CO)

^{1}H NMR ($CDCl_3$): δ 1,60 (S; 3H, CH_3C); 4,56 (S,2H, CH_2O); 7,10 - 8,10 (m; 12H, $3C_6H_4$)

Surprisingly, some aromatic anhydrides were obtained as by-products (≈20%)

p-toluoic anhydride:

IR ($CHCl_3$): ν CO 1720 cm^{-1}(m) and 1785 cm^{-1} (S)

^{1}H NMR ($CDCl_3$): δ 2,40 (S; 6H, $2CH_3Ph$); 7,06-8,10 (AA'BB', 8H, $2C_6H_4$)

Mass spec.: m/e 254 [M]+; 119 [CH_3PhCO]+; 91[CH_3Ph]+

p-methoxybenzoic anhydride

IR ($CHCl_3$): ν CO 1715 cm^{-1}(m) and 1780 cm^{-1} (S)

Mass spec.: m/e 286 [M]+; 135 [CH_3OPhCO]+; 107[CH_3OPh]+

p-chlorobenzoic anhydride

IR ($CHCl_3$): ν CO 1730 cm^{-1}(m) and 1792 cm^{-1} (S)

Mass spec.: m/e 294 [M]+; 139 [ClPhCO]+; 111[ClPh]+

2.3.2.5 Attempted Synthesis of 1,2-t-Butylacetyldiaziridinyl t-Butylacetate

When 3-hydroxymethyl-3-methyldiaziridine was treated with t-butylacetyl chloride according to the procedure described for the

synthesis of 1,2-diaroyldiaziridinyl aroates, no protected diaziridine could be obtained. Thermal rearrangement of the 1,2-t-butylacetyl-diaziridinyl t-butylacetate, initially formed, afforded a 4,5-dihydro-oxadiazole (42).

IR ($CHCl_3$): ν CO 1736 cm^{-1}(O=CO); 1645 cm^{-1} (O=CN)

'H NMR ($CDCl_3$): δ 1,02 [S; 27H, $3(CH_3)_3C$); 1,76(S; 3H; CH_3CN)

2,16 (S; 4H, $2CH_2C=O$); 2,46 (S; 2H, CH_2 C=N); 4,49 (AB quartet, 2H, CH_2O).

^{13}C NMR ($CDCl_3$): δ 24,45 ($\underline{CH_3}$-C); 33,44 ($3(\underline{CH_3})_3$ C);

43,06 (CH_2); 49,95 (CH_2); 51,60 (CH_2); 67,66 (CH_2O);

101 (O-C-N); 158 (O-C=N); 172 (N-C=O); 175 (O-C=O)

Mass spec.: m/e 382 [M]+; 367 [M-CH_3]+, 99

[$(CH_3)_3$ CCH_2CO]+; 155 [$(CH_3)_3$ CCH_2 CO_2 CH_2 CN]+

2.3.2.6 Synthesis of 1-Methyl-2-butyl-3,3-butamethylenediaziridine (41)

First, N-butylcyclopentanimine was prepared. It was obtained by stirring cyclopentanone and butylamine in benzene, for 4 hours at 80°C, using the azeotropic distillation technique[80]. Distillation under reduced pressure afforded 81% of the imine.

IR (benzene): ν C=N 1680 cm^{-1}

'H NMR ($CDCl_3$): δ 0,90 (t; 3H, $\underline{CH_3}CH_2$); 1,34 (m; 2H, $CH_2\underline{CH_2}CH_3$);

1,55-1,82 (m; 6H, $3CH_2$); 2,14 (t; 2H, CH_2 C=N);

2,30 (t; 2H, CH_2 C=N); 3,15 (t; 2H, CH_2N)

^{13}C NMR ($CDCl_3$): δ 14,04 (CH_3); 20,80 ($\underline{CH_2}CH_3$);

24, 34(CH_2); 25,00 (CH_2); 28,85 (CH_2); 33,04 (CH_2); 36,42 (CH_2); 53,44 (CH_2N); 179,63 (C=N).

Mass spec.: m/e 139 [M]+, 124 [M-CH_3]+, 110 [M-CH_2CH_3]+, 96 [M-$CH_2CH_2CH_3$]+

1-Methyl-2-butyl-3,3-butamethylenediaziridine was then synthesised by reaction of the N-butylcyclopentanimine with methylhydroxylamine - o- sulfonic acid, according to known methodology [81-82]. Purification by thin layer chromatography (alumina), using pentane as the eluant, afforded the diaziridine in 75% yield.

^1H NMR ($CDCl_3$): δ 0,91 (t; 3H, CH_3C); 1,32-1,83 (m; 12H, $6CH_2$); 2,19-2,28 (m; 1H, NCH); 2,40 (S;3H, NCH_3); 2,46-2,55 (m; 1H, NCH).

^{13}C NMR ($CDCl_3$): δ 14,20 (C-$\underline{CH_3}$); 20,76 ($\underline{CH_2}CH_3$); 24,81 (CH_2); 24,91 (CH_2), 28,59 ($\underline{CH_2}CN\underline{CH_2}$), 31,40 ($CH_2$-$\underline{CH_2}CH_2$) 42,01 ($CH_3N$); 54,83 ($CH_2N$); 72,97 (NCN)

Mass spec.: m/e 168 [M]+, 153 [M-CH_3]+, 125 [M-$CH_2CH_2CH_3$]+, 96 [M-C_5H_{12}]+, 68 [M-$CH_3NNCH_2CH_2CH_2CH_3$]+

2.3.3 Reaction of 1,3-Dimethyl-2-p-toluoyl-3-phenyldiaziridine with Organotransition-metal Complexes

2.3.3.1 General Procedure For Reaction Under Carbon Monoxide at Atmospheric Pressure

A mixture of diaziridine (0,20g; 0,75 mmol) and dry benzene (10-15 ml) was degassed by bubbling nitrogen through the solution for 10

min at room temperature. After having replaced nitrogen by carbon monoxide, the metal complex (0,15-0,75 mmol) was added. The solution was stirred under carbon monoxide at room temperature or at 65°C for one to four days. The reaction was followed by infrared spectroscopy.

Work-up was effected by filtering the reaction mixture through Celite. Rotary evaporation of the filtrate gave the crude product. A ^{1}H-NMR of the crude product was done and, when necessary, the mixture was purified by silica gel thin layer chromatography using 7:3 hexane/ethyl acetate as the eluant.

2.3.3.2 General Procedure for Reaction Under Carbon Monoxide Pressure

A 45 ml autoclave containing the diaziridine (0,20g; 0,75 mmol), the metal complex (0,15-0,75 mmol), and dry degassed benzene (10-15 ml) was purged twice with 7 atm of carbon monoxide before being loaded with 30 atm of carbon monoxide. The reaction mixture was stirred for 1 day under 30 atm. The pressure was released and work-up was effected as described in the general procedure for the reaction at atmospheric pressure.

2.3.3.3 Attempted Carbonylation with Different Organotransition-metal Complexes

Attempted carbonylation with $RuCl_2(PPh_3)_3$

A benzene (10 ml) solution of diaziridine (0,073g, 0,27 mmol) and

$RuCl_2(PPh_3)_3$ (0,053g; 0,055 mmol) was stirred at 65°C under CO bubbling. Analysis after 4 days indicated that no reaction occurred.

Attempted carbonylation with $Co_2(CO)_8$

A benzene (10 ml) solution of diaziridine (0,20g; 0,75 mmol) and $Co_2(CO)_8$ (0,257g; 0,75 mmol) was stirred at 65°C under 1 atm of N_2. After 2 days only the diaziridine was recovered.

Attempted carbonylation with $[Rh(CO)_2Cl]_2$

a) A solution of diaziridine (0,20g; 0,75 mmol) and $[Rh(CO)_2Cl]_2$ (0,074g; 0,19 mmol) in benzene (10 ml) was stirred at 65°C under carbon monoxide. After 1 or 2 days ^{1}H-NMR of the crude product showed the presence of 20% acetophenone and 80% diaziridine.

b) A benzene solution of diaziridine (0,20g; 0,75 mmol) and $[Rh(CO)_2Cl]_2$ (0,146g; 0,38 mmol) was stirred at 65°C under CO bubbling. After 1 day the reaction was stopped. In the flask there was an orange precipitate and a yellow solution. The mixture was filtered, the precipitate was washed with benzene, and dried (brown solid).

An infrared spectrum of the precipitate was taken in chloroform: ν CO 2018 cm^{-1} and 2085 cm^{-1}. These carbonyl bands are different from those of $[Rh(CO)_2Cl]_2$ (2040 cm^{-1} and 2100 cm^{-1}). An ^{1}H-NMR of the complex was recorded in $CDCl_3$: δ 2,36 (S,3H), 3,60 (S,3H), 7,03-7,53 (AA'BB' pattern, 4H).

The filtrate was concentrated by rotary evaporation. The crude residue was chromatographed using a silica gel thin layer plate (7:3 hexane/ethyl acetate as eluant) to give 45% of diaziridine and 37% of acetophenone. IR of acetophenone (benzene) ν CO 1685cm^{-1}; ^{1}H-NMR of acetophenone ($CDCl_3$): δ 2,53 (S; 3H, CH_3); 7,23-7,97 (m; 5H, C_6H_5).

c) A benzene (10 ml) solution of diaziridine (0,096g; 0,36 mmol) and $[Rh(CO)_2Cl]_2$ (0,028g; 0,072 mmol) was stirred under 30 atm of carbon monoxide, at 22°C. After 1 day, 19% of acetophenone and 81% of diaziridine were present (^{1}H NMR ratio).

d) A 4-methyl-2-pentanone (11 ml) solution of diaziridine (0,17g; 0,65 mmol) and $[Rh(CO)_2Cl]_2$ (0,050g; 0,13 mmol) was stirred under carbon monoxide at 22°C. After 1 day the reaction was stopped. Silica gel chromatography afforded 46% of diaziridine and 26% of acetophenone.

Attempted Carbonylation with $IrCl(CO)(PPh_3)_2$

a) A benzene (10 ml) solution of diaziridine (0,20g; 0,75 mmol) and $IrCl(CO)(PPh_3)_2$ (0,12g; 0,15 mmol) was stirred under carbon monoxide at 65°C for 3 days. There was no reaction.

b) No reaction was observed when a benzene (10 ml) solution of diaziridine (0,20g; 0,75 mmol) and $IrCl(CO)(PPh_3)_2$ (0,12g; 0,15 mmol) was stirred under 30 atm of carbon monoxide, at 65°C, for 1 day.

Attempted carbonylation with $[Ir(COD)Cl]_2$

A solution of diaziridine (0,13g; 0,49 mmol) and $[Ir(COD)Cl]_2$ (0,054g; 0,081 mmol) in benzene (15 ml) was stirred at 65°C (carbon

monoxide) for 1 or 2 days. No precipitate was observed. The solution turned from orange to dark brown. An infrared spectrum of the reaction mixture showed ν CO at 2080 and 2005 cm^{-1} (in benzene). An ^{1}H-NMR of the crude residue showed the presence of 24% acetophenone and 76% diaziridine.

Attempted carbonylation with $Ni(CO_2)(PPh_3)_2$

A benzene (15 ml) solution of diaziridine (0,20g; 0,75 mmol) and $Ni(CO)_2(PPh_3)_2$ (0,096g; 0,15 mmol) was stirred under carbon monoxide for 2 days, at 65°C. No reaction was observed.

Attempted carbonylation with $Pd(PPh_3)_4$

a) A benzene (10 ml) solution of diaziridine (0,20g; 0,75 mmol) and $Pd(PPh_3)_4$ (0,17g; 0,15 mmol) was stirred, at 65°C under 30 atm of carbon monoxide. After 1 day, there was 8% of acetophenone and 92% of diaziridine (^{1}H-NMR ratio).

b) Diaziridine (0,097g; 0,36 mmol) and $Pd(PPh_3)_4$ (0,20g; 0,18 mmol) were stirred in benzene (10 ml) under carbon monoxide at 65°C. After 1 or 4 days, 36% of acetophenone and 64% of diaziridine was formed (^{1}H-NMR ratio). An infrared spectrum of the reaction mixture, in benzene, showed a carbonyl band at 1943 cm^{-1}.

2.3.3.4 General Procedure for Carbonylation of Diaziridine at Atmospheric Pressure Under Phase Transfer Catalysis Conditions using Cetyltrimethylammonium Bromide (CTAB)

Freshly prepared 0,5N sodium hydroxide solution (12 ml) and distilled benzene (12 ml) were placed in a 50 ml three-necked round bottomed flask. The mixture was degassed by bubbling nitrogen through the stirred solution for 30 minutes at room temperature. The gas was changed to carbon monoxide, cetyltrimethylammonium bromide (0,19 mmol) and the metal complex (0,19 mmol) were added, and the mixture was stirred for about 30 minutes. The diaziridine (0,75 mmol) was then added (in those cases where methyl iodide (21 mmol) was used, it was added to the mixture five minutes before the diaziridine), and the reaction mixture was stirred at room temperature or 60°C, for one day.

The two layers were separated, and the aqueous layer was extracted with 12 ml of benzene. The benzene extracts were combined, dried over $MgSO_4$ and concentrated (rotary evaporator) to give the crude products. The aqueous phase was neutralized with dilute hydrochloric acid and extracted several times with 10 ml portions of methylene chloride. The organic extracts were dried ($MgSO_4$) and concentrated. When necessary, the mixture was purified by silica gel thin layer chromatography.

2.3.3.5 General Procedure for Carbonylation of Diaziridines Under Pressure and Phase Transfer Catalysis Conditions

The reaction mixture was prepared as described in the previous procedure. Five minutes after the addition of the diaziridine, the mixture was transferred to an autoclave. It was purged once with 7 atm of carbon monoxide before being loaded with 30 atm of the gas. The

reaction mixture was stirred at room temperature, 35°C or 60°C, for 1 or 2 days. The pressure was released and the reaction was worked-up as described above.

2.3.3.6 Attempted Carbonylation with Different Organotransition-metal Complexes Under Phase Transfer Conditions

Reaction with $Co_2(CO)_8$ and MeI (PTC using (CTAB)

Under 30 atm of carbon monoxide, the diaziridine was recovered after attempted reaction at 22°C and at 35°C. However, after 2 days at 60°C reaction did occur. The aqueous phase was neutralized and extracted several times with 20 ml portions of methylene chloride. The combined organic extracts were dried and concentrated on a rotary evaporator. Purification of the mixture on silica plates, using 7:3 ethyl acetate/ hexane as eluant, afforded 15% of diaziridine, 20% of acetophenone, 55% of 1-acetyl-2-methyl-1-p-toluoylhydrazine (43) and traces of 1,1-dimethyl-2-p-toluoylhydrazine (44) or 1,2-dimethyl-1-p-toluoylhydrazine (45).

43:

m.p. = 143-145°C; IR ν CO($CHCl_3$): 1655 cm^{-1} and 1710 cm^{-1};

^1H NMR ($CDCl_3$): δ 1,73 (S; 3H, CH_3CON); 2,30 (S; 3H, $\underline{CH_3}Ph$); 3,13 (S; 3H, CH_3N); 6,90-7,40 (m; 4H, C_6H_4); 8,83 (S; 1H, NH)

Mass Spec.: m/e 206 $[M]^+$; 164 $[M-CH_2CO]^+$; 119 $[pCH_3PhCO]^+$; 91 $[pCH_3Ph]^+$

44 or 45:

Mass Spec.: m/e 178 $[M]^+$; 119 $[pCH_3PhCO]^+$; 91 $[pCH_3Ph]^+$

Reaction with $Co_2(CO)_8$ (PTC using TEBAC)

The diaziridine (0,20g; 0,75 mmol), $Co_2(CO)_8$ (0,26g; 0,75 mmol) and benzyltriethylammonium chloride (TEBAC, 0,056g; 0,25 mmol) were stirred in benzene (8 ml) and NaOH 5N (8 ml), at 60°C (carbon monoxide atmosphere). There was no reaction after 24 hours.

Reaction with $Ni(CN)_2.4H_2O$

The diaziridine (0,20g; 0,75 mmol), $Ni(CN)_2.4H_2O$ (0,017g; 0,09 mmol) and tetrabutyl ammonium hydrogen sulfate (0,015g; 0,045 mmol) were stirred with benzene (5 ml) and NaOH 5N (5 ml), at 60°C (carbon monoxide). After 1 day there was no reaction.

2.3.4 Reaction of 1,2-Diaroyldiaziridines with Organotransition-metal Complexes

2.3.4.1 Conversion of 1,2-Diaroyldiaziridines into Dihydrooxazoles (48)

General procedure for the reaction of dicobalt octacarbonyl with 1,2-diaroyldiaziridinyl aroates (40)

A mixture of 40 (0,38 mmol) and $Co_2(CO)_8$ (0,38 mmol) in dry benzene (10 ml) was stirred under nitrogen at 65-70°C. The reaction was monitored by infrared spectroscopy and thin-layer chromatography. After 75 minutes the reaction was essentially complete, but stirring was continued overnight. The solution was cooled and filtered. The filtrate

was washed with 1N NaOH to remove the carboxylic acid which was isolated by acidification of the aqueous layer. The benzene layer was dried over $MgSO_4$ and concentrated by rotary evaporation. The dihydrooxazole was purified by silica gel thin-layer chromatography using hexane/ethyl acetate (7:3 for R=Me or Cl; 4:6 for R=OMe) as the eluant.

Reaction with 1,2-di-p-toluoyldiaziridinyl p-toluoate

48, R=CH_3, was isolated in 51% yield of analytically pure material.

m.p.: 165-167°C

IR (benzene):ν 3437 cm^{-1}(NH); 1662cm^{-1}(C=O); 1643 cm^{-1} (C=N)

^{1}H NMR ($CDCl_3$): δ 1,76(S; 3H, CH_3); 2,36(S; 6H, 2$\underline{CH_3}C_6H_4$); 4,58 (AB quartet; 2H, CH_2O); 6,90-7,90 (m;9H, 2C_6H_4 and NH)

^{13}C NMR ($CDCl_3$): δ 21,40 ($\underline{CH_3}C_6H_4$); 21,59 ($\underline{CH_3}C_6H_4$); 26,73 ($\underline{CH_3}CN_2$); 78,54 (CH_2O); 83,07 (N-C-N); 124,20; 126,95; 128,49; 129,13; 129,16; 131,09; 142,09; 142,50; 165,95 (NC=O)

Mass Spec.: m/e 293 [M-CH_3]+; 119 [CH_3PhCO]+

C.I. 309[M+1]+

Elemental analysis: calculated C 74,00 H 6,54 N 9,08

found 74,07 6,56 8,70

Reaction with 1,2-di-p-methoxybenzoyldiaziridinyl p-methoxybenzoate

48, R=OCH_3, was obtained in 59% yield.

IR (benzene):ν 3437 cm^{-1}(NH); 1660 cm^{-1} (C=O); 1642 cm^{-1} (C=N)

'H NMR ($CDCl_3$): δ 1,75 (S; 3H, CH_3C); 3,76 (S; 6H, $2CH_3O$); 4,58 (AB quartet, 2H, CH_2O); 6,63-7,90 (m; 9H, $2C_6H_4$ and NH)

Mass Spec.: m/e 325 $[M-CH_3]+$; 135 $[CH_3OPhC=O]+$

C.I. 341 $[M+1]+$

Elemental analysis: calculated C 67,04 H 5,92 N 8,23

found 67,38 5,99 8.19

Reaction with 1,2-di-p-chlorobenzoyldiaziridinyl p-chlorobenzoate

48, R=Cl, was isolated in 79% yield.

m.p. = 168-170°C

IR (benzene):ν 3440 cm^{-1} (NH); 1662 cm^{-1} (C=O); 1640 cm^{-1} (C=N)

'H NMR ($CDCl_3$): δ 1,80 (S; 3H, CH_3); 4,58 (AB quartet, 2H, CH_2O); 6,90 (broad S; 1H, NH); 7,16-7,93 (m; 8H, $2C_6H_4$)

^{13}C NMR ($CDCl_3$): δ 26,78 (CH_3); 78,47 (CH_2O); 83,10 (N-C-N); 125,45; 128,39; 128,78; 128,82; 129,77; 129,86; 132,21; 138,06; 138,34; 164,98 (NC=O).

Mass spec.: m/e 333 $[M-CH_3]+$; 139 $[ClPhCO]+$

C.I. 349 $[M+1]+$

Elemental analysis: calculated C 58,47 H 4,04 N 8,02

found 58,26 4,09 7,86

Variation in reaction conditions

Replacement of nitrogen by carbon monoxide

Use of a carbon monoxide atmosphere instead of nitrogen also afforded the dihydrooxazoles. For instance, 40(R=CH_3) gave 48 (R=CH_3) in 79% yield.

Use of a catalytic amount of dicobalt octacarbonyl under carbon monoxide

When a catalytic amount of dicobalt octacarbonyl (10:1) was used, under a carbon monoxide atmosphere, the diaziridine was converted to a 1,3,4-oxadiazoline (49). This product was also obtained quantitatively in the absence of dicobalt octacarbonyl (N_2 atmosphere).

49 (R=CH_3):

m.p. = 92-94°C

IR (benzene): ν CO: 1643 cm^{-1} (N-C=O); 1732 cm^{-1} (O-C=O)

^1H NMR ($CDCl_3$): δ 2,06 (S; 3H, CH_3); 2,27 (S; 3H, $\underline{CH_3}C_6H_4$); 2,31 (S; 3H, $\underline{CH_3}C_6H_4$); 2,36 (S; 3H, $\underline{CH_3}C_6H_4$); 4,93 (AB quartet, 2H, $CH_2OC=O$); 6,90-7,96 (m; 12H, $3C_6H_4$)

^{13}C NMR ($CDCl_3$): δ 20,80(CH_3); 21,53($\underline{CH_3}C_6H_4$); 21,57 ($\underline{CH_3}C_6H_4$); 21,59($\underline{CH_3}C_6H_4$); 64,72($\underline{CH_2}OC=O$); 100,19(O-C-N); 121,63; 126,70; 126,82; 128,39; 128,99; 129,22; 129,65; 129,83; 131,19; 141,48; 141,89; 143,69; 154,72(O-C=N); 164,72(N-C=O); 165,73(O-C=O)

Mass spec.: C.I. 443 $[M+1]^+$

Elemental Analysis:				
calculated	C 73,28	H 5,92	N 6,33
found	73,55	6,01	6,30

49 ($R=OCH_3$):

m.p.=120-122°C

IR (benzene): ν CO: 1640 cm^{-1} (N-C=O); 1727 cm^{-1} (O-C=O)

^1H NMR ($CDCl_3$) : δ 2,03 (S; 3H, CH_3); 3,76 (S; 9H, $3CH_3O$); 4,89 (AB quartet; 2H, $CH_2OC=O$); 6,60-8,00 (m; 12H, $3C_6H_4$)

Mass spec.: C.I. 491 [M+1]+

49 (R=Cl):

m.p.= 104-105°C

IR (benzene): ν CO: 1647 cm^{-1} (N-C=O); 1735 cm^{-1} (O-C=O)

^1H NMR ($CDCl_3$) : δ 2,04 (S; 3H, CH_3); 4,90 (AB quartet; 2H, $CH_2OC=O$); 7,02-7,94 (m; 12H, $3C_6H_4$)

^{13}C NMR ($CDCl_3$) : δ 24,64(CH_3); 68,82(CH_2O); 104,78(N-C-O); 126,54; 132,03; 132,70; 133,00; 134,81; 135,12; 135,98; 141,50; 141,89; 143,69; 158,09 (O-C=N); 167,72(N-C=O); 168,59 (O-C=O)

Mass spec.: C.I. 504 [M+1]+

Elemental Analysis: calculated C 57,22 H 3,40 N 5,56

found 57,24 3,57 5,52

Use of a catalytic amount of dicobalt octacarbonyl, at 55-58°C (carbon monoxide atmosphere)

The reaction was run using a 10:1 ratio of diaziridine/octacarbonyl dicobalt. No dihydrooxazole was obtained. However, the 1,3,4-oxadiazoline was formed.

Replacement of $Co_2(CO)_8$ by $Co(O\overset{O}{\overset{\|}{C}}C_6H_5)_2$ (carbon monoxide atmosphere).

When $Co_2(CO)_8$ was replaced by $Co(OOCC_6H_5)_2$, and reaction effected at 68°C, the thermal product was obtained in quantitative yield.

Replacement of $Co_2(CO)_8$ by $[Rh(CO)_2Cl]_2$, at 60°C (carbon monoxide atmosphere)

Use of a catalytic amount of chlorodicarbonyl rhodium dimer (10:1 ratio of diaziridine to Rh complex), under 1 atm or 40 atm of CO, afforded the 1,3,4-oxadiazoline in high yield.

2.3.4.2 Conversion of 1,2-Diaroyldiaziridines into 1,2,4-Oxadiazolines

General procedure for the reaction of $Pd(PPh_3)_4$ with 1,2-diaroyldiaziridinyl aroates

A mixture of 1,2-diaroyldiaziridinyl aroate (1,23 mmol) and $Pd(PPh_3)_4$ (0,408 mmol) in dry benzene (36 ml) was stirred under carbon monoxide, at 54°C. After one night, the solution was cooled and filtered through Celite. The filtrate was concentrated by rotary evaporation. The crude product was purified by silica gel (plate or column) chromatography using hexane/ethyl acetate (7:3) as eluant. 1,2,4-Oxadiazolines (51) were obtained along with some thermal product (49).

Reaction with 1,2-di-p-toluoyldiaziridinyl p-toluoate

Three times less $Pd(PPh_3)_4$ was used in this reaction than that described in the general procedure, affording 50% of 49 ($R=CH_3$) and 22% of 51 ($R=CH_3$).

51 ($R=CH_3$):

IR (benzene): ν CO: 1672 cm^{-1} (N-C=O); 1702 cm^{-1} and 1726 cm^{-1} (OC=O)

^1H NMR ($CDCl_3$); δ 1,99 (S; 3H, CH_3); 2,33 (S; 9H, $3\underline{CH_3}C_6H_4$); 5,03 (S; 2H, CH_2O); 7,03-7,99 (m; 12H; $3C_6H_4$)

^{13}C NMR ($CDCl_3$); δ 21,47($2CH_3$); 21,71(CH_3); 22,32(CH_3); 67,62(CH_2O); 70,51(N-C-N); 126,56; 127,10; 129,17; 129,27; 129,96; 131,45; 142,28; 144,42; 167,69 (N-C=O); 167,78 (O-C=O)

Mass spec.: m/e: 293 $[M-CH_3PhCO_2CH_2]^+$; 119$[CH_3PhCO]^+$

Reaction with 1,2-di-p-methoxybenzoyldiaziridinyl p-methoxybenzoate

9% of 49 ($R=OCH_3$) and 63% of 51 ($R=OCH_3$) were obtained from this reaction.

51 ($R=OCH_3$):

m.p.: 144-145°C

IR (benzene): ν CO: 1672 cm^{-1} (NC=O); 1700 cm^{-1} and 1722 cm^{-1} (OC=O)

^1H NMR ($CDCl_3$); δ 2,00 (S; 3H, CH_3C); 3,80 (S; 9H, $3CH_3O$); 5,04 (S; 2H, $CH_2OC=O$); 6,70-8,06 (m; 12H; $3C_6H_4$)

^{13}C NMR ($CDCl_3$); δ 22,27($\underline{CH_3}C$); 55,39($2CH_3O$); 55,47(CH_3O); 67,62 (CH_2O); 70,61 (N-C-N); 113,76; 121,62; 126,61; 128,97; 132,03; 162,39; (OC=N);

163,86(N-C=O); 167,25 (O-C=O)

Mass spec.: m/e: 325 [M-$CH_3OPhCO_2CH_2$]+; 135[CH_3OPhCO]+

C.I.: 491 [M+1]+

Elemental Analysis: calculated C 66,11 H 5,34 N 5,71

found 66,23 5,78 5,84

Reaction with 1,2-di-p-chlorobenzoyldiaziridinyl p-chlorobenzoate

The reaction afforded 4% of 49 (R=Cl) and 77% of 51 (R=Cl).

51 (R=Cl)

m.p. = 174-175°C

IR (benzene): ν CO: 1665 cm^{-1} (NC=O); 1705 cm^{-1} and 1725 cm^{-1} (OC=O)

^{1}H NMR ($CDCl_3$): δ 1,96 (S; 3H, CH_3); 5,00 (S; 2H, CH_2O); 7,13-8,03 (m; 12H, $3C_6H_4$)

Mass spec.: C.I. 504 [M+1]+

The reaction using a catalytic amount (10:1 ratio of diaziridine to Pd) of $Pd(PPh_3)_4$ or $Pd(dba)_2$ at room temperature failed to give the 1,2,4-oxadiazoline. After 3 days the diaziridine was recovered.

Formation of 1,2,4-oxadiazolines by cobalt complexes

A mixture of p-toluoyldiaziridinyl p-toluoate (0,45 mmol) and $Co_2(CO)_8$ (0,09 mmol) was stirred in tetrahydrofuran (15 ml) at 35°C (carbon monoxide atmosphere). After 2 days, the reaction was stopped,

filtered through Celite, and evaporation of the solvent gave 71% of unreacted diaziridine and 29% of the corresponding 1,2,4-oxadiazoline ('H NMR yield).

When a benzene solution of p-toluoyldiaziridinyl p-toluoate (0,45 mmol) and $Co_2(CO)_8$ (0,15 mmol) was stirred under nitrogen, at room temperature for 3 days, 14% of 1,2,4-oxadiazoline and 18% of dihydro-oxazole were obtained ('H-NMR yield). No 1,3,4-oxadiazoline was formed.

Moreover, 9% of 1,2,4-oxadiazoline was obtained when p-toluoyl-diaziridinyl p-toluoate (0,45 mmol) and $Co_4(CO)_{12}$ (0,09 mmol) were stirred in benzene (15 ml) at room temperature (carbon monoxide atmosphere).

2.3.5 Carbonylation of 1-Methyl-2-butyl-3,3-butamethylenediaziridine

To a degassed solution (nitrogen) containing 1-methyl-2-butyl-3,3-butamethylenediaziridine (0,300g; 1,78 mmol) in dry benzene (15 ml) was added $Co_2(CO)_8$ (0,305g; 0,89 mmol). Then the reaction mixture was heated to 100°C (the reaction was followed by infrared spectroscopy). After 10 minutes, the carbonyl bands of dicobalt octacarbonyl had disappeared. They had been replaced by a broad carbonyl band at 1890 cm^{-1}. A band at 1775 cm^{-1} showed the presence of some diazetidinone. Another absorption at 1680 cm^{-1} indicated that N-butylcyclopentanimine had been formed. After 5 hours the band at 1890 cm^{-1} had almost disappeared and that at 1775 cm^{-1} was qualitatively of the same intensity while the absorption band at 1680 cm^{-1} increased. The reaction was stopped and the

solution was filtered through a small amount of aluminium oxide to remove most of the cobalt. Concentration of the filtrate on a rotary evaporator gave the crude product which was purified by alumina thin layer chromatography using 7,5: 2,5 pentane/ethyl ether as eluant. The 1,3-diazetidinone (52) was obtained in 11% yield. (Note: silica gel plates should not be used for purification as the product decomposes in such a case).

The yield (41%) of N-butylcyclopentanimine was determined by gas chromatography using decane as internal standard.

52:

IR (benzene): ν CO: 1775 cm^{-1}

^1H NMR ($CDCl_3$): δ 0,90 (t; 3H, CH_3C); 1,23-1,89 (m; 12H, $6CH_2$); 2,66 (S; 3H, NCH_3); 3,02 (t; 2H, NCH_2)

Mass spec.: m/e 196 [M]+; 139 [M-CH_3NCO]+; 97 [M-BuNCO]+

Elemental Analysis:	calculated	C 67,32	H 10,27	N 14,27
	found	67,00	10,41	14,59

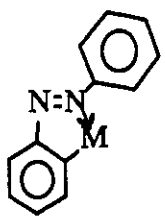
Chapter 3

Acylation of Diazenes

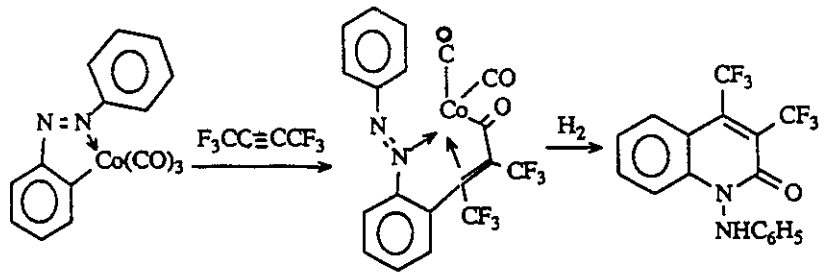
3.1 Introduction

In the presence of dicobalt octacarbonyl, under phase transfer catalysis, 1,3-dimethyl-2-p-toluoyl-3-phenyldiaziridine afforded an acylated diazene. It was of considerable interest to determine if diazenes themselves can be acylated under phase transfer catalysis.

A few transition metal induced reactions of azoarenes are known. They usually proceed via an o-metallated intermediate where the azo ligand is chelated to the metal via a nitrogen σ-donor bond and a metal-carbon σ-bond forming a five-membered ring (54)[91]. For example, both the dicobalt octacarbonyl and the palladium chloride - catalysed carbonylation of azobenzene are thought to proceed via an o-metallated intermediate; carbonyl insertion into the metal-carbon σ-bond leads to the 2-phenylindazolone[46].



N-Anilinoquinolone can be obtained by reaction of (azobenzene) $Co(CO)_3$ with hexafluorobut-2-yne followed by hydrogenation[92]:



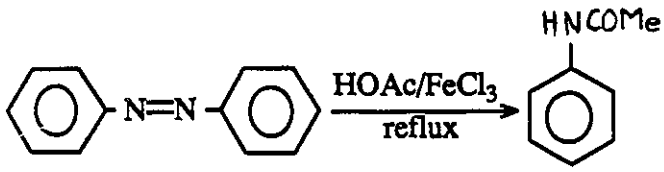
In the presence of palladium (II), azobenzene is selectively halogenated by chlorine and bromine ortho to the azo function, affording mono and polyhalogenated azobenzenes[93-94].

A wide variety of methods have been used to reduce azoarenes to hydrazoarenes[95].

$$ArN{=}NAr \longrightarrow \underset{H}{ArN}\text{-}\underset{H}{NAr}$$

For example, this conversion may be readily brought about by the use of lithium aluminium hydride in presence of certain metal halides (e.g. $MoCl_5$, $TiCl_4$, VCl_3, $FeCl_3$)[96]. Catalytic hydrogenation is also a useful means for the reduction of an azoarene. [$RhCl_3py_3$+$NaBH_4$] is a good catalyst source[97].

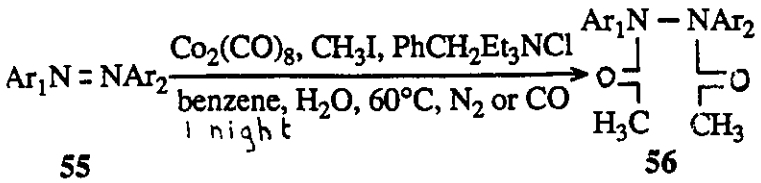
When a solution of azobenzene in acetic acid, containing ferric chloride, is refluxed for an extended period of time, acetanilide is obtained[98]:



The organotransition-metal induced conversion of azo compounds to carboxylic acid hydrazides and 2-acylhydrazides is not known, and therefore the mono and diacylation of azoarenes was investigated.

3.2 Results and Discussion

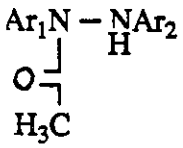
A variety of azo compounds were treated with dicobalt octacarbonyl and methyl iodide under phase transfer conditions. When benzyltriethylammonium chloride was used as the phase transfer agent, in the presence of two equivalents of $Co_2(CO)_8$, azoarenes (**55**) gave acetic acid 1,2-diaryl-2-acetylhydrazides (**56**) in fair to good yields.



55 **56**

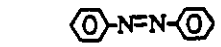
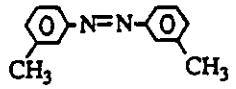
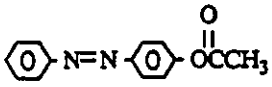
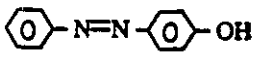
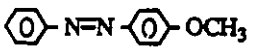
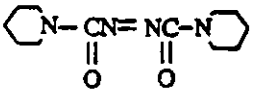
The results are listed in Table 4. Other metal catalysts, including $Ru_3(CO)_{12}$ and $[Rh(CO)_2Cl]_2$ were ineffective for this reaction.

The best yields (52-54%) were obtained with azobenzene, 4,4'-dimethylazobenzene, 3,3'-dimethylazobenzene and 4-acetoxyazobenzene while 4,4'-dichloroazobenzene was slightly less reactive (36% of **56**). For those five azoarenes the acylation was very selective while with azobenzene and 4-acetoxyazobenzene, 1% of the acetic acid 1,2-diarylhydrazide (**57**) was also isolated.



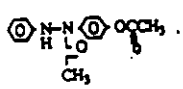
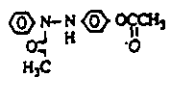
57

Table 4 Acylation of Azo Compounds (55) by $Co_2(CO)_8$ and Methyl Iodide Under Phase Transfer Catalysis[a].

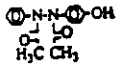
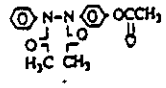
SUBSTRATE (55)	Recovered Substrate %[b]	Acetic Acid Hydrazide (57) %[b]	Acetic Acid 2-Acetylhydrazide (56) %[b]	Amide (58) %[b]
	16	1	54	0
	23	0	52	0
	28	0	52	0
	38	0	36	0
	28	1[c]	53	0
	14[d]	0	28[e]	17
	38	0	18	13
	20	0	14	32
	0	93	0	0

a) Reaction conditions: 1 atm N_2, 60°C, 1 night, benzene/H_2O (24 ml of each), substrate (2,0 mmol), $Co_2(CO)_8$ (4,0 mmol), CH_3I (62 mmol), $C_6H_5CH_2Et_3NCl$ (0,5 mmol)

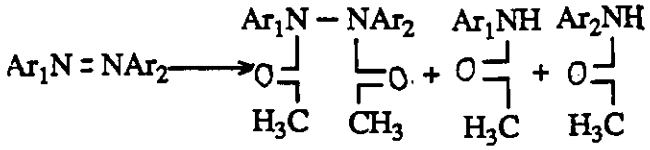
b) Isolated yields

c) 1:1 mixture of  and 

d) 23% of  were also isolated

e) 9% of  and 19% of 

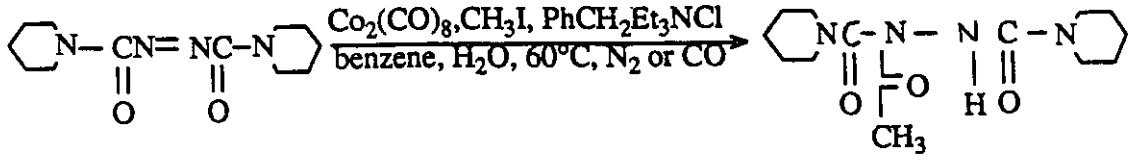
4-Hydroxyazobenzene, 4-methoxyazobenzene and 4,4'-dimethoxyazobenzene afforded the acetic acid 1,2-diaryl-2-acetylhydrazides in fair yields. However cleavage of the nitrogen-nitrogen bond also occurred, yielding amides (58):



58

4-Hydrozyazobenzene and 4-methoxyazobenzene were slightly more selective for the acetic acid 2-acetylhydrazide derivative affording 2-acetylhydrazide/amides in a ratio of 62/38 and of 58/42 respectively. 4,4'-Dimethoxyazobenzene principally underwent acylation with cleavage of the nitrogen-nitrogen bond $\left(\frac{\text{2-acetylhydrazide}}{\text{amides}} = \frac{30}{70}\right)$. Under the reaction conditions, acylation of the hydroxy group of 4-hydroxyazobenzene was also observed with 4-acetoxyazobenzene formed in 23% yield.

Surprisingly, 1,1'-(azodicarbonyl)dipiperidine was converted quantitatively into the acetic acid hydrazide:



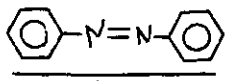
59 **60**

Interestingly, under the same reaction conditions, acetic acid 1,2-diphenylhydrazide (**57**, Ar_1=Ar_2=C_6H_5) afforded acetic acid 1,2-diphenyl-2-acetylhydrazide (**56**, Ar_1=Ar_2=C_6H_5) in quantitative yield. Also, acylation of hydrazobenzene (**61**, Ar_1=Ar_2=C_6H_5) gave 4% of **56** and 8% of **57** along with recovered hydrazobenzene.

61

Unfortunately, the acylation of azoarenes was not catalytic in $Co_2(CO)_8$ (see Table 5). A high proportion of dicobalt octacarbonyl (1:2 ratio of azobenzene to $Co_2(CO)_8$) was required in order to achieve a good conversion of azobenzene. This finding is not surprising since the previously reported acylation of an azadiene with dicobalt octacarbonyl, carbon monoxide and methyl iodide under phase transfer catalysis conditions is not catalytic either[37].

Table 5 Influence of the Quantity of $Co_2(CO)_8$ on the Acylation of Azobenzene Using Benzyltriethylammonium Chloride

 $Co_2(CO)_8$ (molar ratio)	Recovered Azobenzene (55) %[a]	Acetic Acid 1,2-Diphenyl-hydrazide (57) %[a]	Acetic Acid 1,2-Diphenyl-2-Acetylhydrazide (56) %[a]	Selectivity[b] in Acetic Acid 1,2-Diphenyl-2-Acetylhydrazide (56) %[a]
1/2 [c]	16	1	54	98
1/1 [c]	57	12	18	60
2/1 [d]	70	7	5	42

a) Isolated yields

b) $$\% \text{ Selectivity} = \frac{\% \text{ 2-acetylhydrazide} \times 100\%}{\% \text{ 2-acetylhydrazide} + \% \text{ hydrazide}}$$

c) reaction time : 1 night

d) reaction time : 2 days

Several reactions were tried, using azobenzene, in order to better understand the acylation reaction. Reactions run at temperatures lower than 60°C led to either very low yields of acetic acid 1,2-diphenyl-2-acetylhydrazide or there was no reaction (e.g. at room temperature) even after two days. At 60°C, the reaction was quite fast initially. Indeed, after four hours, 32% of acetic acid 1,2-diphenyl-2-acetylhydrazide and 5% of acetic acid 1,2-diphenylhydrazide were already formed. After 15 hours no more acylated products were produced but some hydrazobenzene was obtained (8% after two days). To check whether the reaction stopped because there was no methyl iodide left in the mixture, another quantity of CH_3I was added, but further acylation did not occur. When the reaction was carried out in the absence of methyl iodide, 15% of hydrazobenzene and 85% of azobenzene were obtained.

The acylation reaction is essentially inhibited by addition of an equimolar quantity of triphenylphosphine or tri-n-butylphosphine. For example, acetic acid 1,2-diphenyl-2-acetylhydrazide and acetic acid 1,2-diphenylhydrazide were obtained in yields of 5% each when tri-n-butylphosphine was used (90% recovered azobenzene). This inhibition by addition of a phosphine might be explained by the formation of $Co_2(CO)_7PR_3$ or $Co_2(CO)_6(PR_3)_2$ either of which would be less reactive than $Co_2(CO)_8$.

Only traces of acetic acid 1,2-diphenylhydrazide and of hydrazobenzene were obtained in the absence of benzyltriethylammonium chloride. This result shows the importance of the phase transfer catalyst in the acylation of diazenes. Methylene chloride can be used as the organic phase instead of benzene but the yield of acetic acid 1,2-diphenyl-2-acetylhydrazide (20%) decreases in favor of acetic acid

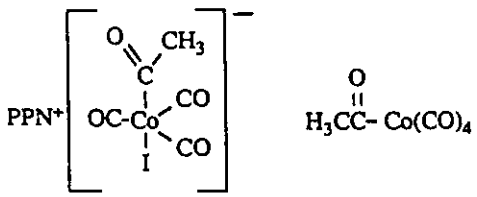
1,2-diphenylhydrazide (8%) and hydrazobenzene (24%), (29% of azobenzene is recovered). It is important to note that the isolated yield of hydrazobenzene is certainly a minimum one, and is true for all isolated yields reported for hydrazobenzene. Indeed it was observed that some hydrazobenzene is converted to azobenzene on silica gel.

Use of 0,5M sodium hydroxide solution as aqueous phase was not advantageous since it led to lower conversion. Furthermore, azobenzene did not react in the absence of an aqueous phase and phase transfer agent.

Similar results were obtained using an atmosphere of either nitrogen or carbon monoxide. However, the use of carbon monoxide/ hydrogen (3/1) afforded acetic acid 1,2-diphenylhydrazide (22%) as the major product together with acetic acid 1,2-diphenyl-2-acetylhydrazide (19%) and hydrazobenzene (7%) (with 22% recovered azobenzene).

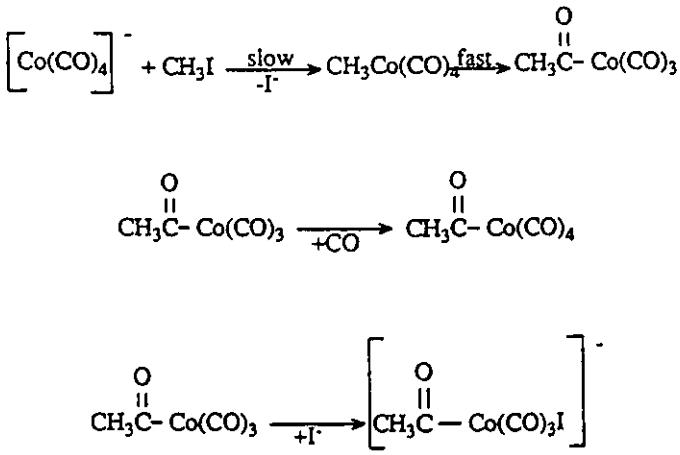
The acylation of diazenes under nitrogen occurred in modest yields using bis(triphenylphosphineiminium)tetracarbonylcobaltate (PPN^+ $Co(CO)_4^-$). Since this cobalt complex is insoluble in benzene, methylene chloride was used as the organic phase. Using a 1:1 ratio of PPN^+ $Co(CO)_4^-$ and azobenzene, at 60°C gave 7% of acetic acid 1,2-diphenyl-2-acetylhydrazide and 4% of acetic acid 1,2-diphenyl hydrazide (67% of azobenzene). Similar results were obtained when the reaction was repeated at lower temperatures (5°, 10°, or 35°C). In these reactions it is essential that azobenzene be added prior to methyl iodide as only traces of **56** and **57** (Ar_1=Ar_2=C_6H_5) were formed otherwise. This suggests that the species formed by reaction of methyl iodide with $PPN^+Co(CO)_4^-$ is quite unstable. To verify this point, $PPN^+Co(CO)_4^-$ was dissolved in degassed methylene chloride and methyl iodide was added under a carbon

monoxide atmosphere at 55°C. An infrared spectrum recorded after 2 minutes did not show a carbonyl band at 1885 cm^{-1} characteristic of $PPN^{+}Co(CO)_4^{-}$. Instead, there were carbonyl bands at 2110 cm^{-1} (W), 2050-2010 cm^{-1}(S), 1955 cm^{-1} (M), 1938 cm^{-1}(M) and acyl bands at 1710 cm^{-1}(M) and 1655 cm^{-1}(W). No carbonyl bands were present in an infrared spectrum taken after 45 minutes. Note that a precipitate of $PPN^{+}I^{-}$ was formed in the reaction mixture. The carbonyl frequencies of the species formed initially is in accord with a mixture of two cobalt complexes (**62** and **63**):

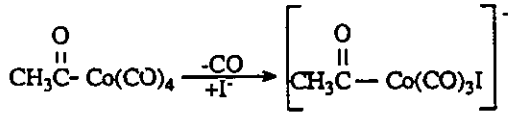


62 63

Indeed, at the same time this experiment was done, Röper, Schieren and Heaton[99] reported that $PPN^{+}Co(CO)_4^{-}$ reacts with methyl iodide in methylene chloride, at 0°C and under argon, to yield **62** and **63**:

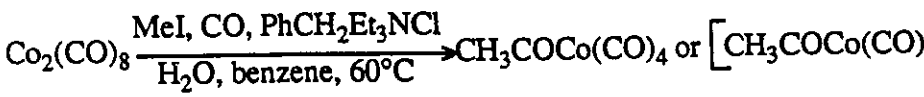


An infrared spectrum of **62**, in tetrahydrofuran, shows carbonyl bands at 2029 cm^{-1}(W), 1953 cm^{-1}(VS), 1933 cm^{-1}(VS) and 1657 cm^{-1}(S) while those of **63** occur at 2110 cm^{-1}(W), 2055 cm^{-1}(VS), 2022 cm^{-1}(VS) and 1712(S). Röper, Schieren and Heaton also observed that the ratio of the two complexes formed depends on the counterion of $Co(CO)_4^-$ and on the solvent. With PPN+ in THF or in acetonitrile only **62** is obtained while use of $K[Co(CO)_4]$ in THF leads exclusively to **63**. It was also found[99] that **62** tends to decompose with separation of PPN^+I^- even at temperatures below 0°C. Since the carbonyl bands of **63** had, after 45 minutes, also disappeared from our reaction, it is reasonable to assume that this complex is not very stable either, even under an atmosphere of carbon monoxide. It is also possible that a small amount of **63** is constantly being converted to **62** which then decomposes:



Those results account for the low yields of acylated products and for the necessity of adding azobenzene before methyl iodide.

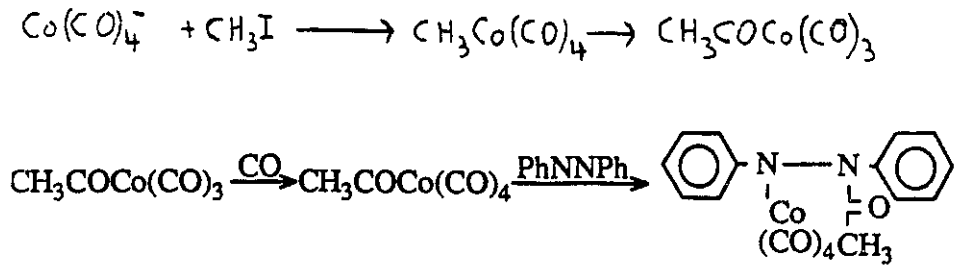
Since $CH_3COCo(CO)_4$ and/or $[CH_3COCo(CO)_3I]^-$ also induced the acylation of diazenes, it seemed conceivable that dicobalt octacarbonyl might be converted into such species under the following reaction conditions:



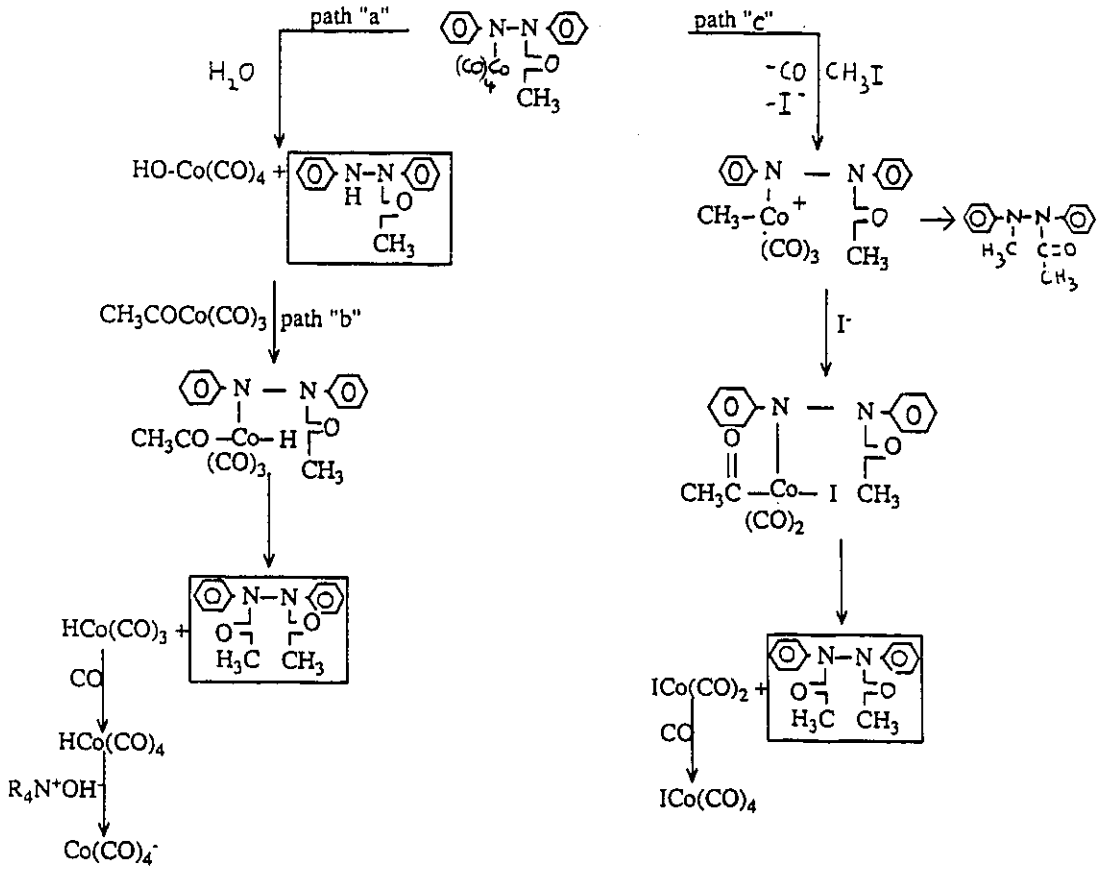
To verify this point, an infrared spectrum was taken 30 minutes after the addition of CH_3I to $Co_2(CO)_8$ in the absence of azobenzene. The presence of carbonyl bands at 2110 cm^{-1}(W), 2050 cm^{-1}(S), 2020 cm^{-1}(S) and 1710 cm^{-1}(M) confirmed the formation of $CH_3COCo(CO)_4$. No bands were present which could be attributed to $Co_2(CO)_8$ or to $[CH_3COCo(CO)_3I]^-$. Perhaps the anion was formed but destroyed in less than 30 minutes. It is also conceivable that, in benzene and with $PhCH_2Et_3N^+$ as counterion, this anion is obtained in very small quantity or not formed at all.

A possible mechanism for the formation of the acylated products is outlined in Scheme 3.1. Path "a" would lead to acetic acid 1,2-diphenylhydrazide. Acetic acid 1,2-diphenyl-2-acetylhydrazide might be formed according to path "b". Path "c" is less probable since it should also have resulted in methylation at nitrogen. The tetracarbonylcobaltate anion is obtained under the phase transfer catalysis conditions.

Scheme 3.1



64

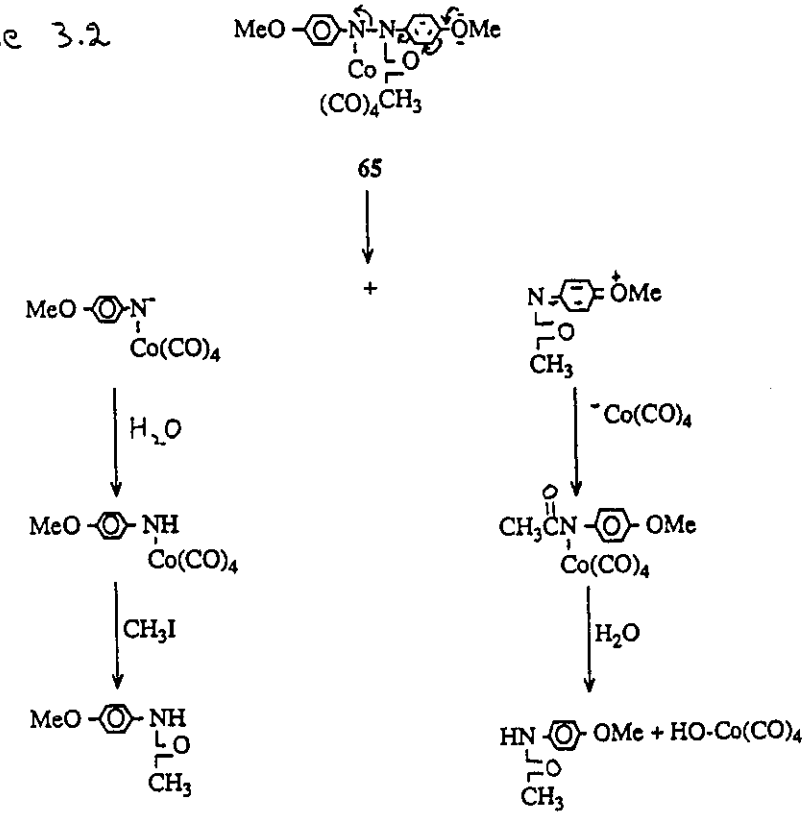


How can one explain the greater selectivity for acetic acid 1,2-diphenyl-2-acetylhydrazide when more $Co_2(CO)_8$ is present? This may be because the acetic acid 1,2-diphenylhydrazide formed has the opportunity to react further with more $CH_3COCo(CO)_3$ or $CH_3COCo(CO)_4$. The results indicate that acetic acid 1,2-diphenylhydrazide is quite reactive since it is converted to acetic acid 1,2-diphenyl-2-acetylhydrazide before the complete conversion of azobenzene. The presence of an acyl group on the neighbouring nitrogen atom seems to activate the N-H of acetic acid 1,2-diphenylhydrazide. Indeed, hydrazobenzene is considerably less reactive than acetic acid 1,2-diphenylhydrazide.

As noted earlier, 1,1'-(azodicarbonyl)dipiperidine afforded only the acetic acid hydrazide derivative in quantitative yield. This conversion probably proceeds according to the same mechanism as described for acetic acid 1,2-diphenylhydrazide.

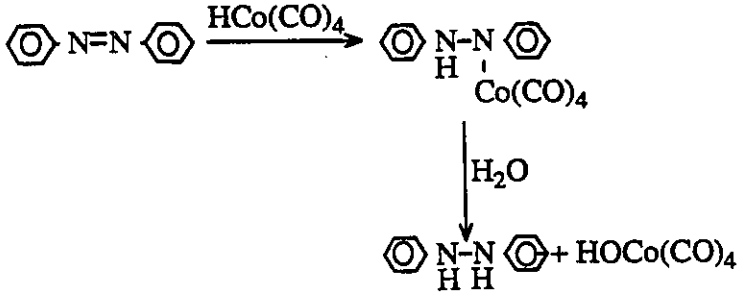
4-Hydroxyazobenzene, 4-methoxyazobenzene and 4,4'-dimethoxyazobenzene afforded amides in addition to the acetic acid 1,2-diaryl-2-acetylhydrazide. This particular behaviour may be due to the presence of an oxygen atom at the 4 position of the arene ring of the azo compound. Cleavage of the nitrogen-nitrogen bond of a reaction intermediate such as **65** may then occur owing to its lone pairs of electrons (illustrated in Scheme 3.2 for 4,4'-dimethoxyazobenzene).

Scheme 3.2



The formation of some hydrazobenzene when the azoarene/$Co_2(CO)_8$ reaction is run in the absence of CH_3I can be rationalized as follows: under neutral phase transfer catalysis conditions, there may be some $HCo(CO)_4$ present which would add to the nitrogen-nitrogen double bond. Cleavage of the cobalt-nitrogen bond by water would then afford the hydrazobenzene (Scheme 3.3).

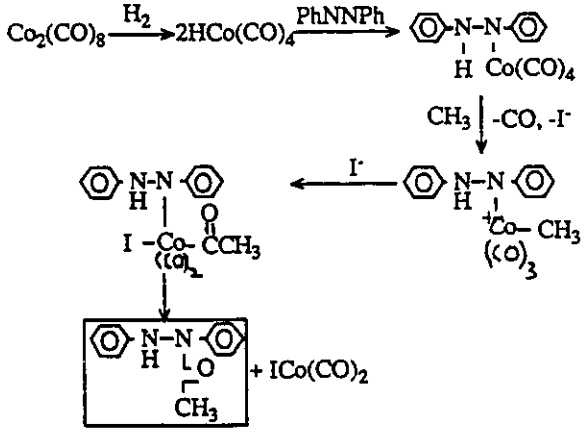
Scheme 3.3



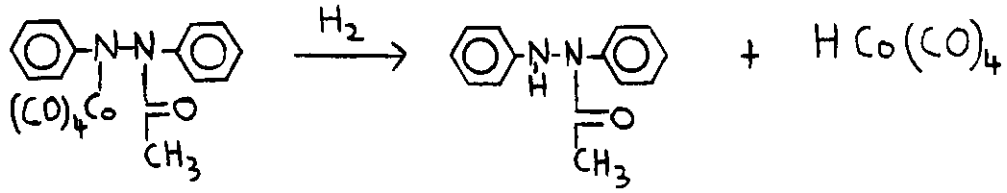
The formation of hydrazobenzene is quite appreciable when methylene chloride is used as the organic phase. However in benzene scheme 3.1 is preferred.

It was shown that the formation of acetic acid 1,2-diphenyl-2-acetylhydrazide is inhibited when hydrogen is present in the reaction involving CH_3I. In such a case, $Co_2(CO)_8$ would be converted principally to $HCo(CO)_4$. The latter may, with CH_3I, ultimately lead to acetic acid 1,2-diphenylhydrazide (Scheme 3.4).

Scheme 3.4



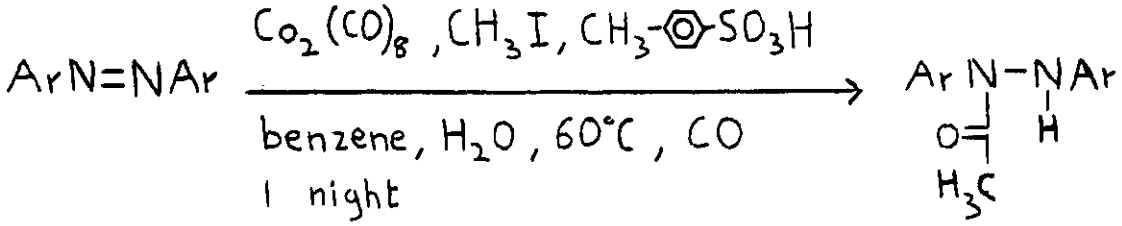
It is also possible that complex 64 (Scheme 3.1) is formed. Cleavage of the nitrogen-cobalt bond would occur affording acetic acid 1,2-diphenylhydrazide:



64

Having found a process to convert azoarenes into acetic acid 1,2-diaryl-2-acetylhydrazides, an investigation was made to develop another method which would lead selectively to acetic acid 1,2-diarylhydrazides. The best results were obtained under acidic phase transfer catalysis.

The azoarenes were converted in fair to good yields into acetic acid 1,2-diarylhydrazides using p-toluenesulfonic acid and a stoichiometric quantity of dicobalt octacarbonyl.

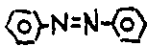
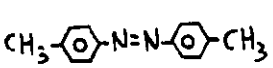
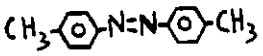
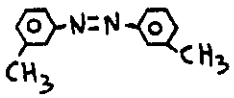
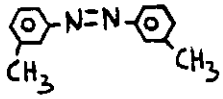
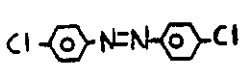
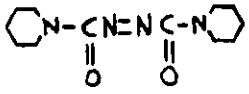


The yields obtained for different diazenes are summarized in Table 6. Using 0,02 equivalent of p-toluenesulfonic acid, the acylation of azobenzene and of 1,1'-(azodicarbonyl)dipiperidine was highly selective affording 48% and 80% of the acetic acid hydrazide derivative, respectively. A good result was also obtained with 4,4'-dichloroazobenzene although some hydrazo compound was isolated as a by-product. However, with 3,3'-and 4,4'-dimethylazobenzene it was necessary to use more p-toluenesulfonic acid (0,06-0,10 equivalent) in order to achieve good selectivity. Otherwise the acetic acid 1,2-diaryl-2-acetylhydrazide and, surprisingly, amides were also obtained to some extent.

The high selectivity for reductive monoacylation may be due to the fact that under acidic conditions $HCo(CO)_4$ should be the major cobalt species present and the latter would give the acetic acid hydrazide compound (scheme 3.4). Several reactions, using azobenzene, were conducted under modified conditions to define the best reaction conditions. At lower temperatures little or no acetic acid 1,2-diphenylhydrazide was formed. Replacement of carbon monoxide by carbon monoxide/hydrogen (1/1) afforded hydrazobenzene as the major product while use of a stoichiometric amount of p-toluenesulfonic acid led to low conversion and less selectivity, with more hydrazobenzene being obtained.

An increase in the quantity of $Co_2(CO)_8$ resulted in decrease in selectivity. For example use of a 2:1 ratio of $Co_2(CO)_8$ to azobenzene led to 29% of acetic acid 1,2-diphenylhydrazide and 14% of acetic acid 1,2-diphenyl-2-acetylhydrazide. No reaction occurred when methanol was used as solvent instead of water and benzene.

Table 6 Acylation of Azo Compounds (55) Using p-Toluenesulfonic Acid and $Co_2(CO)_8$[a].

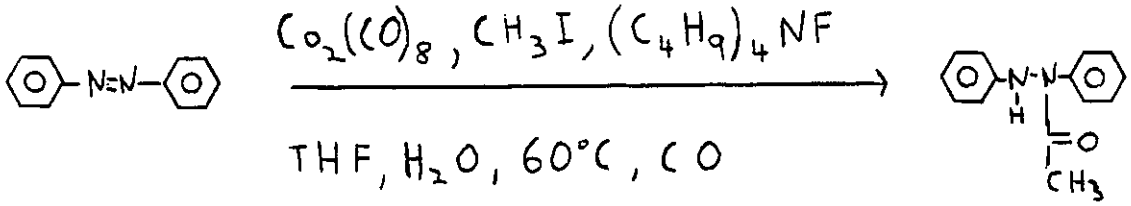
SUBSTRATE (55)	Acid Equivalent	Recovered Substrate (55) %[b]	Acetic Acid Hydrazide Derivative (57) %[b]	Acetic Acid 2-Acetylhydrazide Derivative (56) %[b]	Hydrazine Derivative (61) %[b]	Amide (58) %[b]
	0,02	39	48	0	traces	0
	0,02	54	13	11	traces	11
	0,06	50	29	6	traces	5
	0,02	41	14	4	18	4
	0,10	48	28	0	5	0
	0,02	39	37	0	8	0
	0,02	0	80	0	0	0

a) reaction conditions: 1 atm CO, 60°C, benzene/H_2O (24 ml of each), substrate (2 mmol), $Co_2(CO)_8$ (2 mmol), CH_3I (62 mmol)

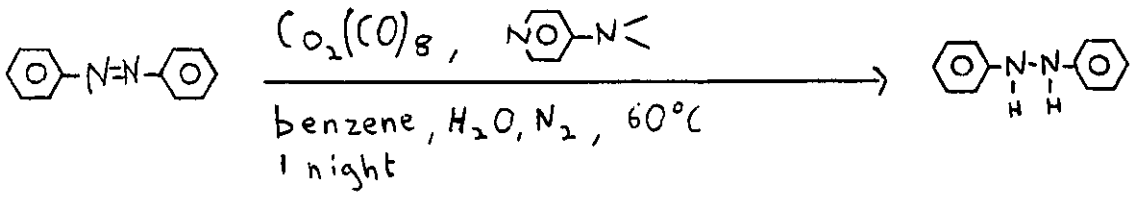
b) Isolated yields

When the acylation was conducted in the presence of sodium dodecylbenzenesulfonate (0,1 equivalent) instead of p-toluenesulfonic acid, 28% of acetic acid 1,2-diphenylhydrazide and 11% of acetic acid 1,2-diphenyl-2-acetylhydrazide were obtained along with 47% of azobenzene. When p-toluenesulfonic acid was replaced by the same quantity of HBF_4, only 21% of acetic acid 1,2-diphenylhydrazide was isolated. Hydrazobenzene (24%) was the major product. If 20% HBF_4 is employed as the aqueous phase instead of a catalytic amount of the acid, then acetic acid 1,2-diphenylhydrazide was not obtained. Rather, benzidine was isolated in 46% yield. This product probably arises from rearrangement of the in situ generated hydrazobenzene. Indeed, under acid conditions, hydrazobenzene is known to afford benzidine. This acid-induced rearrangement is usually performed in ethanol or dioxane solution on the addition of aqueous HCl or H_2SO_4[100].

During these investigations it was also found that good selectivity for acetic acid 1,2-diphenylhydrazide results when azobenzene is exposed to carbon monoxide and an equimolar quantity of $Co_2(CO)_8$ and tetrabutylammonium fluoride in tetrahydrofuran and water. At 60°C, 29% of acetic acid 1,2-diphenylhydrazide, 3% of acetic acid 1,2-diphenyl-2-acetylhydrazide and 41% of recovered azobenzene were obtained.



Furthermore, azobenzene is quantitatively converted to hydrazobenzene using a 1:1 ratio of 4-dimethylaminopyridine and $Co_2(CO)_8$. This is true even in the presence of methyl iodide.



By infrared spectroscopy it was shown that, before adding azobenzene, $Co_2(CO)_8$ is converted to a new complex with carbonyl bands at 1895 cm^{-1}(S), 1930 cm^{-1}(M) and 2030 cm^{-1}(M). It is probably an adduct of $HCo(CO)_4$ with 4-dimethylaminopyridine. Indeed it is known[101] that triethylamine gives an adduct with $HCo(CO)_4$. This adduct contains a Co-H-N bond; its infrared spectrum in the ν(C=O) region is similar to the one of our complex [IR (toluene): 2015 cm^{-1}(W), 1932 cm^{-1}(S), 1895 cm^{-1}(VS)].

In conclusion, depending on the reaction conditions, dicobalt octacarbonyl is able to convert azoarenes to predominantly acetic acid 1,2-diaryl-2-acetylhydrazides, acetic acid 1,2-diarylhydrazides, or hydrazoarenes.

3.3 Experimental Data

3.3.1 General Comments

The general comments described in chapter 2 also apply here.

Azobenzene, 4-hydroxyazobenzene and 1,1'-(azodicarbonyl)dipiperidine were purchased from Aldrich.

3.3.2 Synthesis of Azo Compounds

Some of the azo compounds used were not commercially available and had to be synthesized according to literature procedures.

Synthesis of $RC_6H_4N{=}NC_6H_4R$ (R=p-Cl, p-MeO, p-Me, m-Me)

A literature procedure[102] was used to prepare $RC_6H_4N{=}NC_6H_4R$ (R=p-Cl, p-MeO, p-Me, m-Me), by reaction of $RC_6H_4NO_2$ with half the molar amount of $Co_2(CO)_8$ in refluxing benzene for 5 hours (N_2 atmosphere). Recrystallization from hexane afforded the products in 40-49% yields.

Synthesis of $C_6H_5N{=}NC_6H_4O_2CCH_3$-p

4-Phenylazophenol was reacted with acetylchloride in the presence of pyridine, according to the procedure[78] described in chapter 2 for the protection of 1,3-dimethyl-3-phenyldiaziridine with p-toluoylchloride.

The crude product was crystallized by dissolving it in the minimum amount of hot ether and adding a small quantity of hexane and storing overnight at 3°C. Yield of azo compound = 93%.

^{1}H NMR ($CDCl_3$): δ 2,26 (S; 3H, CH_3); 7,09-8,06 (m; 9H, aromatic protons).

Synthesis of $C_6H_5N{=}NC_6H_4OCH_3$-p[103]

A mixture of CH_2Cl_2 (50 ml), water (50 ml), $C_6H_5N{=}NC_6H_4OH$ (10 mmol), NaOH (15 mmol), CH_3I (25 mmol) and benzyltriethylammonium chloride (10 mmol) was stirred at room temperature for 15 hours. The layers were separated and the aqueous layer was extracted three times with 50 ml portions of methylene chloride. The combined organic extracts were concentrated by rotary evaporation. Recrystallisation from ether / pentane afforded the pure product in 90% yield.

^{1}H NMR ($CDCl_3$): δ 3,77 (S; 3H, OCH_3); 6,74-7,94 (m; 9H, aromatic protons)

3.3.3 Synthesis of PPN^+ $Co(CO)_4^-$

PPN^+ $Co(CO)_4^-$ was synthesized according to the method of Gladysz[104]. Recrystallisation from methylene chloride / ether gave $PPN^+Co(CO)_4^-$ in 85% yield.

IR (CH_2Cl_2): ν CO: 1885 cm^{-1}

3.3.4 General Procedure for the Acylation of Azo Compounds Under Phase Transfer Catalysis Conditions Using Benzyltriethylammonium Chloride and $Co_2(CO)_8$

Distilled water (24 ml) and benzene (24 ml) were placed in a 100 ml three-necked round bottomed flask. The mixture was stirred at 60°C and degassed by bubbling nitrogen through the solution for 30 minutes. $Co_2(CO)_8$ (1,36g; 4,0 mmol) was added followed, at 5 minutes intervals, by addition of $C_6H_5CH_2Et_3NCl$ (0,114g; 0,50 mmol), CH_3I (3,0 ml; 62 mmol) and the azo compound (2,0 mmol). The mixture was stirred overnight at 60°C (N_2 atmosphere). At the end of the reaction, the organic phase was orange while the aqueous layer was pink and slightly acid.

The two layers were separated and the aqueous phase was extracted with 24 ml of $CHCl_3$. The combined organic phases were dried over $MgSO_4$ and concentrated by rotary evaporation. The crude products were purified by silica gel chromatography (plates or column) using an appropriate mixture of hexane/ethyl acetate. For the tlc plates, 7:3 or 5:5 mixtures of hexane/ethyl acetate were used as the eluant. For the column a 9,5:0,5 mixture of hexane/ethyl acetate was initially used; when all the azobenzene was recovered the quantity of ethyl acetate was gradually increased. The products were recrystallized from ether when necessary.

3.3.4.1 Acylation of Azobenzene

Acylation of azobenzene afforded:

a) **56** (Ar_1=Ar_2=C_6H_5) in 54% yield.

m.p.= 106-107°C (lit m.p. = 105°C)[105]

IR ($CHCl_3$): ν CO 1700 cm^{-1} and 1677 cm^{-1}

^1H NHR ($CDCl_3$): δ 1,96 (S; 6H, $2CH_3$), 7,29 (S; 10H, aromatic protons)

^{13}C NMR ($CDCl_3$): δ 22,32 ($2CH_3$); 128,17; 128,88; 129,48; 141,27 aromatic carbons; 168,32 (2O=C-N)

Mass spec.: m/e 268 [M]+; 226 [M-CH_2CO]+; 183 [M-CH_2CO-CH_3CO]+; 77 [C_6H_5]+; 43[CH_3CO]+

Elemental analysis: calculated C 71,62 H 6,01 N 10,44

found 71,63 5,76 10,40

b) **57** (Ar_1=Ar_2=C_6H_5) in 1% yield

IR ($CHCl_3$): ν CO: 1673 cm^{-1}

'H NMR ($CDCl_3$): δ 2,22 (S; 3H, CH_3); 6,55-7,69 (m; 11H, aromatic protons + NH)

Mass spec.: m/e 226 [M]+; 183 [M-CH_3CO]+; 77 [C_6H_5]+; 43[CH_3CO]+.

c) **55** (Ar_1=Ar_2=C_6H_5) was recovered in 16% yield

3.3.4.2 Acylation of 4,4'-Dimethylazobenzene

Acylation of 4,4'-dimethylazobenzene gave:

a) **56** (Ar_1= Ar_2= p-$CH_3C_6H_4$) in 52% yield.

m.p. = 126-128°C

IR ($CHCl_3$): ν CO: 1695 cm^{-1} and 1673 cm^{-1}

'H NMR ($CDCl_3$): δ 1,92 (S; 6H, $2CH_3CO$); 2,32 (S; 6H, $2\underline{CH_3}C_6H_4$); 7,09 (broad S; 8H, aromatic protons).

Mass spec.: m/e 296 [M]+; 254 [M-CH_2CO]+; 211 [M-CH_2CO-CH_3CO]+; 91 [$CH_3C_6H_4$]+; 43 [CH_3CO]+

Elemental analysis : calculated C 73,45 H 6,16 N 9,52

found 73,24 6,52 9,61

b) 55 (Ar_1= Ar_2= p-$CH_3C_6H_4$) was recovered in 23% yield.

3.3.4.3 Acylation of 3,3'-Dimethylazobenzene

Acylation of 3,3'-dimethylazobenzene gave:

a) 56 (Ar_1= Ar_2= m-$CH_3C_6H_4$) in 52% yield.

m.p. = 110-111°C

IR ($CHCl_3$): ν CO: 1697 cm^{-1} and 1673 cm^{-1}

'H NMR ($CDCl_3$): δ 1,93 (S; 6H, $2CH_3CO$), 2,29 (S; 6H, $2\underline{CH_3}C_6H_4$); 6,83-7,33 (m; 8H, aromatic protons).

Mass spec.: m/e 296 [M]+; 254 [M-CH_2CO]+; 211 [M-CH_2CO-CH_3CO]+; 91 [$CH_3C_6H_4$]+; 43 [CH_3CO]+

Elemental analysis : calculated C 72,95 H 6,80 N 9,45

found 73,13 7,38 9,71

b) 55 (Ar_1= Ar_2= m-$CH_3C_6H_4$) was recovered in 28% yield.

3.3.4.4 Acylation of 4,4'-Dichloroazobenzene

Acylation of 4,4'-dichloroazobenzene afforded:

a) 56 (Ar_1= Ar_2= p-ClC_6H_4) in 36% yield.

m.p. = 119-121°C

IR ($CHCl_3$): ν CO: 1700 cm^{-1} and 1672 cm^{-1}

'H NMR ($CDCl_3$): δ 1,93 (S; 6H, $2CH_3$), 7,20 (broad S; 8H, aromatic protons).

Mass spec.: m/e 336 [M]+; 294 [M-CH_2CO]+; 251 [M-CH_2CO-CH_3CO]+; 111 [ClC_6H_4]+; 43 [CH_3CO]+

b) 55 (Ar_1= Ar_2= p-ClC_6H_4) was recovered in 38% yield.

3.3.4.5 Acylation of 4-Acetoxyazobenzene

Acylation of 4-Acetoxyazobenzene gave:

a) 56 (Ar_1= C_6H_5; Ar_2= p-$CH_3CO_2C_6H_4$) in 53% yield.

IR ($CHCl_3$): ν CO: 1755 cm^{-1} (O=C-O); 1700 cm^{-1} and 1675 cm^{-1} (O=C-N)

'H NMR ($CDCl_3$): δ 1,93 (S; 6H, $2CH_3CON$); 2,26 (S; 3H, CH_3CO_2); 6,93-7,46 (m; 9H, aromatic protons)

Mass spec.: m/e 326 [M]+; 284 [M-CH_2CO]+; 241 [M-CH_2CO-CH_3CO]+; 135 [$CH_3CO_2C_6H_4$]+; 77 [C_6H_5]+; 43 [CH_3CO]+

b) 57 (Ar_1=C_6H_5; Ar_2 = p-$CH_3CO_2C_6H_4$) and 57 (Ar_1= p-$CH_3CO_2C_6H_4$; Ar_2= C_6H_5) in 1% yield (1:1 mixture)

IR ($CHCl_3$): ν CO: 1755 cm^{-1} (O=C-O); 1675 cm^{-1} (O=C-N)

'H NMR ($CDCl_3$): δ 2,18 (S; 3H, CH_3CON), 2,22 (S; 3H, CH_3CON); 2,24 (S; 6H, $2CH_3CO_2$); 6,68-7,52 (m; 20H, aromatic and amino protons)

Mass spec.: m/e 284 [M]+; 241 [M-CH_3CO]+; 135 [$CH_3CO_2C_6H_4$]+; 77 [C_6H_5]+; 43 [CH_3CO]+

c) 55 (Ar_1=C_6H_5; Ar_2= p-$CH_3CO_2C_6H_4$) was recovered in 28% yield.

3.3.4.6 Acylation of 4-Hydroxyazobenzene

Acylation of 4-hydroxyazobenzene afforded:

a) 56 (Ar_1= C_6H_5; Ar_2= p-HOC_6H_4) in 9% yield.

IR ($CHCl_3$): ν CO: 1694 cm^{-1} and 1670 cm^{-1}

'H NMR ($CDCl_3$): δ 1,93 (S; 6H, $2CH_3$), 6,60-7,38 (m; 10H, aromatic and hydroxyl protons)

Mass spec.: m/e 284 [M]+; 242 [M-CH_2CO]+; 199 [M-CH_2CO-CH_3CO]+; 93 [HOC_6H_4]+; 77 [C_6H_5]+; 43 [CH_3CO]+

b) **56** (Ar_1= C_6H_5; Ar_2= p-$CH_3CO_2C_6H_4$) in 19% yield.

c) **58** (Ar_1= C_6H_5) and **58** (Ar_2= p-HOC_6H_4) in 17% yield.

Mass spec.: m/e 135 [M]+ and 151 [M]+

d) **55** (Ar_1= C_6H_5; Ar_2= p-$CH_3CO_2C_6H_4$) in 23% yield.

e) **55** (Ar_1= C_6H_5; Ar_2= p-HOC_6H_4) was recovered in 14% yield.

3.3.4.7 Acylation of 4-Methoxyazobenzene

Acylation of 4-methoxyazobenzene afforded:

a) **56** (Ar_1= C_6H_5; Ar_2= p-$CH_3OC_6H_4$) in 18% yield.

IR ($CHCl_3$): ν CO: 1695 cm^{-1} and 1675 cm^{-1}

'H NMR ($CDCl_3$): δ 1,90 (S; 6H, $2CH_3CO$); 3,73 (S; 3H, CH_3O); 6,56-7,27 (m; 9H, aromatic protons)

Mass spec.: m/e 298 [M]+; 256 [M-CH_2CO]+; 213 [M-CH_2CO-CH_3CO]+; 107 [$MeOC_6H_4$]+; 77 [C_6H_5]+; 43 [CH_3CO]+

b) **58** (Ar_1= C_6H_5) in 13% yield.

c) **58** (Ar_2= p-$CH_3OC_6H_4$) in 13% yield.

IR ($CHCl_3$): ν CO: 1680 cm^{-1}

'H NMR ($CDCl_3$): δ 2,10 (S; 3H, CH_3CO); 3,53 (S; 3H, OCH_3); 6,36-7,30 (m; 5H, aromatic and amino protons)

Mass spec.: m/e 165 [M]+; 123 [M-CH_2CO]+; 43 [CH_3CO]+

d) **55** (Ar_1= C_6H_5; Ar_2= p-$CH_3OC_6H_4$) was recovered in 38% yield.

3.3.4.8 Acylation of 4,4'-Dimethoxyazobenzene

Acylation of 4,4'-dimethoxyazobenzene afforded:

a) **56** (Ar_1= Ar_2= p-$CH_3OC_6H_4$) in 14% yield.

IR ($CHCl_3$): ν CO: 1694 cm^{-1} and 1673 cm^{-1}

'H NMR ($CDCl_3$): δ 1,88 (S; 6H, $2CH_3CO$); 3,70 (S; 6H, $2CH_3O$); 6,63-6,90 (m; 8H, aromatic protons)

b) **58** (Ar= p-$CH_3OC_6H_4$) in 32% yield.

c) **55** (Ar_1= Ar_2= p-$CH_3OC_6H_4$) was recovered in 20% yield.

3.3.4.9 Acylation of 1,1'-(Azodicarbonyl)dipiperidine

Acylation of 1,1'-(azodicarbonyl)dipiperidine afforded 93% of **60**.

m.p.= 153-154°C

IR ($CHCl_3$): ν CO: 1680 cm^{-1} (3 N-C=O)

'H NMR ($CDCl_3$): δ 1,36-1,83 (m; 12H, 2 $C(CH_2)_3C$); 2,09 (S; 3H, CH_3CO); 3,13-3,69 (m; 8H, $2CH_2$ NCH_2); 8,33 (S; 1H, NH)

Mass spec.: m/e 296 [M]+; 254 [M-CH_2CO]+; 112 [$C_5H_{10}NCO$]+

Elemental Analysis:		C	H	N
	calculated	56,71	8,17	18,91
	found	56,93	8,10	18,65

3.3.5 Variation in Reaction Conditions

3.3.5.1 Addition of More CH_3I After One Night

A reaction was done using azobenzene as described in the general procedure. However, after 1 night, an additional 3,0 ml of CH_3I was added and the reaction mixture was stirred for 24 more hours. The results were similar to those without the added portion of CH_3I.

3.3.5.2 Variation in the Aqueous Phase

A reaction was done using 0,5M NaOH as aqueous phase. After one night 30% of acetic acid 1,2-diphenyl-2-acetylhydrazide was obtained along with 45% of recovered azobenzene.

3.3.6 Reaction of $PPN^+ Co(CO)_4^-$ with MeI

Methyl iodide (3,0 ml; 62 mmol) was added to a methylene chloride solution (25 ml) containing 2,0 mmol of $PPN^+Co(CO)_4^-$ (CO atm; 55°C). The color of the solution turned immediately from blue to brown. After 2 minutes an infrared spectrum was taken and showed no carbonyl band at 1885 cm^{-1}. All the $PPN^+Co(CO)_4^-$ was converted to other cobalt species with ν(CO) at 2110 cm^{-1}(W), 2050 cm^{-1}-2010 cm^{-1}(S), 1955 cm^{-1}(M), 1938 cm^{-1}(M) and ν(acyl) at 1710 cm^{-1}(M) and 1655 cm^{-1}(W). After 45 minutes, a second infrared spectrum was done, and showed that no more carbonyl bands were present. A precipitate was formed. Its infrared spectrum (KBr pellet), similar to the one of PPN^+Cl^-, showed that it was PPN^+I^-.

IR of PPN^+Cl^-: ν 504,42 cm^{-1}; 535,28 cm^{-1}; 550,72 cm^{-1}; 682,49 cm^{-1}; 723,36 cm^{-1}; 996,30 cm^{-1}; 1114,0 cm^{-1}; 1232,6 cm^{-1}; 1431,3 cm^{-1}.

IR of PPN^+I^-: ν 486,70 cm^{-1}; 535, 28 cm^{-1}; 549,75 cm^{-1}; 692,49 cm^{-1}; 724,32 cm^{-1}; 996,30 cm^{-1}; 1114,0 cm^{-1}; 1265,4 cm^{-1}; 1437,1 cm^{-1}.

3.3.7 Acylation of Azobenzene Using $(C_4H_9)_4NF$ and $Co_2(CO)_8$

To $Co_2(CO)_8$ (0,68g; 2,0 mmol) dissolved in degassed THF (30 ml) and water (0,1 ml), was added $(C_4H_9)_4NF$ (2,0 ml of 1M solution in THF; 2,0 mmol) at 60°C under CO. After 8 minutes, CH_3I (1,0 ml; 21 mmol) was added followed 2 minutes later by azobenzene (0,36g; 2,0 mmol). The reaction mixture was stirred overnight, and the THF was removed by rotary evaporation. Methylene chloride (25 ml) was added to the residue, and then it was treated first with 1M NaOH and then with water. The organic phase was dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude product was purified by column chromatography using silica gel with hexane/ethyl acetate as the eluant: 29% of acetic acid 1,2-diphenylhydrazide, 3% of acetic acid 1,2-diphenyl-2-acetylhydrazide and 41% of azobenzene were obtained. The conversion of azobenzene was lower (22%) in the absence of water.

3.3.8 General Procedure for the Acylation of Azoarenes Using p-Toluenesulfonic Acid and $Co_2(CO)_8$

Distilled water (24 ml), benzene (24 ml) and p-toluenesulfonic acid (0,04-0,20 mmol) were placed in a 100 ml three-necked round bottomed flask. The mixture was stirred at 60°C and degassed (nitrogen). The gas was changed to carbon monoxide, $Co_2(CO)_8$ (0,68g; 2 mmol) and CH_3I (3,0 ml; 62 mmol) were added, and after 30 minutes the azo compound (2 mmol) was added to the solution. The reaction mixture was stirred overnight at 60°C under carbon monoxide. The benzene phase became orange-brown, the aqueous phase was pink and a green precipitate was

present. The precipitate was removed by filtration and the two layers were separated. The aqueous phase was neutralized and extracted with 24 ml of $CHCl_3$. The combined organic phases were dried over $MgSO_4$, concentrated by rotary evaporation and the crude products were purified by silica gel chromatography using an appropriate mixture of hexane/ethyl acetate (7:3 or 5:5) as the eluant.

3.3.8.1 Acylation of Azobenzene

Acylation of azobenzene using 0,02 equivalent of p-toluenesulfonic acid afforded:

a) **57** (Ar_1= Ar_2= C_6H_5) in 48% yield.

b) traces of **61** (Ar_1= Ar_2= C_6H_5)

Mass spec.: m/e 184 [M]+

^{1}H NMR ($CDCl_3$): δ 5,50 (S; 2H, 2NH); 6,56-7,39 (m; 10H, aromatic protons)

c) **55** (Ar_1= Ar_2= C_6H_5) was recovered in 39% yield.

3.3.8.2 Acylation of 4,4'-Dimethylazobenzene

Acylation of 4,4'-dimethylazobenzene using 0,02 equivalent of p-toluenesulfonic acid afforded:

a) **57** (Ar_1= Ar_2= p-$CH_3C_6H_4$) in 13% yield

m.p.= 141-142°C

IR ($CHCl_3$): ν CO: 1672 cm^{-1}

^{1}H NHR ($CDCl_3$): δ 2,23 (S; 3H, CH_3CO); 2,26 (S; 6H, $2\underline{CH_3}C_6H_4$); 6,43-7,26 (m; 9H, aromatic and amino protons)

Mass spec.: m/e 254 [M]+; 211 [M-CH_3CO]+; 91 [$CH_3C_6H_4$]+; 43 [CH_3CO]+.

b) **56** (Ar_1= Ar_2= p-$CH_3C_6H_4$) in 11% yield.

c) traces of **61** (Ar_1= Ar_2= p-$CH_3C_6H_4$)

Mass spec.: m/e 212 [M]+

d) **58** (Ar= p-$CH_3C_6H_4$) in 11% yield

IR ($CHCl_3$): ν: 3430 cm^{-1} (NH); 1683 cm^{-1} (N-C=O)

Mass spec.: m/e 149 [M]+; 107 [M-CH_2CO]+; 106 [M-CH_3CO]+

e) **55** (Ar_1= Ar_2 = p-$CH_3C_6H_4$) was recovered in 54% yield.

When the acylation reaction was carried out using 0,06 equivalent of p-toluenesulfonic acid, 29% of the acetic acid 1,2-diarylhydrazide, 6% of the acetic acid 1,2-diaryl-2-acetylhydrazide, traces of 4,4'-dimethylhydrazobenzene, 5% of amide and 50% of recovered starting material were obtained.

3.3.8.3 Acylation of 3,3'-Dimethylazobenzene

Acylation of 3,3'-dimethylazobenzene using 0,02 equivalent of p-toluenesulfonic acid gave:

a) **57** (Ar_1= Ar_2= m-$CH_3C_6H_4$) in 14% yield

IR ($CHCl_3$): ν CO:1672 cm^{-1}

'H NMR ($CDCl_3$): δ 2,22 (S; 3H, CH_3CO); 2,26 (S; 6H, 2$CH_3C_6H_4$); 6,36-7,30 (m; 9H, aromatic and amino protons)

Mass spec.: m/e 254 [M]+; 211 [M-CH_3CO]+; 91 [$CH_3C_6H_4$]+; 43 [CH_3CO]+.

Elemental Analysis: calculated C 75,56 H 7,13 N 11,01

found 75,93 7,12 11,09

b) **56** (Ar_1= Ar_2= m-$CH_3C_6H_4$) in 4% yield

c) **61** (Ar_1= Ar_2= m-$CH_3C_6H_4$) in 18% yield

Mass spec.: m/e 212 [M]+

d) **58** (Ar= m-$CH_3C_6H_4$) in 4% yield

Mass spec.: m/e 149 [M]+

e) **55** (Ar_1= Ar_2= m-$CH_3C_6H_4$) was recovered in 41% yield.

When the acylation was done using 0,10 equivalent of p-toluenesulfonic acid, 28% of the acetic acid 1,2-diarylhydrazide, 5% of 3,3'-dimethylhydrazobenzene and 48% of recovered starting material were obtained.

3.3.8.4 Acylation of 4,4'-Dichloroazobenzene

Acylation of 4,4'-dichloroazobenzene using 0,02 equivalent of p-toluenesulfonic acid afforded:

a) **57** (Ar_1= Ar_2= p-ClC_6H_4) in 37% yield

m.p.= 94-96°C

IR ($CHCl_3$): ν CO: 1678 cm^{-1}

^1H NMR ($CDCl_3$): δ 2,16 (S; 3H, CH_3); 6,39-7,33 (m; 9H, aromatic and amino protons)

Mass spec.: m/e 294 [M]+; 251 [M-CH_3CO]+; 111 [ClC_6H_4]+; 43 [CH_3CO]+.

b) **61** (Ar_1= Ar_2= p-ClC_6H_4) in 8% yield.

Mass spec.: 252 [M]+

c) 55 (Ar_1= Ar_2= p-ClC_6H_4) was recovered in 39% yield.

3.3.8.5 Acylation of 1,1'-(Azodicarbonyl)dipiperidine

Acylation of 1,1'-(azodicarbonyl)dipiperidine afforded **60** in 80% yield.

3.3.9 Variation in Reaction Conditions

Several reactions using azobenzene were conducted under modified conditions. They were carried out as in the general procedure except for the following:

3.3.9.1 Replacement of Carbon Monoxide by CO/H_2 (1/1)

Acylation of azobenzene under CO/H_2 (1/1) bubbling afforded only 6% of acetic acid 1,2-diphenylhydrazide together with 39% of hydrazobenzene and 40% of azobenzene.

3.3.9.2 Variation in Temperature

When the reaction was run at 40°C, 15% of hydrazobenzene and 85% of azobenzene were obtained ('H-NMR yields).

At 50°C, 24% of acetic acid 1,2-diphenylhydrazide, 21% of hydrazobenzene and 40% of azobenzene were isolated.

3.3.9.3 Substitution of p-Toluenesulfonic Acid by HBF_4

When p-toluenesulfonic acid was replaced by HBF_4 (0,10 mmol), 21% of acetic acid 1,2-diphenylhydrazide, 3% of acetic acid 1,2-diphenyl-2-acetylhydrazide, 24% of hydrazobenzene and 29% of azobenzene were obtained.

Acylation was attempted according to the general procedure except that p-toluenesulfonic acid was replaced by HBF_4-Et_2O (2 mmol) and that no water was used. After 1 night only azobenzene was isolated.

Some reactions were carried out using 20% HBF_4 as the aqueous phase and sodium dodecylbenzenesulfonate (0,20 mmol) instead of p-toluenesulfonic acid. Acetic acid 1,2-diphenylhydrazide was not obtained under those conditions. Benzidine was isolated in 46% yield together with azobenzene. A good yield of benzidine was obtained even at room temperature.

3.3.10 General Procedure for the Hydrogenation of Azobenzene Using 4-Dimethylaminopyridine and $Co_2(CO)_8$

A mixture of distilled water (24 ml) and benzene (24 ml) was stirred at 60°C and degassed (nitrogen) for 30 minutes. To this solution was added $Co_2(CO)_8$ (1,36g; 4,0 mmol) and, after 30 minutes, 4-dimethylaminopyridine (0,489g; 4,0 mmol). One hour later, the water was pale pink while the benzene layer was violet. An infrared spectrum of the benzene solution showed carbonyl bands at 1895 cm^{-1}, 1930 cm^{-1} and 2030 cm^{-1}. Azobenzene (0,365g; 2,0 mmol) was added and the mixture was stirred overnight at 60°C under nitrogen. At the end of the

reaction, there was a violet precipitate in the organic phase which was filtered, and the two layers of the filtrate were separated. The orange-brown organic phase was dried over $MgSO_4$ and concentrated by rotary evaporation. An 'H-NMR of the crude product showed that the azobenzene had been completely converted into hydrazobenzene. In order to remove all the cobalt, the product was purified by chromatography using a silica gel column and a mixture of 95% hexane and 5% ethyl acetate as eluant. An 'H-NMR of the product showed a mixture of 58% hydrazobenzene and 42% azobenzene. Some hydrazobenzene had been converted to azobenzene during the chromatography.

3.3.11 Variation in Reaction Conditions

3.3.11.1 Use of a Catalytic Amount of $Co_2(CO)_8$ and 4-Dimethylamino-pyridine Under Carbon Monoxide Atmosphere

When the reaction was carried out under carbon monoxide using only 0,20 mmol of $Co_2(CO)_8$ and 0,20 mmol of 4-dimethylaminopyridine, no hydrazobenzene could be detected by 'H-NMR. Only azobenzene was recovered.

3.3.11.2 Use of CH_3I (Carbon Monoxide Atmosphere)

When the reaction was conducted like that described in the general procedure but under carbon monoxide and in the presence of CH_3I (3,0 ml; 62 mmol), all the azobenzene was converted to hydrazobenzene.

3.3.11.3 Use of CH_3I and Benzyltriethylammonium Chloride (Carbon Monoxide Atmosphere)

The reaction was effected as in the general procedure except that it was run under carbon monoxide and that CH_3I (3,0 ml; 62 mmol) and benzyltriethylammonium chloride (0,114g; 0,50 mmol) were added before azobenzene. Acetic acid 1,2-diphenyl-2-acetylhydrazide and hydrazobenzene were obtained in 13% and 87% yields, respectively.

Chapter 4

Carbonylation of Azetidines

4.1 Introduction

Azetidines are an interesting class of compounds. They form a bridge between the highly strained aziridines and the less-strained larger rings. Several reviews have been written on the chemistry of azetidines[106-110].

The azetidine ring is puckered with an angle of 10-20° from planarity[109]. Although the ring is somewhat strained, the gas phase basicity of azetidine, which reflects orbital hybridization, closely resembles that of pyrrolidine. Indeed the proton affinity for cyclic amines decreases in the order pyrrolidine (229 kcal/mol) > azetidine (227,5 kcal/mol) > aziridine (220,1 kcal/mol)[111-112]. This correlates well with an increase in lone pair s-character in the series.

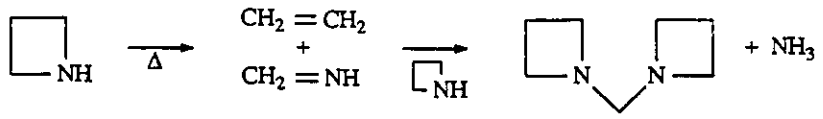
This introduction briefly reviews some organic reactions of azetidines which occur with ring cleavage as well as the organo-transition metal chemistry of these heterocycles.

4.1.1 Organic Chemistry of Azetidines

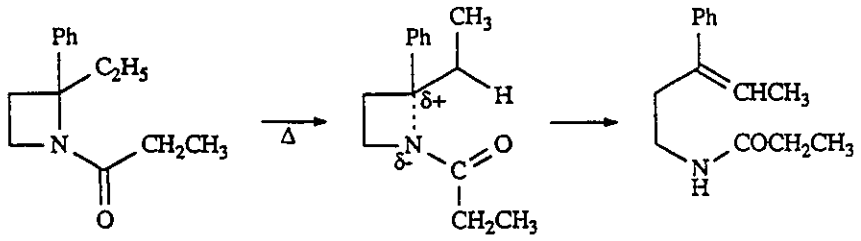
Azetidines undergo ring opening with greater ease than larger ring nitrogen heterocycles, but much less readily than aziridines. The ring

cleavage can be induced thermally or by attack of either nucleophiles or electrophiles[110].

At 420°C, there is cycloreversion of the azetidine to ethylene and methylene amine followed by addition of unreacted azetidine to the latter[113]:

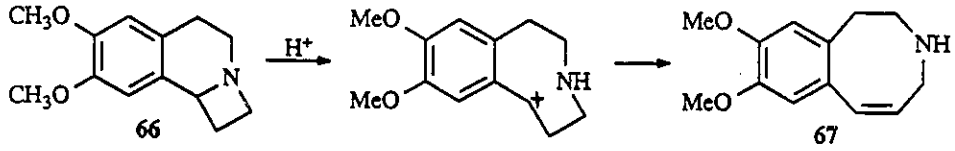


Ring opening has been observed on heating 1-propionyl-2-ethyl-2-phenylazetidine at 150°C[114]:



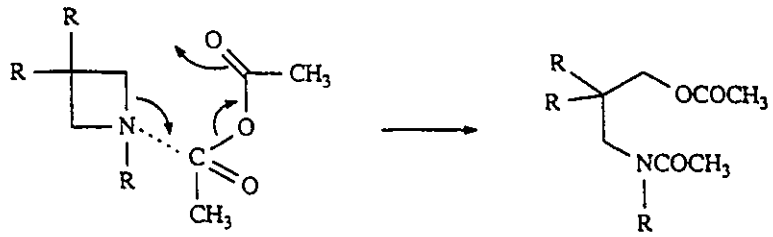
The 2,2-diethyl and the 2-ethyl derivatives did not react under the same conditions.

When heated in the presence of hydrochloric acid, 6,7-dimethoxy-tetrahydroazeto[2,1-a]isoquinoline (**66**) affords benzo[4,5-d]azocine (**67**) [115]:

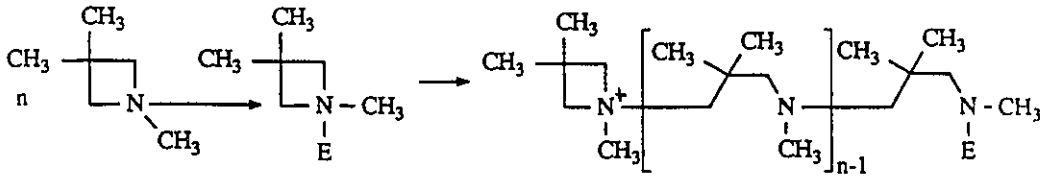


Similarly, 2-arylazetidines, in the presence of acids, easily undergo ring cleavage with elimination to give cinnamylamines[116].

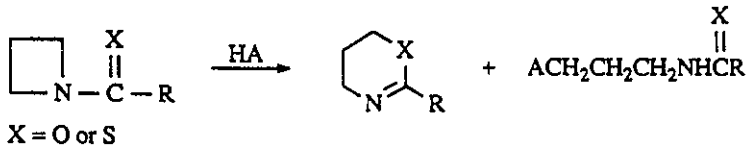
Cleavage of the ring of 1-alkyl-3,3-disubstituted azetidines occurs on heating with acetic anhydride[116]:



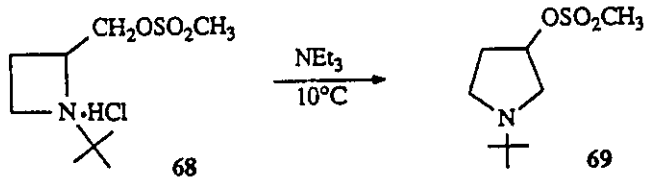
The propensity of azetidines to give polymeric products is well known[109]. For example, polymerization of 1,3,3-trimethylazetidine can be initiated by a variety of electrophiles at temperatures above 60°C[117]. The polymerization proceeds by successive alkylation of monomer units.



1-Acyl and thioacylazetidines afford 1,3-oxazines and 1,3-thiazines respectively, when heated with catalysts such as p-toluenesulfonic acid or boron trifluoride. With acids having a nucleophilic counterion such as chloride, the open-chain product is also obtained[118-119].

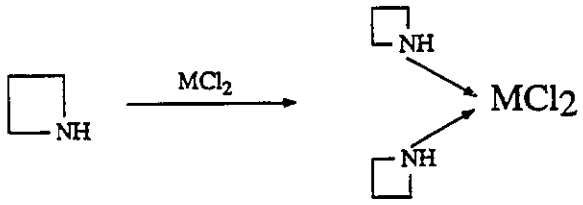


Treatment of the sulfonyloxymethylazetidine hydrochloride (**68**) with triethylamine in methylene chloride gave the sulfonyloxypyrrolidine (**69**) [120]:

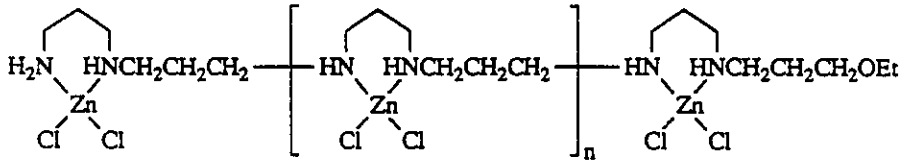


4.1.2 Organometallic Chemistry of Azetidines

Little is known concerning the organometallic chemistry of azetidines. Azetidine and 2-acetylazetidine form complexes with metal chlorides[121]:

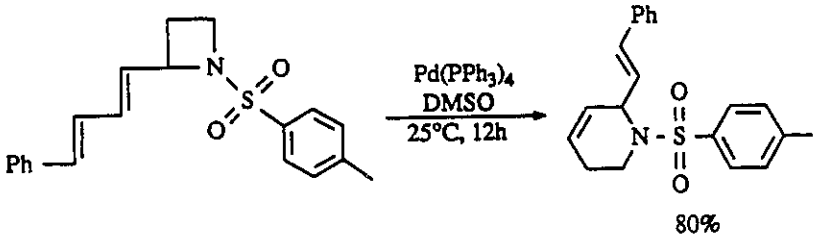


where M= Zn, Cd, Co, Ni, Pt. The platinum complex, $PtCl_2.(azetidine)_2$ has good antitumor activity against leukemia in mice[76]. The zinc chloride complex reacts with ethanol, at 120°C to give **70** (n=3-8)[122]:



70

Dienylazetidines bearing a N-p-toluenesulfonyl group smoothly rearrange to vinylpiperidine in presence of a catalytic amount of $Pd(PPh_3)_4$[123]:



80%

The presence of the N-p-toluenesulfonyl group and of the dienyl moiety is essential for the rearrangement. It has been proposed[123] that the reaction proceeds via nucleophilic attack of Pd(0) on the diene group to form a zwitterion consisting of a π-pentadienylpalladium and a stabilized tosylamide anion. The attack of Pd(0) on the C-NTs bond would be another possible route to the zwitterion[123].

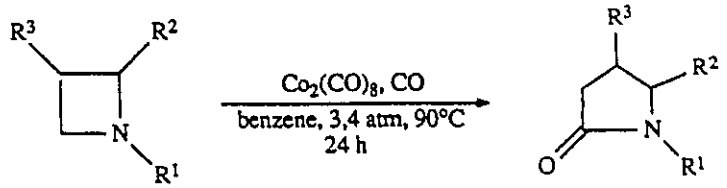
It was anticipated that the metal complex catalyzed carbonylation of azetidines may afford a novel route to pyrrolidones. In this chapter are described the interesting results of this investigation.

4.2 Results and Discussion

A variety of azetidines were prepared according to literature procedures[124-142]. An investigation of their behaviour was made using an organotransition metal complex and carbon monoxide.

At first 1-p-tosylazetidine was utilized as the substrate. Dicobalt octacarbonyl, chlorodicarbonylrhodium dimer, triruthenium dodecacarbonyl, tetrakistriphenylphosphinepalladium, palladium acetate/triphenylphosphine (1:4), and palladium iodide/1,4 bis(diphenylphosphino)butane (1:1) were all unable to carbonylate 1-p-tosylazetidine. No reaction occurred even at high temperature (170°C) and high pressure (60 atm) of carbon monoxide.

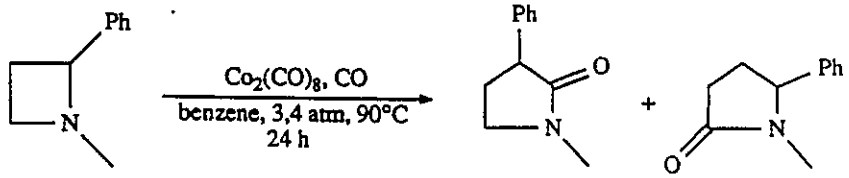
The lack of reactivity of 1-p-tosylazetidine may have been a result of the low basicity of the heterocyclic nitrogen atom. Therefore, a study was undertaken of the more basic 1-t-butyl-2-methylazetidine. This azetidine was converted quantitatively and regiospecifically into 1-t-butyl-5-methylpyrrolidin-2-one when exposed, for 24 hours, to a catalytic amount of dicobalt octacarbonyl (10/1 ratio of substrate/catalyst) in benzene or toluene at 90°C and under 3,4 atm of carbon monoxide. Likewise, 1-t-butyl-2-methoxycarbonylazetidine, 1-t-butyl-2-hydroxymethylazetidine, 1-t-butyl-2-methoxymethylazetidine, 1-t-butyl-2-acetoxymethylazetidine, and 7-methyl-cis-7-azabicyclo [4,2,0]octane, were also converted into the corresponding 5-substituted pyrrolidin-2-ones (table 7). The reactions were completely regiospecific except that of 1-t-butyl-2-methoxycarbonylazetidine which afforded traces of the 3-substituted pyrrolidin-2-one along with a low yield of by-product tentatively identified as 1-t-butyl-6,6-dimethoxycarbonyl-1,2-5,6,7,8-hexahydroazocin-2-one.



where R^1= $(CH_3)_3C$; R^3= H and R^2= CH_3, CO_2CH_3, CH_2OH, CH_2OCH_3 or $CH_2O_2CCH_3$

or R^1= CH_3; R^2, R^3= $-(CH_2)_4-$

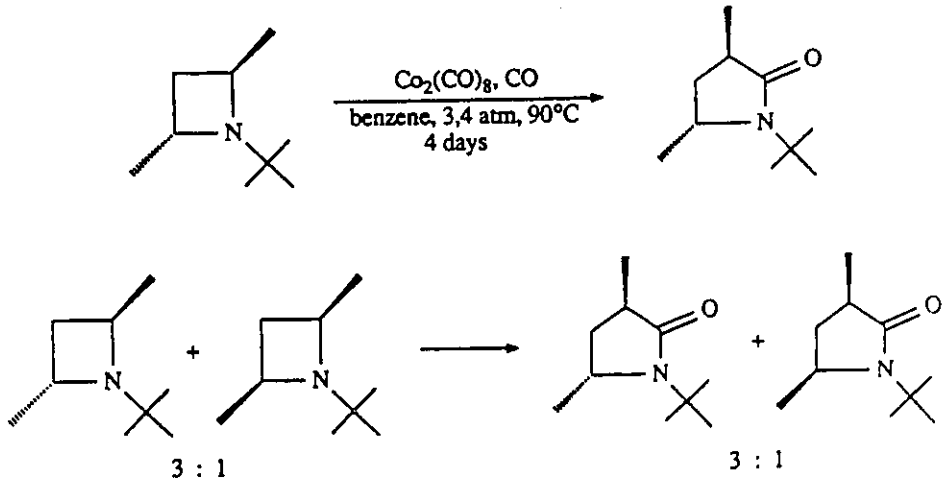
In contrast, the carbonylation of 1-methyl-2-phenylazetidine afforded 1-methyl-3-phenylpyrrolidin-2-one in a highly regiospecific manner.



94 : 6
(GC ratio)

The same selectivity was observed at 160°C.

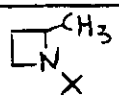
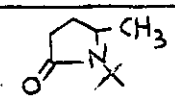
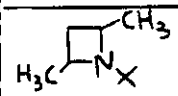
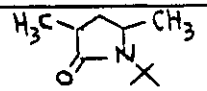
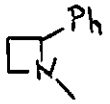
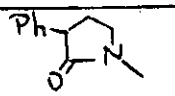
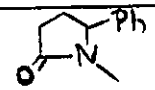
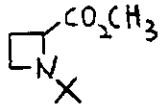
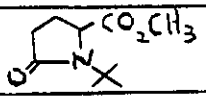
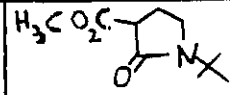
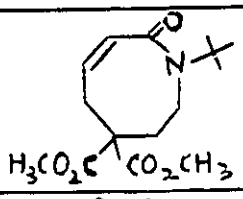
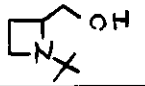
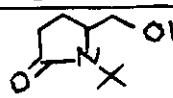
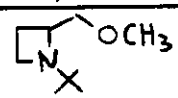
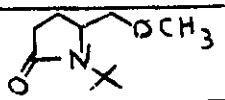
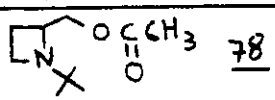
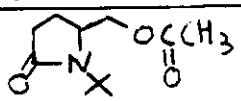
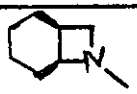
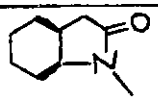
The carbonylation of 1-t-butyl-2,4-dimethylazetidine was stereospecific. Indeed, the <u>trans</u>- and the <u>cis</u>- azetidines afforded respectively the <u>trans</u>- and the <u>cis</u>- pyrrolidin-2-ones.



The reactivity of 1-t-butyl-2,4-dimethylazetidine was low. At 90°C, it took four days for completion of the reaction. At 120-124°C, the reaction was somewhat faster, only two days being required to carbonylate all the azetidine. Moreover, the trans-azetidine reacted faster than its cis-isomer. After 23 hours at 124°C, almost all the trans-azetidine had been carbonylated while only 61% of the cis-azetidine had been transformed into cis-pyrrolidin-2-one.

The results of the carbonylation of the azetidines are listed in Table 7. The products were identified by infrared, proton and carbon nuclear magnetic resonance and mass spectrometry. Assignment of the chemical shifts was made by comparison with the reported nuclear magnetic resonance spectra of 1-methylpyrrolidin-2-one[143-144], 1,5-dimethylpyrrolidin-2-one[145], 1,3-dimethylpyrrolidin-2-one[146], 1-methyl-3-ethoxycarbonylpyrrolidin-2-one[146], 5-methoxymethylpyrrolidin-2-one[147], 1-methyl-3-phenylpyrrolidin-2-one[148] and 1-methyl-5-phenylpyrrolidin-2-one[149]. Spectral data for trans- or cis- 1-t-butyl-3,5-dimethyl-pyrrolidin-2-one are not given in the literature. Nevertheless, it is reasonable to think that the trans- azetidine had been converted stereoselectively into the trans- and not the cis- 1-t-butyl-3,5-dimethyl-pyrrolidin-2-one. By considering the proton magnetic resonance spectra of the trans- and the cis- pyrrolidin-2-ones (see experimental part) one may conclude that the methyl group of cis- CH_3CHCO is at higher field than that of trans-CH_3CHCO by 0,12 ppm (1,12 ppm compared to 1,24 ppm). Moreover the coupling constant (J=7,0Hz) for the cis isomer is lower than that of the trans isomer (J=7,4Hz) by 0,4Hz. Similarly, the signal for the methyl protons of cis- CH_3CHN is at higher field than that of trans- CH_3CHN by 0,09 ppm (1,21 ppm compared to 1,30 ppm). The coupling

Table 7 Carbonylation of Azetidines

AZETIDINE		PRODUCT		YIELD %	
				3,4 atm CO[a]	1 atm CO[b]
	71	none		0	0
	72		80	83	95
	73		81	88[c]	20[d]
	74		82	90	42[e]
			83	traces	3[e]
	75		84	81	33[e]
			85	traces	0[e]
			86	6	0
	76		87	88	83
	77		88	91	92
	78		89	91	89
	79		90	76	—

a) Reaction conditions: benzene; 85-90°C; 24h; 10:1 ratio of azetidine-dicobalt octacarbonyl

b) Reaction conditions: toluene; 90°C; 24h; 10:1 ratio of azetidine-dicobalt octacarbonyl

c) This reaction was carried out at 120-124°C for 40 hours. Use of a 3:1 trans-cis azetidine mixture afforded the pyrrolidinone in a 3:1 trans-cis ratio

d) Using the trans-azetidine

e) GC yields (all the other data refer to isolated yields)

constant (J=5,9Hz) in the cis is also lower than that of the trans isomer (J=6,3Hz) by 0,4Hz. Interestingly, a similar trend is observed in the proton magnetic resonance spectra of the cis- and trans-1-t-butyl-2,4-dimethylazetidines. Indeed, the cis methyl protons are at higher field than the trans methyl protons by 0,08 ppm (δ cis = 1,19 and δ trans = 1,27) while the coupling constant for the cis is lower than the trans methyl by 0,3Hz (J cis = 6,0Hz and J trans = 6,3Hz).

The spectral assignments of **84, 86** and **88** were supported by COSY. A HETCOR spectrum provides evidence for the structure of **86.**

It was of interest to determine if the azetidines could be carbonylated under milder conditions, using 1 atm of carbon monoxide. The results are also summarized in Table 7. 1-t-Butyl-2-methylazetidine, 1-t-butyl-2-hydroxymethylazetidine, 1-t-butyl-2-methoxymethylazetidine and 1-t-butyl-2-acetoxymethylazetidine were converted into their corresponding 1-t-butyl-5-substituted pyrrolidin-2-one in high yields (83-95%). On the other hand, trans-1-t-butyl-2,4-dimethylazetidine, 1-methyl-2-phenylazetidine and 1-t-butyl-2-methoxycarbonylazetidine afforded only 20%, 42%, and 33%, respectively, of the pyrrolidin-2-one derivative. These results might be due to the fact that under 1 atm of carbon monoxide the cobalt catalyst was less stable than under 3,4 atm of carbon monoxide. Indeed after 24 hours under carbon monoxide pressure the reaction mixtures were homogeneous and brown while under 1 atm they were colorless or pale yellow and contained a black precipitate. It is easy to rationalize why 1-t-butyl-2,4-dimethylazetidine is less reactive than the other azetidines (it needed 4 days instead of the usual 24 hours to react completely at 90°C and 3,4 atm) and thus why it afforded pyrrolidin-2-one in low yield. The catalyst was destroyed

before the azetidine had time to react completely. The low yields obtained with 1-t-butyl-2-methoxycarbonylazetidine and 1-methyl-2-phenylazetidine were surprising and not simple to explain.

Dicobalt octacarbonyl can also transform the azetidines into pyrrolidin-2-ones under nitrogen but, of course, the reaction is not catalytic under such conditions. For example, 8% of 1-t-butyl-5-acetoxymethylpyrrolidin-2-one was obtained after 24 hours when 1-t-butyl-2-acetoxymethylazetidine was reacted with dicobalt octacarbonyl (10:1 ratio of substrate/catalyst) in toluene at 90°C under nitrogen.

A study was made of the effect of the temperature and the catalyst on the carbonylation reaction. All the azetidines, except 1-p-tosylazetidine and 1-t-butyl-2,4-dimethylazetidine, are completely converted into pyrrolidin-2-ones after 24 hours at 90°C and under 3,4 atm of carbon monoxide. At lower temperatures the carbonylation reaction also occurred but at a reduced rate. For instance, two days, at 80°C, were necessary to achieve complete conversion of 1-t-butyl-2-methoxycarbonylazetidine, 1-t-butyl-2-acetoxymethylazetidine and of 1-methyl-2-phenylazetidine to the ring expanded products. The reactions were extremely slow at 38°C. Indeed, after four days at this temperature, only 13% of 1-t-butyl-5-methoxymethylpyrrolidin-2-one was obtained from the corresponding azetidine.

At 90°C and under 3,4 atm of carbon monoxide, use of less dicobalt octacarbonyl (for example 20:1 ratio of azetidine to dicobalt octacarbonyl) also afforded the pyrrolidin-2-ones in quantitative yield. However, no reaction occurred either without catalyst or when dicobalt octacarbonyl was replaced by triruthenium dodecacarbonyl. Under the same reaction conditions chloro(1,5 cyclooctadiene)rhodium dimer was

also inert. However, 14% of the 1-t-butyl-5-methylpyrrolidin-2-one was obtained when 1-t-butyl-2-methylazetidine was reacted with a catalytic amount of $[RhCl(1,5COD)]_2$ (10:1 ratio of substrate to catalyst) at 140°C and under 61 atm of carbon monoxide. Only 21% of the azetidine was recovered, and no other organic product was detected by gas or thin layer chromatography. Some polymerization might have occurred here. Similarly, 65% of 1-methyl-2-phenylazetidine reacted under the same conditions, affording 7% of 1-methyl-3-phenylpyrrolidin-2-one (GC conversion and yield).

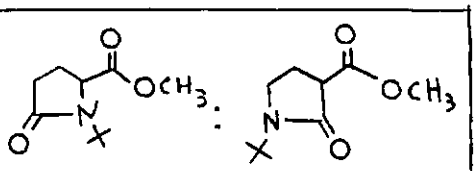
The behaviour of 1-methyl-2-phenylazetidine was studied in the presence of chlorodicarbonylrhodium dimer, at different temperatures. The reactions were followed by gas chromatography using decane as internal standard. No reaction occurred when the azetidine (1,0 mmol) was treated with chlorodicarbonylrhodium dimer (0,1 mmol) in benzene for 24 hours, at 85°C and under 27 atm of carbon monoxide. At 110°C, 18% of the azetidine reacted but no carbonylation product was detected. All the azetidine reacted at 160°C, affording only 24% of 1-methyl-3-phenyl-pyrrolidin-2-one after purification by chromatography (no 1-methyl-5-phenylpyrrolidin-2-one was detected).

Having observed that traces of 1-t-butyl-3-methoxycarbonyl-pyrrolidin-2-one were obtained at 90°C, attempts were made to increase the selectivity of the carbonylation towards this pyrrolidin-2-one. We studied the influence of the concentration, quantity of dicobalt octa-carbonyl, addition of triruthenium dodecacarbonyl or diphenylacetylene, temperature and the solvent. The reactions were followed by gas chromatography, using decane as internal standard.

The concentration of azetidine was 0,35M using the general method. The use of a solution either three times more dilute or more concentrated did not affect the ratio of the two formed pyrrolidin-2-ones. Likewise use of a 3:1 instead of 10:1 ratio of azetidine to dicobalt octacarbonyl, had no significant effect on the selectivity (at 80°C). Being aware of the value of bimetallic catalysis, we checked the influence of triruthemium dodecacarbonyl on the carbonylation reaction. Use of a 1:1 mixture of dicobalt octacarbonyl and triruthenium dodecacarbonyl as catalyst, at 80°C, afforded the same results as those obtained with dicobalt octacarbonyl alone.

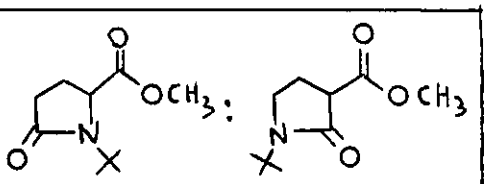
The reaction temperature not only influences the rate of the carbonylation reaction but also has an appreciable effect on the selectivity. Indeed, the reaction was very slow at 38°C, only 23% of the azetidine having reacted after seven days, while at 90°C or 115°C the reaction was complete after 24 hours. At 115°C only the 1-t-butyl-5-methoxycarbonylpyrrolidin-2-one was obtained while at 38°C and at 43°C, 1-t-butyl-5-methoxycarbonylpyrrolidin-2-one and 1-t-butyl-3-methoxycarbonylpyrrolidin-2-one were obtained in a ratio of 59:41. The results of the study of the effect of temperature on this reaction are summarized in Table 8.

Table 8 Effect of the Temperature on the Ratio of 1-t-Butyl-3-and 5-methoxycarbonyl pyrrolidin-2-ones Obtained from a 1-t-Butyl-2-methoxycarbonylazetidine[a] (75)

Temperature (°C)	Time (h)	Conversion of Azetidine (%)	Yield of pyrrolidin-2-ones (%)			
115	24	100	90	100	:	0
90	24	100	91	97	:	3
78	43	100	88	93	:	7
43	168	36	32	59	:	41
38	168	23	20,5	59	:	41

a) Reaction conditions: 3,4 atm CO; benzene; 10:1 azetidine-$Co_2(CO)_8$
b) The conversion, the yield and the ratio of pyrrolidin-2-ones were calculated using gas chromatography.

Table 9 Effect of the Solvent on the Ratio of 1-t-Butyl-3 and 5-methoxycarbonylpyrrolidin-2-ones Obtained from 1-t-Butyl-2-methoxycarbonyl azetidine[a] (75).

Solvent	Time (h)	Conversion of Azetidine (%)	Yield of pyrrolidin-2-ones (%)			
benzene	43	100	88	93	:	7
toluene	43	100	91	93	:	7
4-methyl-2-pentanone	48	76	62	85	:	15
t-amylalcohol	48	40	36	86	:	14

a) Reaction conditions: 3,4 atm CO; 78-80°C; 10:1 azetidine-$Co_2(CO)_8$
b) The conversion, the yield and the ratio of pyrrolidin-2-ones were calculated by gas chromatography.

A reaction was run at 40°C and under 3,4 atm of carbon monoxide in the presence of diphenylacetylene dicobalt hexacarbonyl as the catalyst. After seven days only 20% of the azetidine reacted affording 1-t-butyl-5-methoxycarbonylpyrrolidin-2-one and 1-t-butyl-3-methoxycarbonylpyrrolidin-2-one in a ratio of 58:42. The purpose of this experiment was to determine the effect of having a more electron withdrawing group on the cobalt. The results show that the influence of diphenylacetylene is negligible.

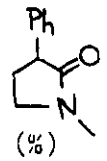
The nature of the solvent has little influence on the selectivity of the reaction. The results are summarized in Table 9. The same selectivity was obtained using either benzene or toluene (93:7 ratio of 5- to 3-methoxycarbonylpyrrolidin-2-one). The formation of 3-methoxycarbonylpyrrolidin-2-one was slightly more favored in more polar solvents like 4-methyl-2-pentanone and t-amyl alcohol (85:15 and 86:14 of 5- to 3-methoxycarbonylpyrrolidin-2-one). In the more polar solvents, especially in t-amyl alcohol, the reaction was slower. In order to combine the influence of temperature and of solvent, a reaction was conducted in 4-methyl-2-pentanone at 34°C and under 3,4 atm of carbon monoxide. Only 13% of the azetidine was carbonylated after 7 days giving 1-t-butyl-5- and 3-methoxycarbonylpyrrolidin-2-ones in a ratio of 53:47. This is the best selectivity reached for the 3-methoxycarbonylpyrrolidin-2-one isomer. Acetonitrile was also used as solvent but it inhibited the reaction. For example, no reaction occurred at 35°C even after 7 days. It is probably due to the fact that acetonitrile binds to dicobalt octacarbonyl rather than the azetidine.

During our study of the influence of several parameters on the selectivity of the two formed pyrrolidin-2-ones, a by-product tentatively identified as 1-t-butyl-6,6-dimethoxycarbonyl-1,2,5,6,7,8-hexahydroazocin-2-one could be generated in modest amount subject to the concentration of the azetidine. Indeed its formation was obtained in 3%, 7% and 14% yield when the concentration in azetidine was respectively 0,10M, 0,35M and 1,20M, at 80°C and under 3,4 atm of carbon monoxide, (GC yields). This product was not observed when the carbonylation was carried out at atmospheric pressure.

It is interesting to note that 1-t-butyl-2-hydroxymethylazetidine, 1-t-butyl-2-methoxymethylazetidine and 1-t-butyl-2-acetoxymethylazetidine did not afford any 3-substituted pyrrolidin-2-one, on attempted carbonylation at 80°C. A reaction was run at 38°C with 1-t-butyl-2-methoxymethylazetidine to see if any of this pyrrolidin-2-one would be formed. None was, the reaction being very slow but afforded only 1-t-butyl-5-methoxymethylpyrrolidin-2-one.

Conceptually, it seemed possible to induce chirality during the cobalt catalysed carbonylation of 1-methyl-2-phenylazetidine in the presence of an added chiral ligand. For this reason, an investigation was initiated of the influence of adding 2S,3S(-)bis(diphenylphosphino)-butane to the reaction mixture. When about half of the azetidine had reacted, the reactions were stopped and worked-up. No optical activity could be induced using a ratio 1:1 of dicobalt octacarbonyl to 2,3-bis(diphenylphosphino)butane. The use of twice the amount of 2,3-bis(diphenylphosphino)butane completely inhibited the formation of pyrrolidin-2-one. With $Co_2(CO)_8$ and chiraphos, $Co_2(CO)_4(CH_3(PPh_2)$-$CHCH(PPh_2)CH_3)_2$ had probably been formed and was unable to carbonylate the azetidine. The results are shown in Table 10. Attempts to

Table 10 Effect of 2S,3S(-)Bis(diphenylphosphino)butane on the Carbonylation of 1-Methyl-2-phenylazetidine (74)

$Co_2(CO)_8$[a]: $CH_3(PPh_2)CHCH(PPh_2)CH_3$	Temperature (°C)	Time (h)	 (%)	Optical Activity
1 : 1	97	3	50	No
1 : 1	75	48	42	No
1 : 2	110	24	0	
1 : 2	150[b]	24	0	

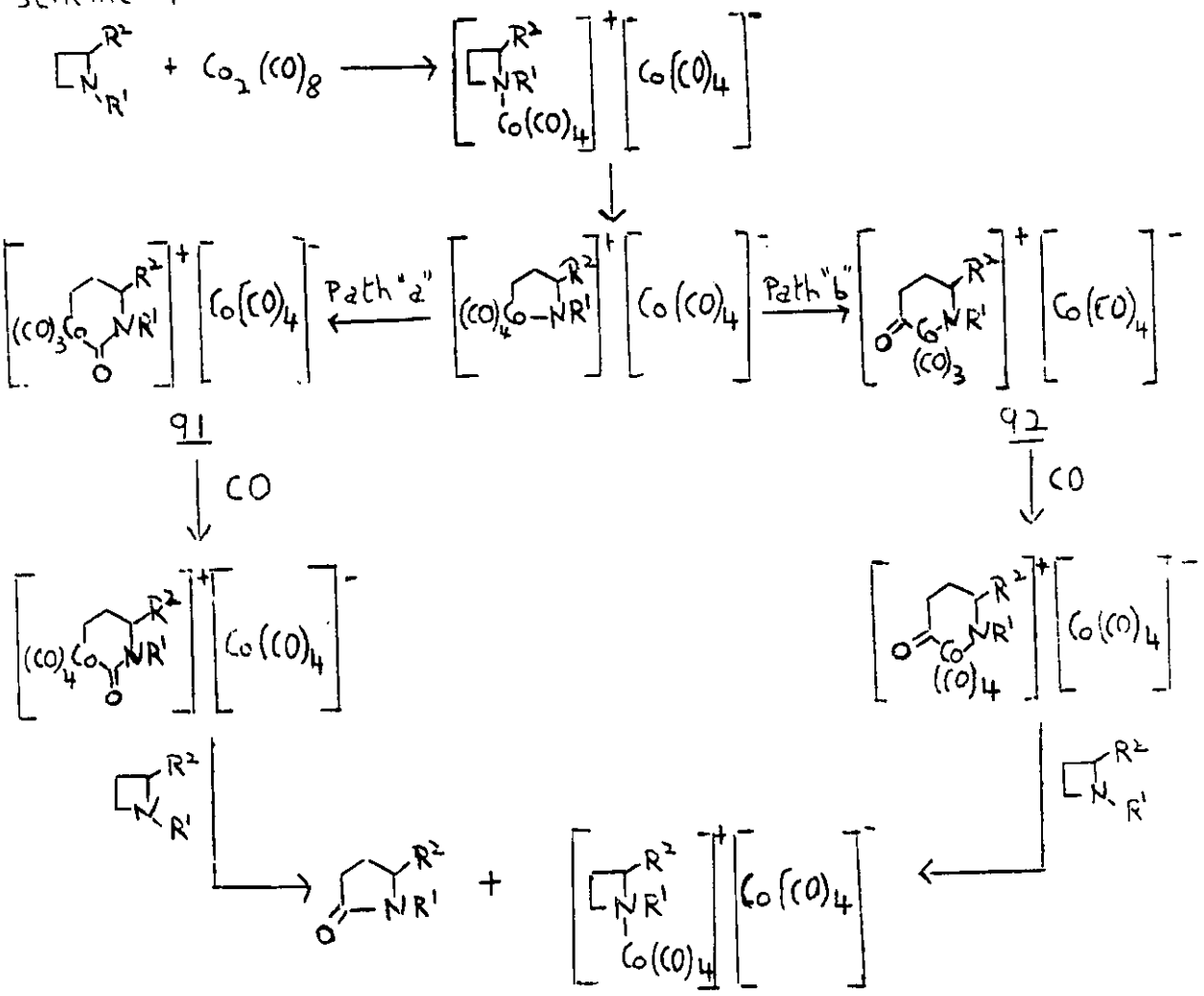
a) A 10:1 ratio of azetidine :$Co_2(CO)_8$ was used.

b) At that temperature all the azetidine reacted, affording a black glue-like material.

carbonylate enantioselectively 1-methyl-2-phenylazetidine in the presence of l-menthol and dicobalt octacarbonyl also failed, racemic pyrrolidin-2-one being obtained. On the other hand, use of cobalt acetate instead of dicobalt octacarbonyl, in the presence of l-menthol, failed to carbonylate the azetidine even at 160°C.

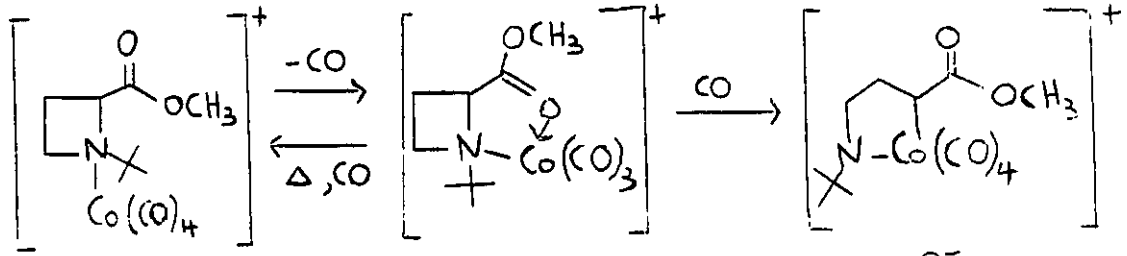
The dicobalt octacarbonyl induced carbonylation of 1,2-dialkyl-azetidines affording 5-substituted pyrrolidin-2-ones can take place by the pathway described in scheme 4.1. The insertion of CO might occur into the N-Co bond (path "a") to give **91** or into the C-Co bond (path "b") to afford **92.**

Scheme 4.1



Recently, Bryndza[150] has reported that (DPPE)PtCH$_3$[N(CH$_2$C$_6$H$_5$)(H)] reacts with CO to give (DPPE)PtCH$_3$[C(O)N(CH$_2$C$_6$H$_5$)(H)] where DPPE is 1,2-bis(diphenylphosphino)ethane. This shows that insertion into the Pt-N bond is preferred to insertion into the Pt-C bond. If the same trend is applicable with cobalt, path "a" would be followed in scheme 4.1. 5-and not 3-Substituted pyrrolidin2-ones are obtained because the cobalt prefers to insert into the less substituted nitrogen-carbon bond since there is a smaller steric effect.

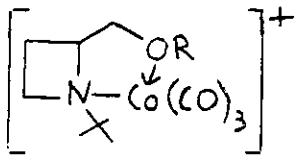
The carbonylation of 1-t-butyl-2-methoxycarbonylazetidine also gives some 1-t-butyl-3-methoxycarbonylpyrrolidin-2-one. This might be explained by the fact that even though the ester group causes steric bulkiness it is capable of binding to the cobalt (**94**), thus fixing the position of insertion regarding the formation of the azacobaltacyclopentane complex.



93 94 95

This binding between the oxygen and the cobalt would be very weak, allowing the formation of complex **94** only at low temperatures (for example, 38°C). At high temperatures (for example, 115°C), only complex **93** would be present.

It is surprising that 1-t-butyl-2-hydroxymethylazetidine, 1-t-butyl-2-methoxymethylazetidine and 1-t-butyl-2-acetoxymethylazetidine do not afford 3-substituted pyrrolidin-2-ones. Indeed, coordination of the oxygen atom of the azetidine to the cobalt should also occur at low temperatures giving **96** and facilitating the migration of the cobalt in that direction.



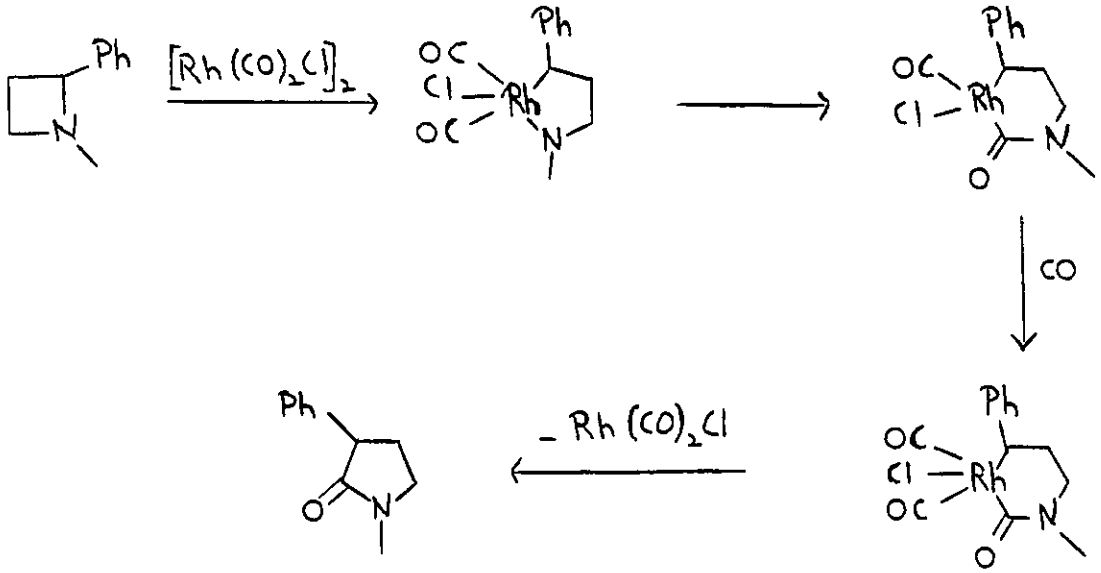
96

The experimental results seem to indicate that the Co-O bond is stronger in complex **94** than in complex **96:** However, the reason for this is not obvious.

1-Methyl-2-phenylazetidine forms 1-methyl-3-phenylpyrrolidin-2-one almost exclusively perhaps because the cobalt inserts into the nitrogen-carbon bond bearing the phenyl group. The phenyl group with its πelectrons is capable of coordinating to cobalt prior to migration.

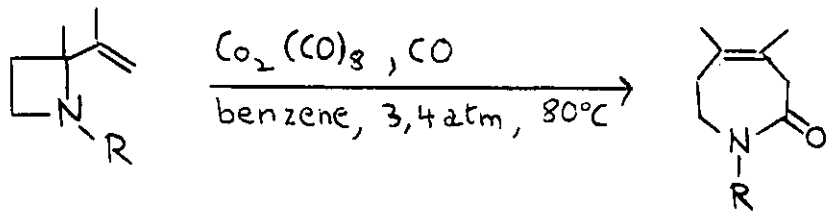
The chlorodicarbonylrhodium dimer induced carbonylation of azetidines might be accounted for by a mechanism similar to the one which has been proposed for the carbonylation of aziridines[49]:

Scheme 4.2



It was interesting to know the reaction course for azetidines bearing a vinyl group at the 2-position of the ring in presence of dicobalt octacarbonyl. Would such reactants also form pyrrolidin-2-ones? If so, by analogy with 1-methyl-2-phenylazetidine, would the CO insert regiospecifically into the nitrogen-carbon bond bearing the vinyl group? In order to answer these questions a variety of 2-methyl-2-(2-propenyl)azetidines were synthesized and their behaviour was examined in the presence of dicobalt octacarbonyl.

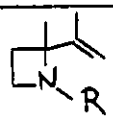
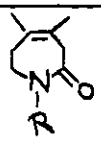
It was found that 2-methyl-2-(2-propenyl)azetidines are converted into 4,5-dimethyl-1,2,6,7-tetrahydro-3H-azepin-2-ones by a catalytic amount of dicobalt octacarbonyl, under 3,4 atm of carbon monoxide:



R = H, $CH_2CH_2COCH_3$, $CH_2CH_2CO_2CH_3$ or CH_2CH_2CN

The results are summarized in Table 11. The highest yields were obtained at 80°C, using a concentration of 0,06M azetidine. At higher concentrations polymerization of the azetidine occurs. For example, when a 0,35M solution of 1-(-3-oxobutyl)-2-methyl-2-(2-propenyl)azetidine was reacted at 80°C, only traces of 1-(-3-oxobutyl)-4,5-dimethyl-1,2,6,7-tetrahydro-3H-azepin-2-one were obtained. The rest of the azetidine had been destroyed, probably due to polymerization. On the other hand, at lower temperatures, the carbonylation reaction was slower, giving time for polymerization to be more competitive. For example, all the 1-(-3-oxobutyl)-2-methyl-2-(2-propenyl)azetidine

Table 11 Carbonylation of 2-Methyl-2-(2-propenyl)azetidines[a]

 R		T (°C)	 yield (%)[b]	
H	**97**	80	52	**101**
$CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$	**98**	50	54	**102**
$CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_3$	**99**	50	60	**103**
$CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_3$		80	83	
CH_2CH_2CN	**100**	80	86[c]	**104**

a) Reaction conditions: benzene; azetidine 0,061M; dicobalt octacarbonyl 0,0061M; 3,4 atm of carbon monoxide; 24h

b) isolated yields

c) after 72 hours

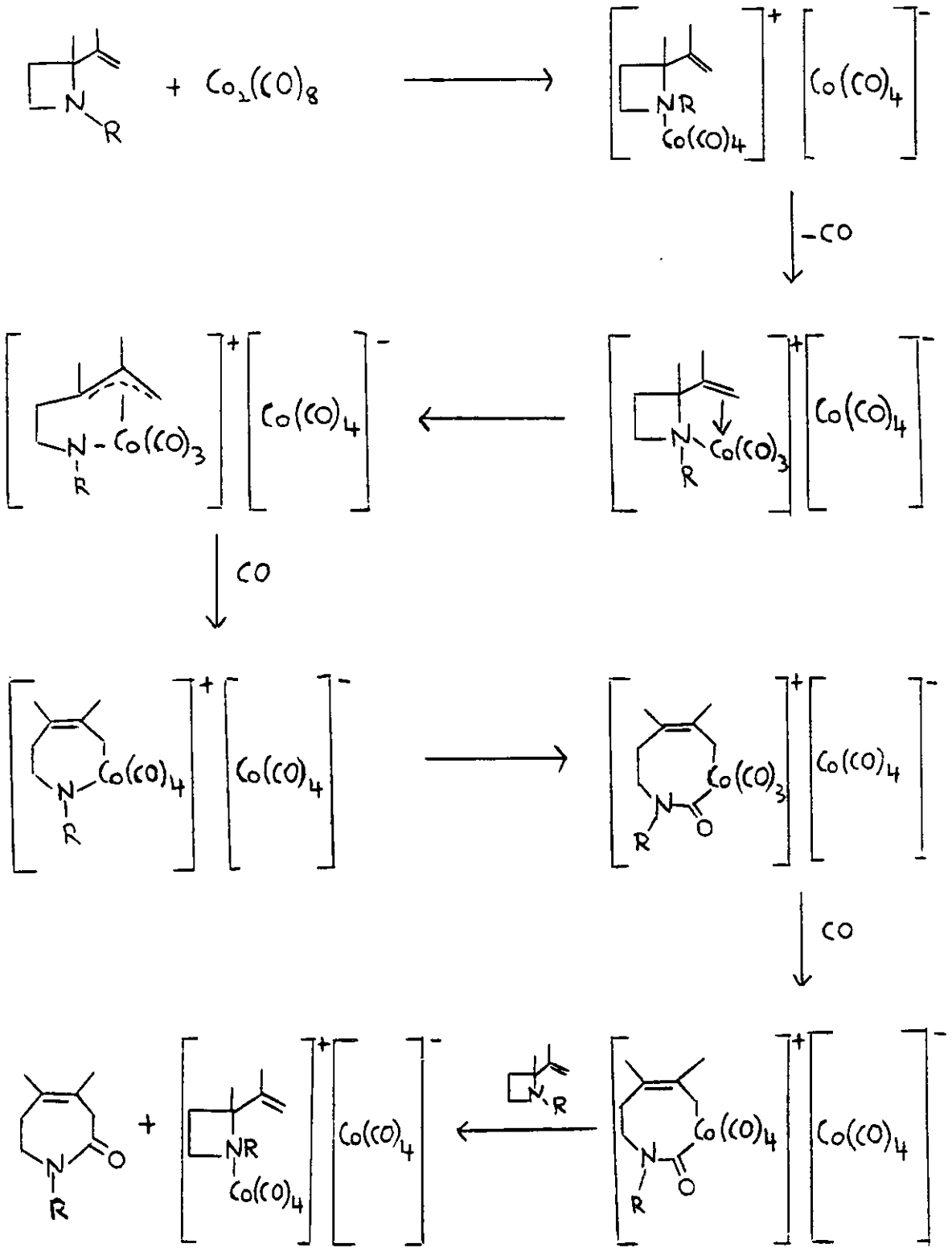
reacted after 2 days at 30°C, affording only 32% of the 1-(-3-oxobutyl)-4,5-dimethyl-1,2,6,7-tetrahydro-3H-azepin-2-one. Furthermore, it is necessary to have a certain pressure of carbon monoxide in order to obtain the 3H-azepin-2-one derivatives. Indeed, similar results were obtained at 3,4 or 61 atm of carbon monoxide while no carbonylation occurred at 1 atmosphere.

Chloro(1,5-cyclooctadiene)rhodium dimer is unable to induce the formation of 4,5-dimethyl-1,2,6,7-tetrahydro-3H-azepin-2-ones even under 61 atm of carbon monoxide. The azetidine is completely destroyed under the reaction conditions.

The 4,5-dimethyl-1,2,6,7-tetrahydro-3H-azepin-2-ones were identified on the basis of analytical and spectral data. In order to assign the ^{13}C chemical shifts of the various carbon atoms, comparison was made to the chemical shifts of hexahydroazepin-2-one and of 1-methylhexahydroazepin-2-one reported by Rae[143]. We observed that N-alkylation causes deshielding of the ring-carbon α to nitrogen as well as shielding of the carbon of the carbonyl adjacent to nitrogen. This parallels the effects of N-alkylation of hexahydroazepin-2-one observed by Rae[143].

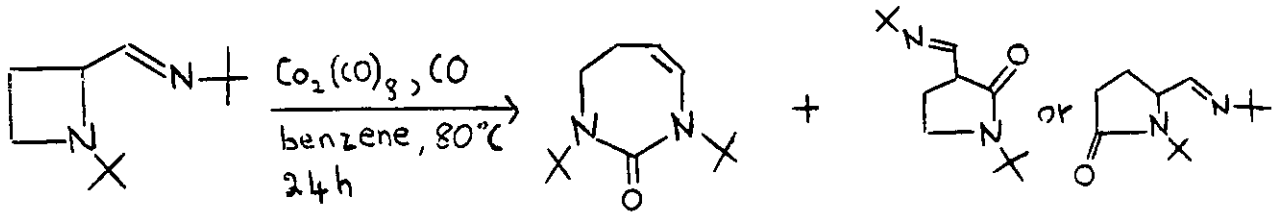
A possible mechanism for the formation of 4,5-dimethyl-1,2,6,7-tetrahydro-3H-azepin-2-ones is outlined in Scheme 4.3.

Scheme 4.3



Fascinated by this remarkable carbonylation with ring expansion of 2-methyl-2-(2-propenyl)azetidines, it was important to know how an azetidine bearing an iminyl group instead of the vinyl group would react with carbon monoxide in the presence of $Co_2(CO)_8$.

1-t-Butyl-2-t-butyliminylazetidine (**105**) was prepared from 1-t-butyl-2-formylazetidine and t-butylamine. A catalytic amount of dicobalt octacarbonyl transforms this azetidine mainly into 1,3-di-t-butyl-2,3,6,7-tetrahydro-1H-1,3-diazepin-2-one (**106**). 1-t-Butyl-3 or 5-t-butyliminylpyrrolidin-2-one is also obtained during the reaction, in low yield.

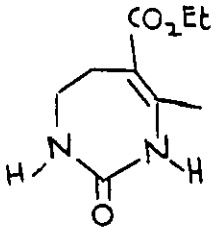


105 106 107 108

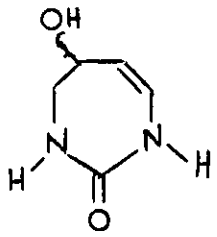
5 : 1

Analogous to the reaction of 2-methyl-2-(2-propenyl)azetidine, the highest yield observed was at 80°C, using a concentration 0,06M of azetidine. At higher concentrations polymerization was predominant.

Unfortunately, the 1,3-di-t-butyl-2,3,6,7-tetrahydro-1H-1,3-diazepin-2-one decomposed easily, even in the freezer under nitrogen. For this reason only 11% of this product, not completely pure, could be isolated by preparative thin layer chromatography on alumina. It was identified by infrared, proton magnetic resonance and mass spectroscopy. As expected, there was no iminyl hydrogen (HC=N-) in the proton NMR spectrum. The chemical shifts of the hydrogens of carbon 6 (2,56 and 2,69 ppm) and of carbon 7 (3,36 ppm) agree well with those reported for ethyl-2,3,6,7-tetrahydro-4-methyl-1H-1,3-diazepin-2-one-5-carboxylate (compound **109**, multiplet at 2,65 and at 3,25 ppm).[151] However, the olefinic hydrogens (6,42 and 7,07 ppm) are at lower field than those reported for 6-hydroxy-2,3,6,7-tetrahydro-1H-1,3-diazepin-2-one (compound **110**, olefinic hydrogens at 4,88 and 5,82 ppm)[152].



109



110

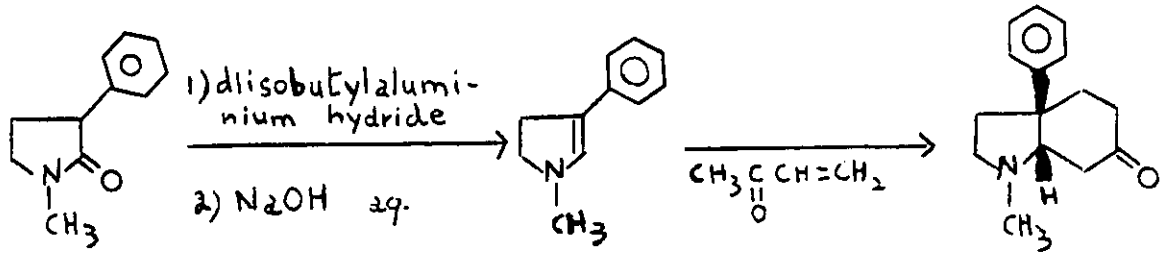
The low stability of 1,3-di-t-butyl-2,3,6,7-tetrahydro-1H-1,3-diazepin-2-one is rather surprising since the syntheses of **109** and **110** have been reported without reference to their instability[151-152]. It is possible that the t-butyl groups decrease the stability of the 2,3,6,7-tetrahydro-1H-1,3-diazepin-2-one.

Several attempts to obtain pure pyrrolidin-2-one failed since the imine group hydrolysed easily. This is why it can not be said with certainty which of the two possible pyrrolidin-2-ones is formed during the reaction. In any case, the yield is low.

Our research on the carbonylation ring expansion of azetidines has been outstandingly fruitful. It provides new routes leading respectively to 1,5-dialkylpyrrolidin-2-ones, 1-alkyl-3-arylpyrrolidin-2-ones, 1,2,6,7-tetrahydro-3H-azepin-2-ones and 2,3,6,7-tetrahydro-1H-1,3-diazepin-2-ones. All these compounds are important, either for their pharmaceutical properties or for their use in synthesis.

Pharmacological investigations have shown that 1-methyl-3 or 5-methyl or phenylpyrrolidin-2-ones possess a high antispasmodic activity[153]. The sedative and antimicrobial actions of 5-alkylpyrrolidin-2-ones have also been observed[154]. Pyrrolidin-2-ones derivatives have been tested for cardiovascular activity. 4-(p-Tolyl)pyrrolidin-2-one was found to be the most active, decreasing arterial pressure by 30-40% at 50mg/kg[155].

1-Alkyl-5-hydroxymethylpyrrolidin-2-ones are used in the synthesis of pharmaceutical compounds[156]. 1-Methyl-3-phenylpyrrolidin-2-one is the starting material of an efficient two steps synthesis of desdimethoxymesembrine (**111**) [157]:

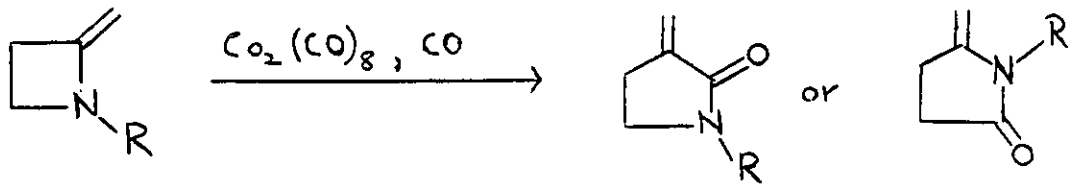


111

An enormous amount of work by synthetic organic chemists[157] has been done on these compounds due to their central nervous system activity. Because of this important application, the synthesis of 1-methyl-3-phenylpyrrolidin-2-one has been studied recently. This compound was obtained in 35-40% yield by allowing 3,2 equivalents of lithium isopropylcyclohexylamide to react with 2,0 equivalents of 1-methylpyrrolidin-2-one at -78°C and then by adding 1,0 equivalent of bromobenzene at 20°C. Use of lithium diisopropylamide afforded only 18% of the 1-methyl-3-phenylpyrrolidin-2-one[148]. The carbonylation with ring expansion of 1-methyl 2-phenylazetidine induced by dicobalt octacarbonyl is a new, simple alternative route for the synthesis of 1-methyl-3-phenylpyrrolidin-2-one in high yield.

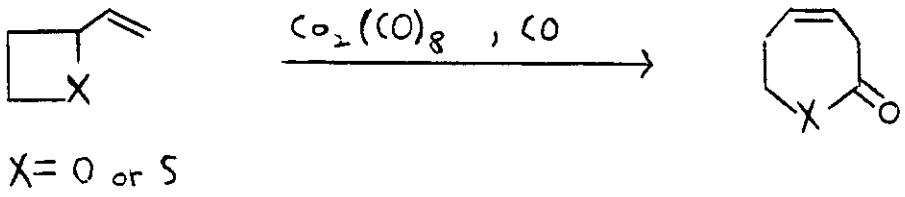
Many azepinones[158-160] and 1,3-diazepin-2-one derivatives[152] are biologically active.

Our discovery of the cobalt induced carbonylation and ring expansion of azetidines provides ideas for others investigations. For example, it would be interesting to see if 2-methyleneazetidines (112) can also be carbonylated with ring expansion:



112

The carbonylation with ring expansion of 2-vinyloxetanes or 2-vinylthietanes could also be investigated:



X= O or S

In the course of our investigations, we observed that chlorodicarbonylrhodium dimer is also able to carbonylate azetidines albeit in low yields, polymerization being a significant side-reaction. It would be worthwhile to undertake a detailed study of the carbonylation of 1-methyl-2-phenylazetidine with chlorodicarbonylrhodium dimer. It would be nice to achieve quantitative conversion of the azetidine into pyrrolidin-2-one. Then, in presence of optically active menthol and using the ideal reaction conditions for carbonylation, asymmetric induction might be achieved, in view of the remarkable enantioselective carbonylation of aziridines[17]. This would constitute an elegant route to optically active 1-methyl-3-phenylpyrrolidin-2-one.

4.3 Experimental Data

4.3.1 General Comments

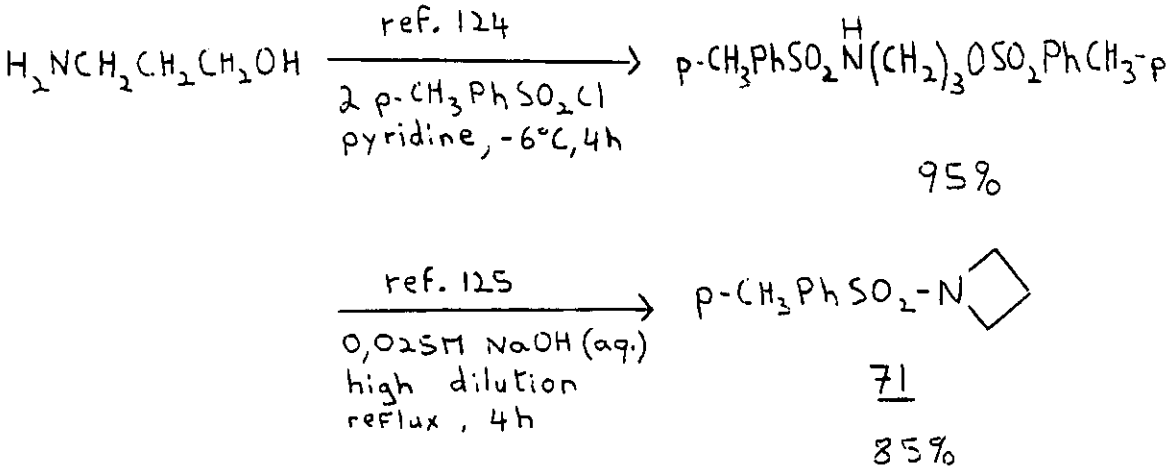
The general comments of chapter 2 are also applicable here.

A Perkin-Elmer 241 Polarimeter (Na lamp) was used for measurement of optical activity.

4.3.2 Synthesis of Azetidines

The azetidines were prepared according to the literature. The reaction sequence leading to each azetidine synthesized is presented below. Some characteristic data of the azetidines are also given.

4.3.2.1 Synthesis of 1-p-Tosylazetidine

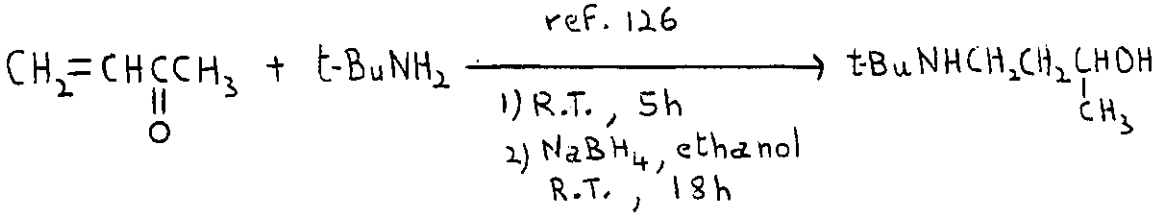


71:

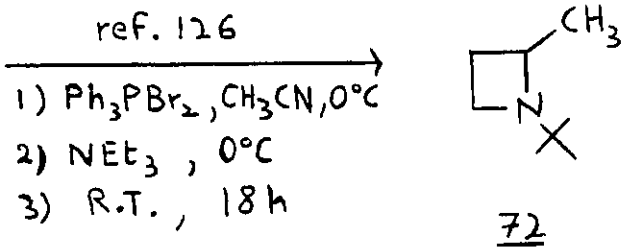
m.p. = 125-126°C (lit[125] m.p. = 123-124°C)

^{1}H NMR($CDCl_3$): δ 2,06 (quintuplet; 2H, $CH_2\underline{CH_2}CH_2$); 2,47 (S; 3H, CH_3); 3,77 (t; 4H, $2CH_2N$); 7,57 (AA'BB' pattern; 4H, aromatic protons).

4.3.2.2 Synthesis of 1-t-Butyl-2-methylazetidine



80%



72

44%

72:

b.p. = 125-127 °C

^{1}H NMR($CDCl_3$): δ 0,87(S; 9H, $(CH_3)_3C$); 1,10 (d; 3H, $\underline{CH_3}CH$); 1,43-2,00 (m; 2H, $CH_2\underline{CH_2}CH$); 2,73-3,03 (m; 2H, CH_2N); 3,32 (m; 1H, CHN)

^{13}C NMR ($CDCl_3$): δ 24,22 ($\underline{CH_3}CH$); 24,62 ($CH_2\underline{CH_2}CH$); 25,30 [$(\underline{CH_3})_3C$]; 43,12 (CH_2N); 52,52 (CN); 54,53 (CHN).

4.3.2.3 Synthesis of 1-t-Butyl-2,4-dimethylazetidine

1-t-Butyl-2,4-dimethylazetidine (73) was prepared according to the method of Freeman and Mondron[126] described for 1-t-butyl-2-methylazetidine except that 3-penten-2-one was used instead of methylvinylketone. The azetidine was obtained in 81% yield as a 3:1 trans/cis mixture (^{1}H NMR and GC ratio). The isomers were separated and purified by silica gel chromatography (plates) using ethyl acetate as eluant. Freeman and Mondron did not prepare this azetidine however they synthesized a similar one, 1-benzyl-2,4-dimethylazetidine, which was also obtained as a 3:1 trans/cis mixture.

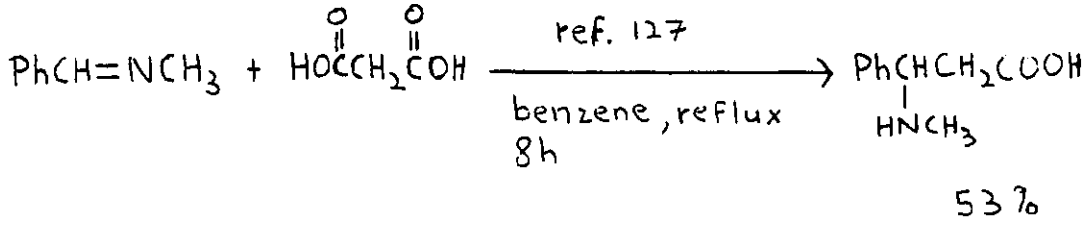
73 trans:

^{1}H NMR($CDCl_3$): δ 1,09 (S; 9H, $(CH_3)_3C$); 1,27 (d, J = 6,3Hz; 6H, $2\underline{CH_3}CH$); 1,80 (t; 2H, CH_2); 3,89 (m; 2H, 2CHN)

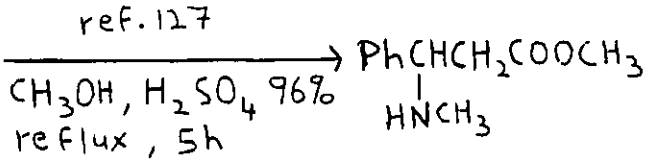
73 cis:

^{1}H NMR($CDCl_3$): δ 0,98 (S; 9H, $(CH_3)_3C$); 1,19 (d,J = 6,0Hz; 6H, $2\underline{CH_3}CH$); 3,26 (m; 2H, 2CHN)

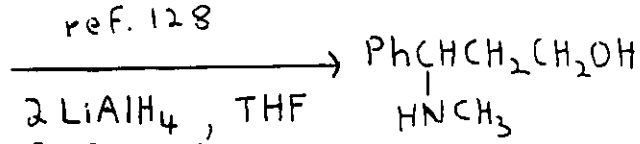
4.3.2.4 Synthesis of 1-Methyl-2-phenylazetidine



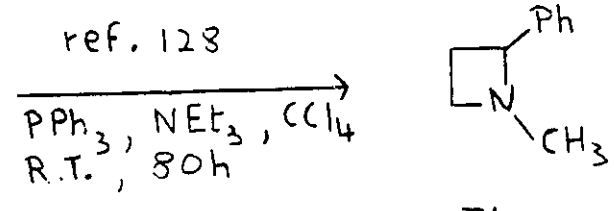
53 %



92 %



93%



74

43%

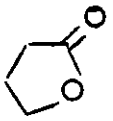
74:

b.p. = 46-47°C (1 mm Hg) [lit[128] b.p. = 46-47°C (1 mm Hg)]

^{1}H NMR($CDCl_3$): δ 2,10-2,28 (m; 2H, $CH_2\underline{CH_2}CH$); 2,32 (S; 3H, CH_3N); 2,84 (m; 1H, 1H of CH_2N); 3,45 (m; 1H, 1H of CH_2N); 3,85 (t,J = 7,8Hz; 1H, CHN); 7,21-7,38 (m; 5H, aromatic protons)

^{13}CNMR ($CDCl_3$): δ 27,02 ($CH_2\underline{CH_2}CH$); 44,55 (CH_3); 52,96 (CH_2N); 71,16 (CHN); 126,44; 127,10; 128,22; 142,89 (aromatic carbons).

4.3.2.5 Synthesis of 1-t-Butyl-2-methoxycarbonylazetidine



ref. 129

1) PBr_3, Br_2
110-115°C, ½h

2) MeOH, HCl gas
0°C, 10 mn

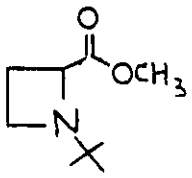
3) R.T., 22 h

$BrCH_2CH_2\underset{Br}{CH}CO_2CH_3$

87%

ref. 130

3 t-$BuNH_2$, CH_3CN
reflux, 24 h

t-$Bu\overset{+}{N}H_3Br^-$ + 

75

75%

75:

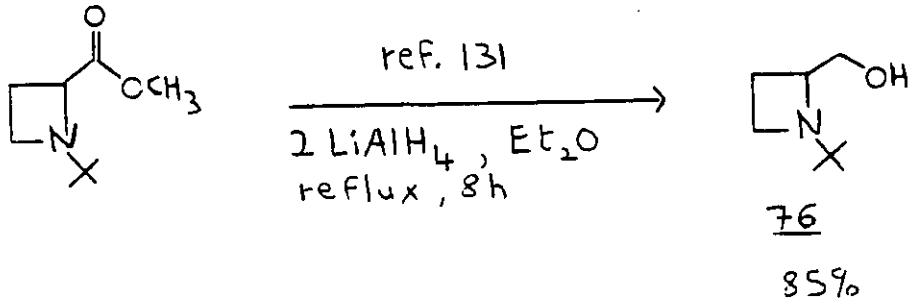
b.p. = 55-56°C (2 mm Hg)[lit[130] b.p. = 55-56°C (2mm Hg)]

IR ($CHCl_3$): $\tilde{\nu}$ CO 1724 cm^{-1} and 1742 cm^{-1}

'H NMR($CDCl_3$): δ 1,00 (S; 9H, $(CH_3)_3C$); 1,98-2,40 (m; 2H, $CH_2\underline{CH_2}CH$); 3,03-3,26 (m; 2H, CH_2N); 3,63 (S; 3H, CO_2CH_3); 3,88 (t; 1H, CHN)

^{13}CNMR ($CDCl_3$): δ 20,47 ($CH_2\underline{CH_2}CH$); 24,43 ($(\underline{CH_3})_3C$); 43,55 (CH_2N); 51,93 (OCH_3); 52,77 (N-C); 58,23 (CHN); 174,01 (C=O).

4.3.2.6 Synthesis of 1-t-Butyl-2-hydroxymethylazetidine



76

85%

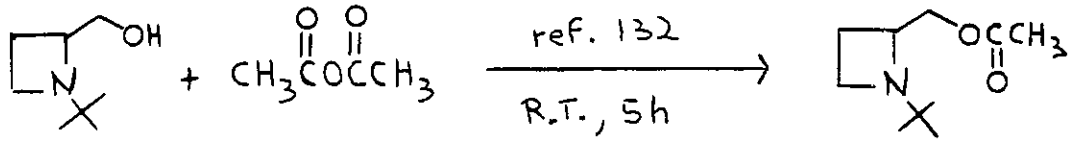
76:

b.p. = 54-55°C (2 mm Hg)

'H NMR($CDCl_3$): δ 0,94 (S; 9H, $(CH_3)_3C$); 1,80 (m; 1H, 1H of $CH_2\underline{CH_2}CH$); 2,06 (m; 1H, 1H of $CH_2\underline{CH_2}CH$); 3,01 (m; 1H, 1H of CH_2N); 3,15 (m; 1H, 1H of CH_2N); 3,27 (d, J = 10,7Hz; 1H, 1H of CH_2O); 3,46 (dd, J = 10,7Hz and J' = 3,5Hz; 1H, 1H of CH_2O; 3,62-3,71 (m; 2H, CHN+OH)

^{13}C NMR ($CDCl_3$): δ 17,46 ($CH_2\underline{CH_2}CH$); 25,09 ($(\underline{CH_3})_3C$); 43,14 (CH_2N); 52,25 (CN); 58,96 (CHN); 63,27 (CH_2O).

4.3.2.7 Synthesis of 1-t-Butyl-2-acetoxymethylazetidine



78

77%

78:

b.p. = 68-69°C (3 mm Hg)(lit[132] b.p. = 88,5-89,5°C (19 mm Hg))

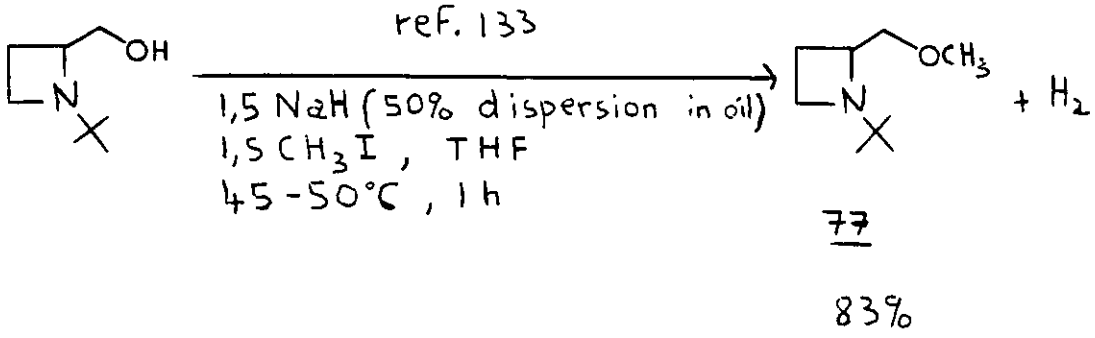
^{1}H NMR($CDCl_3$): δ 0,97 (S; 9H, $(CH_3)_3C$); 1,76-2,15 (m; 2H, $CH_2\underline{CH_2}CH$); 2,04 (s; 3H, CH_3CO); 2,96-3,30 (m; 2H, CH_2N); 3,60 (m; 1H, CHN); 4,05 (d; 1H, 1H of CH_2O); 4,10 (d; 1H, 1H of CH_2O)

^{13}C NMR ($CDCl_3$): δ 19.99 ($CH_2\underline{CH_2}CH$); 20,98 ($\underline{CH_3}CO$); 25,14 ($(\underline{CH_3})_3C$); 43,46 (CH_2N); 52,33 (C-N); 56,63 (CHN); 69,20 (CH_2O); 170,73 (C=O)

4.3.2.8 Synthesis of 1-t-Butyl-2-methoxymethyl azetidine

A variety of procedures are described in the literature for the methylation of alcohols. Unfortunately, 1-t-butyl-2-hydroxymethyl-azetidine is easily converted to 1-t-butyl-3-methoxypyrrolidine if for example the methylation is done using sodium hydroxide under phase transfer catalysis with dimethylsulfate as the alkylating agent. We found that reaction of 1-t-butyl-2-hydroxymethylazetidine with sodium

hydride and methyl iodide, at 50°C, selectively afforded the methylated azetidine. This rapid process for methylation of alcohols has been described by Brown and Barton[133] in the case of L(+)-3-phenyl-2-butanol.



77

83%

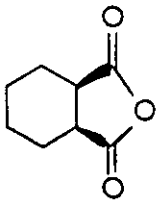
Purification was effected by silica gel column chromatography using first hexane (to remove the oil) and then diethyl ether as the eluant.

77:

^1H NMR($CDCl_3$): δ 0,95 (S; 9H, $(CH_3)_3C$); 1,86-1,96 (m; 2H, $CH_2\underline{CH_2}CH$); 3,06-3,11 (m; 2H, CH_2N); 3,29-3,46 (m; 2H, CH_2O); 3,32 (s; 3H, CH_3O); 3,54 (m; 1H, CHN)

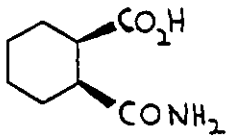
^{13}C NMR ($CDCl_3$): δ 20,31 ($CH_2\underline{CH_2}CH$); 25,18 ($(\underline{CH_3})_3C$); 43,62 (CH_2N); 52,49 (CN); 58,04 (CHN); 59,09 (CH_3O); 78,24 (CH_2O).

4.3.2.9 Synthesis of 7-Methyl-cis-7-azabicyclo[4,2,0]octane



ref. 134

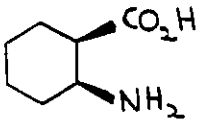
1) NH_4OH, R.T., ½ h
2) HCl



90%

ref. 134

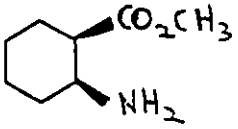
1) 6M NaOH (aq.), Br_2, 0°C, 5 mn
2) 75°C, 2 mn
3) HCl



70%

ref. 127

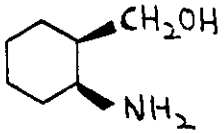
CH_3OH, H_2SO_4 96%
reflux, 18h



91%

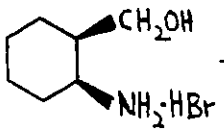
ref. 135

3 $LiAlH_4$, THF
50°C, 3h



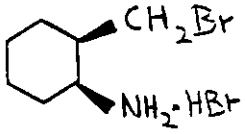
72%

benzene
HBr bubbling
20 mn



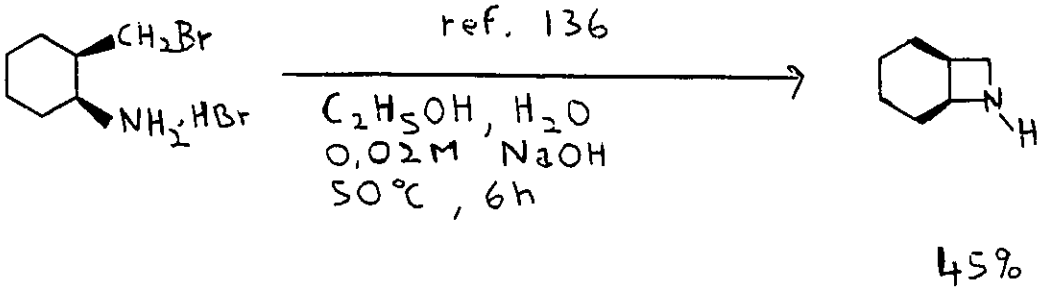
ref. 136

1) $3PBr_3$
reflux, 1h
2) H_2O
reflux, 10 mn

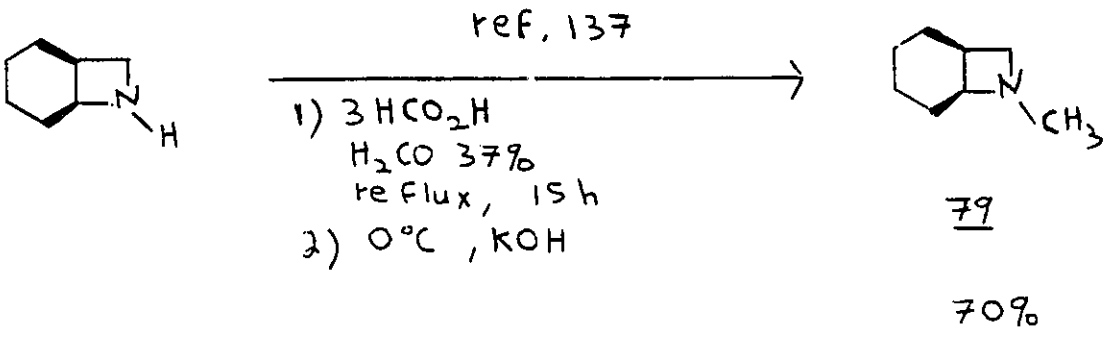


71%

The cis-7-azabicyclo[4,2,0]octane was prepared according to the literature[136] except that the reaction was run under nitrogen, in a three-necked flask equipped with a condenser and a bubbler instead of being carried out in a sealed tube.



45%



79

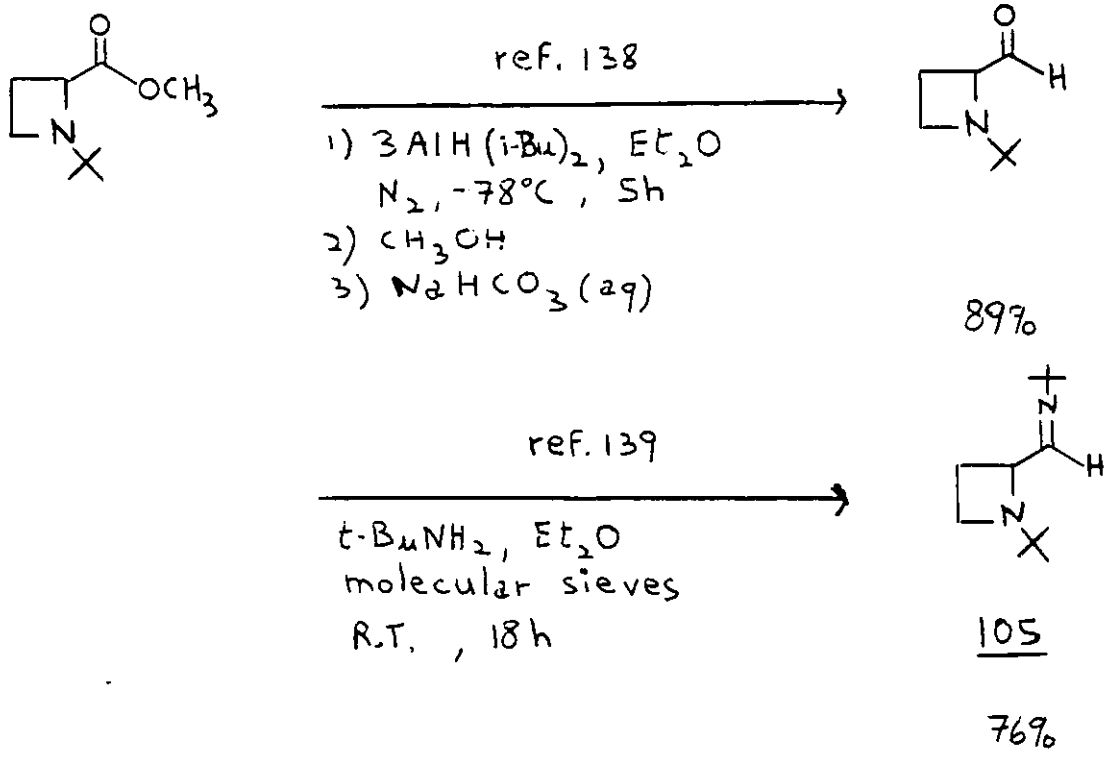
70%

79:

b.p. = 120-125°C (lit[137] b.p. = 125°C)

^{1}H NMR($CDCl_3$): δ 0,84-2,44 (m; 8H, $(C(CH_2)_4C)$; 2,24 (S; 3H, CH_3N); 2,57-3,17 (m; 3H, NCH_2CH); 3,59 (m; 1H, CHN)

4.3.2.10 Synthesis of 1-t-Butyl-2-t-butyliminylazetidine



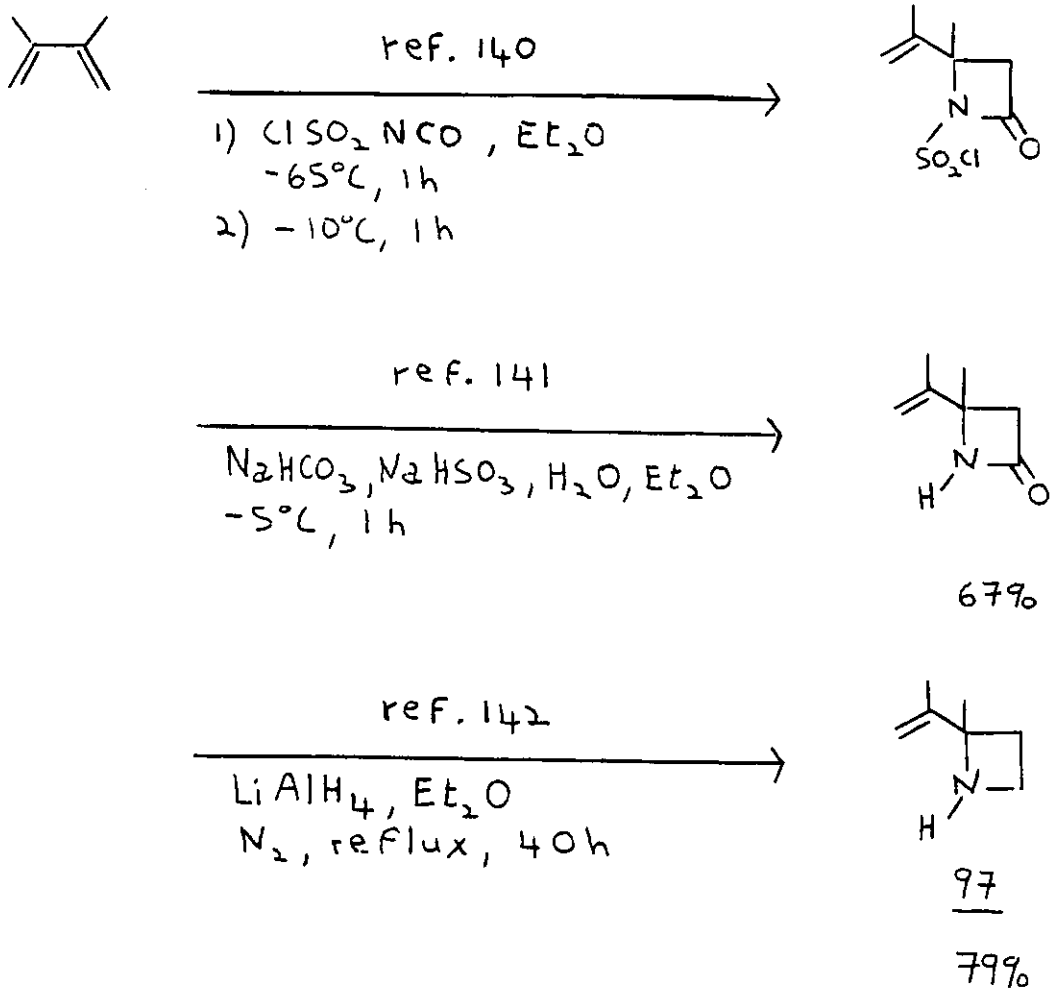
105:

b.p. = 52-54°C (0,9 mm Hg) [lit[139] b.p. = 52-54°C (0,9 mm Hg)]

^{1}H NMR($CDCl_3$): δ 0,88 (S; 9H, $(CH_3)_3C$-N); 1,08 (S; 9H, $(CH_3)_3C$-N); 1,92-2,08 (m; 2H, $CH_2\underline{CH_2}CH$); 3,02-3,20 (m; 2H, CH_2N); 3,92 (quartet, 1H, CHN); 7,56 (d; 1H, HC=N)

^{13}C NMR ($CDCl_3$): δ 20,05 ($CH_2\underline{CH_2}CH$); 24,92 ($(\underline{CH_3})_3CN$); 29,46 ($(CH_3)_3CN$=); 44,27 (CH_2N); 52,70 (C-N<); 56,45 (C-N=); 62,05 (CHN); 163,05 (C=N).

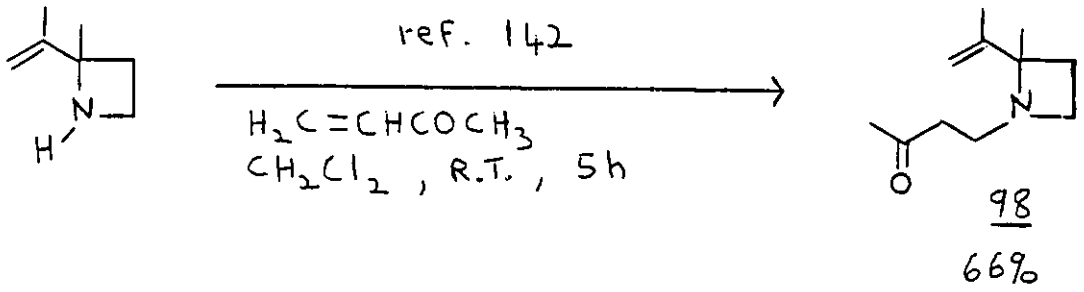
4.3.2.11 Synthesis of 2-Methyl-2-(2-propenyl)azetidine



97:

^1H NMR($CDCl_3$): δ 1,47 (S; 3H, CH_3C); 1,73 (S; 3H, $CH_3C{=}C$); 1,90-2,76 (m; 3H, $NCH_2\underline{CH_2}$ and NH); 3,03-3,76 (m; 2H, NCH_2); 4,77-4,96 (m; 2H, $H_2C{=}C$)

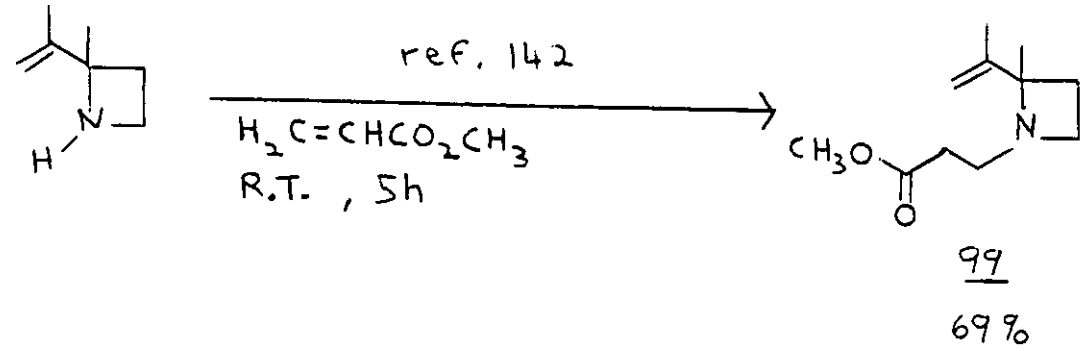
4.3.2.12 Synthesis of 1-(3-Oxobutyl)-2-methyl-2-(2-propenyl)-azetidine



98:

^1H NMR($CDCl_3$): δ 1,29 (S; 3H, CH_3C); 1,72 (S; 3H, $CH_3C=C$); 1,82-2,27 (m; 2H, $NCH_2\underline{CH_2}CCH_3$); 2,15 (S; 3H, CH_3CO); 2,30-3,13 (m; 5H, NCH_2CH_2CO and 1H of $NCH_2\underline{CH_2}CCH_3$); 3,30 (m; 1H, 1H of $N\underline{CH_2}CH_2CCH_3$); 4,70 and 4,83 (m; 2H, $H_2C=C$)

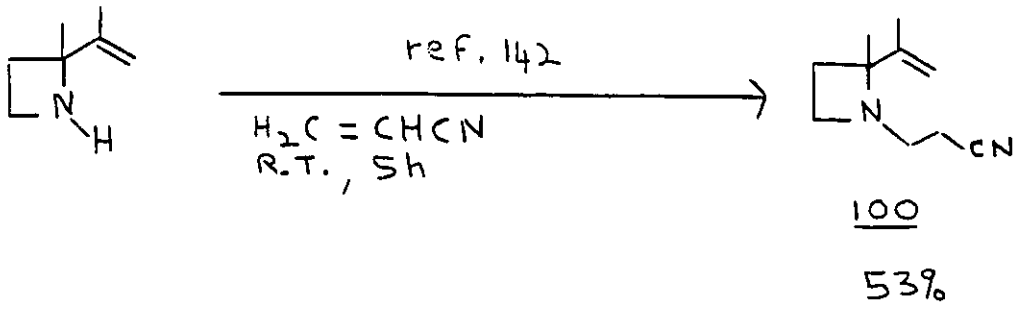
4.3.2.13 Synthesis of 1-(2-Carbomethoxyethyl)2-methyl-2-(2-propenyl) azetidine



99:

^1H NMR($CDCl_3$): δ 1,30 (S; 3H, CH_3C); 1,72 (S; 3H, $CH_3C=C$); 1,83-2,50 (m; 4H, $NCH_2\underline{CH_2}CCH_3$ and $NCH_2\underline{CH_2}CO$); 2,53-3,06 (m; 3H, 1H of $N\underline{CH_2}CH_2CCH_3$ and $N\underline{CH_2}CH_2CO$); 3,29 (m; 1H, 1H of $N\underline{CH_2}CH_2CCH_3$); 3,60 (S; 3H, OCH_3); 4,63 and 4,80 (m; 2H, $H_2C=C$).

4.3.2.14 Synthesis of 1-(2-Cyanoethyl)-2-methyl-2-(2-propenyl)azetidine



100

53%

100:

^1H NMR($CDCl_3$): δ 1,29 (S; 3H, CH_3C); 1,72 (S; 3H, $CH_3C=C$); 1,78-2,48 (m; 4H, $NCH_2\underline{CH_2}CCH_3$ and $CH_2\underline{CH_2}C\equiv N$); 2,52-3,18 (m; 3H, 1H of $N\underline{CH_2}CH_2CCH_3$) and $N\underline{CH_2}CH_2C\equiv N$); 3,41 (m; 1H, 1H of $N\underline{CH_2}CH_2CCH_3$); 4,69 and 4,88 (m; 2H, $H_2C=C$)

4.3.3 General Procedure for the Carbonylation of Azetidines under Carbon Monoxide Pressure

The azetidine (1,40 mmol), dicobalt octacarbonyl (0,048g; 0,14 mmol), dry benzene (4 ml), and a small magnetic stirring bar were placed in an autoclave containing a glass liner. The space between the glass and the lower part of the autoclave was filled with dry benzene (ca 1,5 ml). The autoclave was quickly closed, purged twice with carbon monoxide and loaded with 3,4 atm of carbon monoxide. The mixture was stirred for 24 hours at 85-90°C (oil bath temperature). After cooling to room temperature, the pressure was slowly released and the autoclave was opened. The brown homogeneous mixture was poured into a vial and allowed to stand for 6 to 12 hours in air. A mauve cobalt complex precipitated. The mixture was filtered through a small amount of Celite. The filtrate was concentrated by rotary evaporation and checked by gas chromatography. When only one product was present, it was purified from the last traces of cobalt on a small silica gel column using chloroform as eluant. A yellow cobalt complex was eluted from the column just prior to the product. When the crude mixture contained more than one product, it was purified by preparative thin layer chromatography (silica gel) using diethylether-hexane (8,5:1,5) as the developer. The products were identified by infrared, proton NMR, carbon NMR, and mass spectrometry.

4.3.3.1 Attempted Carbonylation of 1-p-Tosylazetidine

1-p-Tosylazetidine did not react under the reaction conditions of the general procedure.

4.3.3.2 Carbonylation of 1-t-Butyl-2-methylazetidine

The carbonylation of 1-t-butyl-2-methylazetidine afforded 1-t-butyl-5-methylpyrrolidin-2-one (**80**) in 83% yield.

80:

IR (benzene) ν CO: 1688 cm^{-1}

^1H NMR ($CDCl_3$): δ 1,25 (d; 3H, $\underline{CH_3}CH$); 1,46 (S; 9H, $(CH_3)_3C$); 1,60-2,70 (m; 4H, CH_2CH_2); 3,93 (m; 1H, CHN)

^{13}C NMR ($CDCl_3$): δ 21,88 ($\underline{CH_3}CH$); 27,39 ($\underline{CH_2}CH_2C{=}O$); 28,32 ($(\underline{CH_3})_3C$); 31,38 ($\underline{CH_2}C{=}O$); 53,74 (CN); 54,03 (CHN); 174,05 (C=O)

Mass spec.: m/e 155 [M]+; 140 [M-CH_3]+; 112 [M-CH_3-CO]+; 84 [tBuN$\equiv$CH]+

4.3.3.3 Carbonylation of 1-t-Butyl-2,4-dimethylazetidine

It took four days to convert all the trans-1-t-butyl-2,4-dimethyl-azetidine into trans-1-t-butyl-3,5-dimethylpyrrolidin-2-one under the usual reaction conditions (90°C).

A reaction was carried out at 120-124°C, using a 3:1 trans-cis mixture of the azetidine. The reaction was followed by gas chromatography and after 23 hours, almost all the trans-azetidine had been converted into trans-pyrrolidin-2-one. The ratio of trans-cis unreacted azetidine was 1:99. Only 61% of the cis-azetidine had been transformed into cis-pyrrolidin-2-one. The reaction was complete after 40 hours.

Purification by chromatography afforded 88% of pyrrolidin-2-one (81, trans-cis=3:1).

81 trans:

IR (benzene) ν CO: 1680 cm^{-1}

'H NMR ($CDCl_3$): δ 1,24 (d; J = 7,4Hz, 3H, $\underline{CH_3}CHCO$); 1,30 (d; J = 6,3Hz, 3H, $\underline{CH_3}CHN$); 1,41 (S; 9H, $(CH_3)_3C$); 1,69 (m; 1H, 1H of CH_2): 2,33-2,40 (m; 2H, CHCO and 1H of CH_2) 3,85 (m; 1H, CHN)

^{13}C NMR ($CDCl_3$): δ 19,20 ($\underline{CH_3}CHCO$); 26,06 ($\underline{CH_3}CHN$); 28,33 ($(\underline{CH_3})_3C$); 34,24 (CH_2); 37,35 ($\underline{C}HCO$); 52,88 (CHN); 53,90 (CN); 177,23 (CO)

Mass spec.: m/e 169 [M]+; 154 [M-CH_3]+; 126 [M-CH_3-CO]+; 98 [tBuN≡CCH_3]+

81 cis:

IR (benzene) ν CO: 1683 cm^{-1}

'H NMR ($CDCl_3$): δ 1,12 (d; J = 7,0Hz, 3H, $\underline{CH_3}CHCO$); 1,21 (d; J = 5,9Hz, 3H, $\underline{CH_3}CHN$); 1,40 (S; 9H, $(CH_3)_3C$); 1,60-1,84 (m; 2H, CH_2); 2,54 (m; 1H, CHCO); 3,80 (m; 1H, CHN)

Mass spec.: m/e 169 [M]+; 154 [M-CH_3]+; 126 [M-CH_3-CO]+; 98 [tBuN≡CCH_3]+

4.3.3.4 Carbonylation of 1-Methyl-2-phenylazetidine

1-Methyl-2-phenylazetidine was converted into 1-methyl-3-phenyl-pyrrolidin-2-one (94%) and 1-methyl-5-phenylpyrrolidin-2-one (6%) (GC ratio). Purification by silica gel plate chromatography afforded 90% of the 1-methyl-3-phenylpyrrolidin-2-one (**82**) and traces of the other isomer (**83**).

82:

m.p. = 58-59°C (lit m.p. = 58-59°C)[148]

IR (benzene): ν CO: 1698 cm^{-1}

^1H NMR ($CDCl_3$): δ 2,09 (m; 1H, 1H of $\underline{CH_2}CH_2N$); 2,46 (m; 1H, 1H of $\underline{CH_2}CH_2N$); 2,91 (S; 3H, CH_3N); 3,37-3,47 (m; 2H, CH_2N); 3,62 (t; J = 8,8Hz; 1H, CHCO); 7,18-7,33 (m; 5H, C_6H_5).

^{13}C NMR ($CDCl_3$): δ 28,04 (CH_3N); 30,16 ($\underline{CH_2}CH_2N$); 47,72 ($\underline{CH}CO$); 48,05 (CH_2N); 126,81, 127,78, 128,57, and 139,91 (C_6H_5); 172,65 (CO)

Mass spec.: m/e 175 [M]+; 118 [M-CH_3NCO]+; 98 [M-C_6H_5]+

83:

IR (benzene) ν CO: 1700 cm^{-1}

^1H NMR ($CDCl_3$): δ 2,43-2,77 (m; 4H, CH_2CH_2); 2,66 (S; 3H, CH_3N); 4,49 (m; 1H, CHN); 7,16-7,33 (m; 5H, C_6H_5).

Mass spec.: m/e 175 [M]+; 118 [M-CH_3NCO]+; 98 [M-C_6H_5]+

4.3.3.5 Carbonylation of 1-t-Butyl-2-methoxycarbonylazetidine

The carbonylation of 1-t-butyl-2-methoxycarbonylazetidine at 90°C afforded 81% of 1-t-butyl-5-methoxycarbonylpyrrolidin-2-one (**84**), traces of 1-t-butyl-3-methoxycarbonylpyrrolidin-2-one (**85**), and 1-t-butyl-6,6-dimethoxycarbonyl-1,2,5,6,7,8-hexahydroazocin-2-one (**86**) in 6% yield.

84:

m.p. = 82-83°C

IR (benzene): ν CO: 1695 cm^{-1} (N-C=O); 1740 cm^{-1} (O-C=O)

^1H NMR ($CDCl_3$): δ 1,37 (S; 9H, $(CH_3)_3C$); 1,93 (m; 1H, 1H of $\underline{CH_2}CH$);

2,17-2,31 (m; 2H, 1H of $\underline{CH_2}CH$ and 1H of CH_2CO); 2,54 (m; 1H, 1H of CH_2CO); 3,75 (S; 3H, OCH_3); 4,35 (m; 1H, CH); these assignments were confirmed by a COSY spectrum.

^{13}C NMR ($CDCl_3$): δ 17,60 ($\underline{CH_2}CH$); 21,25 (($\underline{CH_3}$)$_3$C); 24,70 ($\underline{CH_2}CO$); 45,78 (OCH_3); 48,13 (CN); 53,10 (CH); 167,31 (CO); 168,76 (CO)

Mass spec.: m/e 199 [M]+; 184 [M-CH_3]+; 140 [M-CH_3-CO_2]+; 84 [tBuN≡CH]+

Elemental Analysis: calculated C 60,28 H 8,60 N 7,03

found 60,16 8,90 7,03

85:

IR (benzene): ν CO: 1695 cm^{-1} (N-C=O); 1740 cm^{-1} (O-C=O)

^1H NMR ($CDCl_3$): δ 1,38 (S; 9H, (CH_3)$_3$C); 2,13 (m; 1H, 1H of $\underline{CH_2}CH_2N$); 2,29 (m; 1H, 1H of $\underline{CH_2}CH_2N$); 3,35-3,43 (m; 2H, CH_2N); 3,55 (m; 1H, CH); 3,75 (S; 3H, OCH_3)

^{13}C NMR ($CDCl_3$): δ 22,20 ($\underline{CH_2}CH_2N$); 27,64, (($\underline{CH_3}$)$_3$C); 44,32 (CH_2N); 50,17 (CH); 52,51 (OCH_3); 54,60 (CN); 169,69 (CO); 170,86 (CO)

Mass spec.: m/e 199 [M]+; 184 [M-CH_3]+; 168 [M-OCH_3]+; 140 [M-CH_3-CO_2]+; 84 [tBuN ≡ CH]+

86:

IR ($CHCl_3$): ν CO: 1687 cm^{-1} (N-C=O); 1723 cm^{-1} with shoulder at 1738 cm^{-1} (O-C=O)

^1H NMR ($CDCl_3$): δ 1,37 (S; 9H, (CH_3)$_3$C); 1,86 (m; 1H, 1H of $\underline{CH_2}CH_2N$); 2,34 (m; 1H, 1H of $\underline{CH_2}CH_2N$); 2,59 (m; 1H, 1H of $\underline{CH_2}CH$=CH); 2,86 (m; 1H, 1H of $\underline{CH_2}CH$=CH); 3,35 (m; 1H, 1H of $CH_2\underline{CH_2}N$); 3,49 (m; 1H, 1H of $CH_2\underline{CH_2}N$); 3,70 (S; 3H, OCH_3); 3,72 (S; 3H, OCH_3); 5,90 (d of t, J = 15,6 and J' = 1,4Hz; $CH_2\underline{CH}$ = CH); 6,82 (m; 1H, $CH_2\underline{CH}$=CH); these assignments were confirmed by a COSY spectrum.

^{13}C NMR ($CDCl_3$): δ 27,35 ($\underline{CH_2}CH_2N$); 25,50 (($\underline{CH_3}$)$_3$C); 36,75 ($\underline{CH_2}CH{=}CH$); 43,32 (CH_2N); 51,57 and 52,83 ($2CH_3O$); 54,74 (quaternary carbon); 56,31 (quaternary carbon); 124,56 ($CH_2CH{=}\underline{CH}$); 143,71 ($CH_2\underline{CH}{=}CH$); 166,26 (NC=O); 170,96 (OC=O); 171,63 (OC=O); these assignments were confirmed by a HETCOR spectrum

Mass spec.: m/e 297 [M]+; 282 [M-CH_3]+; 266 [M-OCH_3]+

4.3.3.6 Carbonylation of 1-t-Butyl-2-hydroxymethylazetidine

1-t-Butyl-5-hydroxymethylpyrrolidin-2-one (87) was isolated in 88% yield.

87:

m.p. = 86-87°C

IR (benzene): ν 1662 cm^{-1} (C=O with intermolecular hydrogen bonding)
1687 cm^{-1} (C=O free)
3200-3500 cm^{-1} (OH with intermolecular hydrogen bonding)
3600 cm^{-1} (OH free)

When the solution is more dilute, the absorptions at 1687 and 3600 cm^{-1} become more intense, showing that there is less hydrogen bonding.

^1H NMR ($CDCl_3$): δ 1,42 (S; 9H, (CH_3)$_3$C); 1,65 (t; 1H, OH); 1,96-2,05 (m; 2H, $CH_2\underline{CH_2}CH$); 2,22 (m; 1H, 1H of CH_2CO); 2,52 (m; 1H, 1H of CH_2CO); 3,58-3,77 (m; 2H, CH_2O); 3,84 (m; 1H, CHN)

^{13}C NMR ($CDCl_3$): δ 22,80 ($CH_2\underline{CH_2}CH$); 28,42, (($\underline{CH_3}$)$_3$C); 31,80 ($\underline{CH_2}CO$); 54,13 (CN); 59,77 (CHN); 64,22 (CH_2O); 175,86 (CO)

Mass spec.: m/e 171 [M]+; 140 [M-CH_2OH]+; 84 [tBuN $\equiv$ CH]+

Elemental Analysis: calculated C 63,13 H 10,01 N 8,18

found 62,79 10,46 8,34

4.3.3.7 Carbonylation of 1-t-Butyl-2-acetoxymethylazetidine

The carbonylation reaction afforded 91% of 1-t-butyl-5-acetoxymethylpyrrolidin-2-one (89)

89:

IR (benzene): ν CO: 1690 cm^{-1} (N-C=O); 1745 cm^{-1} (O-C=O)

^1H NMR ($CDCl_3$): δ 1,42 (S; 9H, $(CH_3)_3C$); 1,88-2,10 (m; 2H, $CH_2\underline{CH_2}CH$); 2,07 (S; 3H, CH_3CO); 2,23 (m; 1H, 1H of CH_2CO); 2,49 (m; 1H, 1H of CH_2CO); 3,95-4,21 (m; 3H, CH_2O and CHN)

^{13}C NMR ($CDCl_3$): δ 20,91 ($\underline{CH_3}CO$); 23,17, ($CH_2\underline{CH_2}CH$); 28,35 (($\underline{CH_3}$)$_3$C); 31,44 ($\underline{CH_2}CO$); 54,18 (CN); 56,48 (CHN); 65,40 (CH_2O); 170,51 (OCO); 175,06 (NCO)

Mass spec.: m/e 198 $[M-CH_3]^+$; 140 $[M-CH_2OCCH_3]^+$; 84 $[tBuN\equiv CH]^+$

4.3.3.8 Carbonylation of 1-t-Butyl-2-methoxymethylazetidine

1-t-Butyl-5-methoxymethylpyrrolidin-2-one (**88**) was obtained in 91% yield.

88:

IR (benzene): ν CO: 1687 cm^{-1}

^1H NMR ($CDCl_3$): δ 1,41 (S; 9H, $(CH_3)_3C$); 1,90-2,00 (m; 2H, $CH_2\underline{CH_2}CH$); 2,18 (m; 1H, 1H of CH_2CO); 2,48 (m; 1H, 1H of CH_2CO); 3,30 (d of d; J =

7,1 and 9,4Hz; 1H, 1H of CH_2O); 3,34 (S; 3H, CH_3O); 3,44 (d of d; J= 3,3 and 9,4Hz, 1H, 1H of CH_2O); 3,86 (m; 1H, CHN); the assignments were confirmed by a COSY spectrum.

^{13}C NMR ($CDCl_3$): δ 23,31 ($CH_2\underline{CH_2}CH$); 28,40 ($(\underline{CH_3})_3C$); 31,69 ($\underline{CH_2}CO$); 53,99 (CN); 57,77 (CHN); 59,18 (CH_3O); 74,59 (CH_2O); 175,42 (CO)

Mass spec.: m/e 185 [M]+; 170 [M-CH_3]+; 140 [M-CH_2OCH_3]+; 84 [tBuN≡CH]+

4.3.3.9 Carbonylation of 7-Methyl-cis-7-azabicyclo[4,2,0]octane

The carbonylation reaction gave 76% of 7-methyl-cis-7-azabicyclo[4,3,0]nonan-8-one (**90**). This compound was not very stable.

90:

IR (benzene): ν CO: 1695 cm^{-1}

^1H NMR ($CDCl_3$): δ 1,23-1,73 (m; 8H,-$(CH_2)_4$-); 2,09 (m; 1H, $CH_2\underline{CH}CH_2$); 2,30 (m; 2H, CH_2CO); 2,78 (S; 3H, NCH_3); 3,44 (m; 1H, CHN)

^{13}C NMR ($CDCl_3$): δ 20,99; 22,75; 26,91; 27,51 (methylene carbons of cyclohexane ring); 27,09 (CH_3N); 32,23 ($CH_2\underline{CH}CH_2$; 37,71 ($\underline{CH_2}CO$); 58,66 (CHN)

Mass spec.: m/e 153 [M]+

4.3.4 Variation in Reaction Conditions

The effect of several parameters was studied by running reactions according to the usual procedure (4.3.3) which had been modified some-

what. Decane was used as internal standard in order to follow the reactions by gas chromatography.

4.3.4.1 Carbonylation under 1 Atm of Carbon Monoxide

The azetidines were carbonylated to pyrrolidin-2-ones using a catalytic amount of dicobalt octacarbonyl. The reactions were run as usual, at 90°C with stirring for 24 hours. However dry toluene was used instead of benzene and the solution was twice as dilute. It was important that CO bubbling through the solution is very slow in order to avoid loss of the solvent, of decane and of the azetidines. After 24 hours, the reaction mixtures were not brown but pale yellow and a black precipitate was present.

Carbonylation of 1-t-Butyl-2-methylazetidine

A significant amount of the azetidine was lost when carbon monoxide was bubbled through the solution during the reaction (followed by GC). Indeed, 1-t-butyl-2-methylazetidine is quite volatile. For this reason, carbon monoxide was bubbled through the solution for only five minutes at the beginning of the reaction. Then it was entered on the top of the condenser in order to maintain an atmosphere of carbon monoxide. After 3 and 6 hours the percentage of conversion of the azetidine was respectively 26% and 46%. After 22 hours the reaction was complete. Chromatography on a small silica gel column afforded 95% of the 1-t-butyl-5-methylpyrrolidin-2-one.

Carbonylation of Trans-1-t-Butyl-2,4-dimethylazetidine

This carbonylation was carried out as described for 1-t-butyl-2-methylazetidine. Only 20% of the trans-1-t-butyl-3,5-dimethylpyrrolidin-2-one was obtained after 24 hours. Similar results were achieved after 48 or 96 hours.

Carbonylation of 1-Methyl-2-phenylazetidine

42% of 1-methyl-3-phenylpyrrolidin-2-one and 3% of 1-methyl-5-phenylpyrrolidin-2-one were obtained after 24 hours, according to gas chromatography. The rest was unreacted azetidine. After 2 days the results were similar.

Carbonylation of 1-t-Butyl-2-methoxycarbonylazetidine

The reaction was followed by gas chromatography. After 16 hours, 33% of the azetidine had been converted into 1-t-butyl-5-methoxycarbonylpyrrolidin-2-one. There was still 67% of unreacted azetidine after 90 hours. 1-t-Butyl-6,6-dimethoxycarbonyl-1,2,5,6,7,8-hexahydroazocin-2-one was not observed.

4.3.5 Study of the Influence of Several Parameters on the Ratio of 1-t-Butyl-3-and-5-methoxycarbonylpyrrolidin-2-ones

The influence of the concentration, temperature, solvent, the quantity of $Co_2(CO)_8$, the presence of $Ru_3(CO)_{12}$ and of diphenylacetylene was studied.

4.3.6 Attempts to Effect Enantioselective Carbonylation of 1-Methyl-2-phenylazetidine

A mixture of 1-methyl-2-phenylazetidine (0,201g; 1,37 mmol), 2S,3S(-)bis(diphenylphosphino)butane (0,057g; 0,13 mmol; Digital Specialty Chemicals), dicobalt octacarbonyl (0,046g; 0,13 mmol), and benzene (4 ml) was stirred under 27 atm of carbon monoxide at 97°C. After 3 hours the reaction was stopped, and preparative thin layer chromatography afforded 50% of 1-methyl-3-phenylpyrrolidin-2-one along with recovered azetidine. The product was racemic. The same reaction, carried out at 75°C and under 7 atm of carbon monoxide, afforded 42% of racemic 1-methyl-3-phenylpyrrolidin-2-one after 48 hours. The reaction was repeated using twice the amount of the phosphine (2:1 ratio of 2,3-bis(diphenylphosphino)butane: $Co_2(CO)_8$), and 7 atm of carbon monoxide. No reaction occurred even at 110°C.

A reaction was also effected in the presence of l-menthol (10:10:1 ratio of azetidine:l-menthol:dicobalt octacarbonyl). After 24 hours at 85°C and under 7 atm of carbon monoxide, 31% of racemic 1-methyl-3-phenylpyrrolidin-2-one was obtained along with recovered azetidine.

4.3.7 Procedure for the Carbonylation of 2-Methyl-2-(2-propenyl)azetidines

A mixture of the azetidine (0,61 mmol), dicobalt octacarbonyl (0,022g; 0,061 mmol) and dry benzene (10 ml) was stirred at 80°C under 3,4 atm of carbon monoxide. The reaction was followed by gas chromatography. When it was complete, work-up was effected as described in 4.3.3.

4.3.7.1 Carbonylation of 2-Methyl-2-(2-propenyl)azetidine

The azetidine was carbonylated following procedure 4.3.7 and 52% of 4,5-dimethyl-1,2,6,7-tetrahydro-3H-azepin-2-one (**101**) was isolated after 24 hours.

101:

m.p. = 109-111°C

IR (benzene); νCO: 1675 cm^{-1}

^1H NMR ($CDCl_3$): δ 1,62 and 1,76 (2S; 6H, $2CH_3$); 2,23 (m; 2H, $\underline{CH_2}CH_2N$); 3,18 (S; 2H, $CH_2C{=}O$); 3,38 (q; J = 6,1Hz; 2H, CH_2N); 5,85 (broad S; 1H, NH)

^{13}C NMR ($CDCl_3$): δ 21,10 and 22,90 ($2CH_3$); 36,77 ($\underline{CH_2}CH_2N$); 39,80 ($\underline{CH_2}C{=}O$); 41,79 (CH_2N); 120,55 and 127,55 (C=C); 175,38 (NC=O)

Mass spec.: m/e 139 [M]+; 124 [M-CH_3]+

4.3.7.2 Carbonylation of 1-(3-oxobutyl)-2-methyl-2-(2-propenyl)azetidine

This carbonylation reaction was conducted as described in 4.3.7 except that the temperature was 50°C instead of 80°C. 1-(3-Oxobutyl)-4,5-dimethyl-1,2,6,7-tetrahydro-3H-azepin-2-one (**102**) was isolated in 54% of yield, after 24 hours.

102:

m.p. = 114-115°C

IR (benzene); ν CO: 1658 cm^{-1} (NC=O); 1718 cm^{-1} ($C_2C{=}O$)

^1H NMR ($CDCl_3$): δ 1,58 and 1,72 (2S; 6H, $CH_3C{=}CCH_3$); 2,14 (S; 3H, $CH_3C{=}O$); 2,18 (m; 2H, $C{=}C\underline{CH_2}CH_2N$); 2,74 (t; J = 6,6Hz; 2H, $NCH_2\underline{CH_2}CO$);

3,17 (S; 2H, $C{=}CCH_2CO$); 3,54 (t, J = 5,9Hz; 2H, $C{=}CCH_2\underline{CH_2}N$); 3,58 (t, J = 6,6Hz; 2H, $NCH_2\underline{CH_2}CO$)

^{13}C NMR ($CDCl_3$): 20,87 and 22,84 ($\underline{CH_3}C{=}C\underline{CH_3}$); 30,26 ($\underline{CH_3}CO$); 35,58 ($C{=}C\underline{CH_2}CH_2N$); 42,61, 42,68 and 42,77 ($3CH_2$); 47,49 ($C{=}CCH_2\underline{CH_2}N$); 121,00 and 126,95 (C=C); 172,88 (NCO); 207,32 ($C_2\underline{C}O$)

Mass spec.: m/e 209 [M]+; 194 [M-CH_3]+

4.3.7.3 Carbonylation of 1-(2-Carbomethoxyethyl)-2-methyl-2-(2-propenyl)azetidine

When the reaction was carried out as described in procedure 4.3.7, 83% of 1-(2-carbomethoxyethyl)-4,5-dimethyl-1,2,6,7-tetrahydro-3H-azepin-2-one was isolated, after 24 hours. Only 60% of the 3H-azepin-2-one (**103**) was obtained when the reaction was run at 50°C instead of 80°C.

103:

IR (benzene): ν CO: 1658 cm^{-1} (NC=O); 1740 cm^{-1} (OC=O)

^1H NMR ($CDCl_3$): δ 1,58 and 1,72 (2S; 6H, $CH_3C{=}CCH_3$); 2,19 (m; 2H, $C{=}C\underline{CH_2}CH_2N$); 2,59 (t; J = 6,8Hz; 2H, CH_2CO_2); 3,20 (S; 2H, $C{=}CCH_2CO$); 3,54 (t, J = 5,9Hz; 2H, $C{=}CCH_2\underline{CH_2}N$); 3,64 (t, J = 6,8Hz; 2H, $\underline{CH_2}CH_2CO_2$); 3,66 (S; 3H, CH_3O)

^{13}C NMR ($CDCl_3$): δ 20,85 and 22,83 ($\underline{CH_3}C{=}C\underline{CH_3}$); 33,47 ($\underline{CH_2}CO_2$); 35,54 ($C{=}C\underline{CH_2}CH_2N$); 42,55 and 43,39 ($2CH_2$); 47,29 ($C{=}CCH_2\underline{CH_2}N$); 51,75 ($CH_3O$); 120,99 and 126,92 (C=C); 172,36 and 172,96 (2CO)

Mass spec.: m/e 225 [M]+; 210 [M-CH_3]+; 166 [M-CH_3-CO_2]+

4.3.7.4 Carbonylation of 1-(2-Cyanoethyl)-2-methyl-2-(2-propenyl)-azetidine

86% of 1-(2-cyanoethyl)-4,5-dimethyl-1,2,6,7-tetrahydro-3H-azepin-2-one (**104**) was obtained after 72 hours using the procedure described in 4.3.7.

104:

m.p. = 54°C-55°C

IR (benzene): ν CO: 1660 cm^{-1}

^1H NMR ($CDCl_3$): δ 1,61 and 1,74 (2S; 6H, $2CH_3$); 2,28 (m; 2H, $C{=}C\underline{CH_2}CH_2N$); 2,63 (t, J = 6,4Hz; 2H, CH_2CN); 3,23 (S; 2H, CH_2CO); 3,62 (t, J = 6,4Hz; 2H, $\underline{CH_2}CH_2CN$); 3,63 (t, J = 5,9Hz; 2H, $C{=}C\underline{CH_2}\underline{CH_2}N$)

^{13}C NMR ($CDCl_3$): δ 17,32 ($\underline{CH_2}CN$); 20,87 and 22,87 ($2CH_3$); 35,48 ($C{=}C\underline{CH_2}CH_2N$); 42,39 ($\underline{CH_2}CO$); 44,10 ($N\underline{CH_2}CH_2CN$); 47,92 ($CH_2N$); 118,40 ($C{\equiv}N$); 120,80 and 127,05 (C=C); 173,11 (C=O)

Mass spec.: m/e 192 [M]+; 177 [M-CH_3]+

Elemental analysis:				
calculated	C 68,72	H 8,39	N 14,57
found	68,29	8,64	14,30

4.3.8 Variation in Azetidine Concentration

The effect of concentration was studied using 1-(3-oxobutyl)-2-methyl-2-(2-propenyl)azetidine as the starting material. When the concentration of the azetidine was higher than 0,06M the yield of the 3H-azepin-2-one derivative was lower, probably due to polymerization of the azetidine. For example, a reaction was carried out at 50°C using a 0,19M solution of azetidine. Gas chromatography showed that all the azetidine reacted after 24 hours. The only product detected in the solution was the 3H-azepin-2-one derivative, obtained in 5% yield. A

dark brown precipitate was also formed during the reaction, which was insoluble in chloroform, methylenechloride, and methanol. Similarly a reaction conducted as described in procedure 4.3.3, using a 0,35M solution of azetidine, afforded only traces of 1-(3-oxobutyl)-4,5-dimethyl-1,2,6,7-tetrahydro-3H-azepin-2-one.

4.3.9 Carbonylation of 1-t-Butyl-2-t-butyliminylazetidine

A solution of 1-t-butyl-2-t-butyliminylazetidine (0,10g; 0,51 mmol), dicobalt octacarbonyl (0,018g; 0,052 mmol) and dry benzene (8,5 ml) was stirred at 80°C under 10 atm of carbon monoxide for 24 hours. Gas chromatography indicated complete reaction and the formation of two products. The GC ratio of the two products, without correction factor was 5:1. An infrared spectrum showed two carbonyl bands, one more intense at 1672 cm^{-1} and the other at 1691 cm^{-1}. Precautions had to be taken during the work-up as the major product decomposes rapidly on silica gel as well as in air at room temperature. That product decomposes quite rapidly even in the freezer under nitrogen. For example, 44% of the major product decomposed when the crude solution was kept in the freezer for 24 hours. It was really unexpected since this product is stable at 80°C under 10 atm of carbon monoxide. At the end of the reaction the solvent was removed by rotary evaporation and the crude residue was rapidly chromatographed on an alumina plate using diethyl-ether-hexane (3:2) as developer. A mixture was obtained consisting of 12 mg of the major product along with 3 mg of the impure minor product. Several attempts to obtain pure products failed due to the decomposition of the major product and the hydrolysis of the minor product. The major

product was identified as being 1,3-di-t-butyl-2,3,6,7-tetrahydro-1H-1,3-diazepin-2-one (**106**) while the minor product was 1-t-butyl-3 or 5-t-butyliminylpyrrolidin-2-one (**107** or **108**).

106:

isolated yield: 11% (not completely pure)

IR (benzene): ν CO: 1672 cm^{-1}

^1H NMR ($CDCl_3$): δ 1,37 and 1,39 (2S; $2(CH_3C)$; 2,56 (t; 1H, 1H of $\underline{CH_2}CH_2N$)); 2,69 (t; 1H, 1H of $\underline{CH_2}CH_2N$); 3,36 (t; 1H, 1H of $CH_2\underline{CH_2}N$); 3,44 (t, 1H, 1H of $CH_2\underline{CH_2}N$); 6,42 (d, J=13Hz; 1H, HC=$\underline{CH}$N); 7,07 (d of t, J=13Hz, J'=2,2Hz; 1H, $\underline{HC}$=CHN); in the ^1H NMR there was also a lot of peaks between 0,96 and 2,25 ppm including two singlets (δ 1,19 and 1,22) corresponding to $(CH_3)_3CN$ of decomposition products; there was no iminyl hydrogen ($\underline{H}$C=N).

Mass spec.: m/e 224 [M]+; 209 [M-CH_3]+

107 or **108:**

isolated yield: 3% (not pure)

IR (benzene): ν CO: 1691 cm^{-1}

'H NMR ($CDCl_3$): it was hard to analyse because of the impurity of the product. However, HC=N was at 7,55 ppm (d, 1H). The hydrogens of t-buNCO gave a singlet at 1,37 pm while those of t-buN=C could be between 1,16 and 1,21 ppm (there was four singlets in this region).

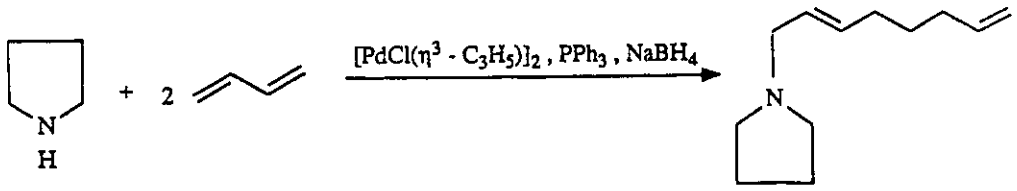
GC. Mass spec.: m/e 224 [M]+; 140 [M-HCNC$(CH_3)_3$]+; 84 [HCNC$(CH_3)_3$]+

Chapter 5

Carbonylation of Pyrrolidines

5.1 Introduction

Because pyrrolidines are not strained ring heterocycles, they do not undergo ring cleavage reactions like diaziridines and azetidines. Their organic chemistry resembles that of diethylamine. They are dehydrogenated, for example when heated with palladium on carbon, to give the corresponding pyrroles[161]. Pyrrolidine telomerizes butadiene in the presence of palladium complexes[162].

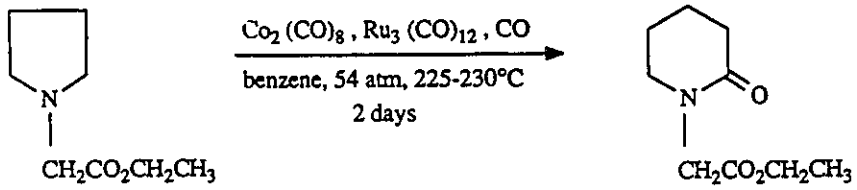


Although pyrrolidines are not strained, they can, in principle, experience carbonylation and ring expansion to give piperidin-2-ones. The results described below demonstrate the viability of this process, as well as a novel rearrangement reaction when appropriately substituted pyrrolidines are employed as reactants.

5.2 Results and Discussion

An investigation was undertaken of the carbonylation of various pyrrolidines in the presence of cobalt, ruthenium and rhodium complexes as catalysts.

Initially, ethyl 1-pyrrolidine acetate **(113)** was used as a model substrate. Good reaction conditions were found to carbonylate this pyrrolidine with ring expansion. Indeed, 59% of ethyl 1-piperidin-2-one acetate **(114)** was isolated when the pyrrolidine (1,10 mmol) was treated with dicobalt octacarbonyl (0,28 mmol) and triruthenium dodecacarbonyl (0,14 mmol), in dry benzene (10 ml). The reaction was carried out at 225-230°C under 54 atm of carbon monoxide. It was important to use vigorous stirring and to control the temperature during the reaction.



113 114

In this reaction, the concentration of reactant should not be too high, otherwise side reactions occur leading to lower yields of piperidin-2-one. This was the case, for example, when a 0,42M pyrrolidine solution was used. Suitable concentrations of **113** were 0,11M and 0,053M. The concentration of 0,11M of **113** was chosen for the best reaction conditions since it requires less benzene.

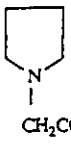
A high carbon monoxide pressure was necessary in order to have a fair yield of piperidin-2-one. For example, the effect of the pressure

was studied at 250-255°C, using a 4:1 ratio of pyrrolidine:dicobalt octacarbonyl with no triruthenium dodecacarbonyl. The concentration of pyrrolidine was 0,11M. The percentage of conversion of pyrrolidine were respectively 30%, 89% and 100% while the corresponding yields of piperidin-2-one were 0%, 1,2% and 36% after one day under 3,4, 20 and 54 atm of carbon monoxide. Under 75 atm the same results were obtained as with 54 atm. A similar trend was observed at 225-230°C, using a 4:1:0,5 ratio of pyrrolidine:dicobalt octacarbonyl:triruthenium dodecacarbonyl. At low pressures pyrrolidine is destroyed by some metal induced reaction (perhaps polymerization). A high pressure of carbon monoxide seems to be indispensable for the life of the catalyst inducing piperidin-2-one formation, at the high temperatures used. Pressures of 54 atm or more afforded fair yields of piperidin-2-one.

Ethyl 1-piperidin-2-one acetate was not obtained at 140°C. The carbonylation with ring expansion occurred from 195 to 255°C. At 225-230°C the reaction was slightly faster than at 195-200°C. While the reaction was even faster at 250-255°C, some of the cobalt complex decomposed to metallic cobalt. Indeed, there was a metallic mirror on the surface of the reaction glass. At such high temperatures the catalyst inducing the carbonylation with ring expansion was rapidly destroyed (in less than 24 hours).

The effect of the nature of the catalyst on the reaction of 113 was studied at 200°C, 230°C and 250°C. The most interesting results are summarized in Tables 12, 13 and 14. Without a metal complex the pyrrolidine did not react even at 250°C. Chloro(1,5-cyclooctadiene)rhodium dimer and triruthenium dodecacarbonyl are not able to afford ethyl 1-piperidin-2-one acetate. However, as can be seen in Table 12, they

Table 12: Influence of the Catalyst on the Carbonylation of Ethyl 1-Pyrrolidine Acetate at 195-200°C[a]

 : $Co_2(CO)_8$: $Ru_3(CO)_{12}$: $[Cl(1,5COD)Rh]_2$	Time day	Conversion of 113 %[b]	Yield of 114 %[b]
1 : 0 : 0 : 0	1	0	0
8 : 1 : 0 : 0	1	34	4,6
	4	67	17
4 : 1 : 0 : 0	1	43	6,7
	4	79	27
8 : 0 : 0 : 1	1	22	0
8 : 1 : 0 : 1	2	63	5
8 : 0 : 1 : 0	1	14	0
8 : 1 : 1 : 0	4	68	46
8 : 1 : 0,5 : 0	4	65	47
4 : 1 : 0,5 : 0	4	85	60

a) 54 atm of carbon monoxide; benzene solution 0,11 M of pyrrolidine.

b) percentages obtained from GC data.

Table 13: Influence of the Catalyst on the Carbonylation of Ethyl 1-Pyrrolidine Acetate at 225-230°C[a]

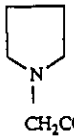
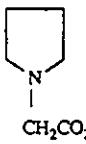
 : $Co_2(CO)_8$: $Ru_3(CO)_{12}$	Time day	Conversion of 113 %[b]	Yield of 114 %[b]
1 : 0 : 0	1	0	0
4 : 1 : 0	2	74	30
4 : 1 : 0,25	2	85	55
4 : 1 : 0,50	2	84	67

Table 14: Influence of the Catalyst on the Carbonylation of Ethyl 1-Pyrrolidine Acetate at 250-255°C[a]

 : $Co_2(CO)_8$: $Ru_3(CO)_{12}$	Time day	Conversion of 113 %[b]	Yield of 114 %[b]
1 : 0 : 0	1	0	0
8 : 1 : 0	1 2	51 87	21 21
4 : 1 : 0	1	100	36
4 : 1 : 0,5	1	100	31

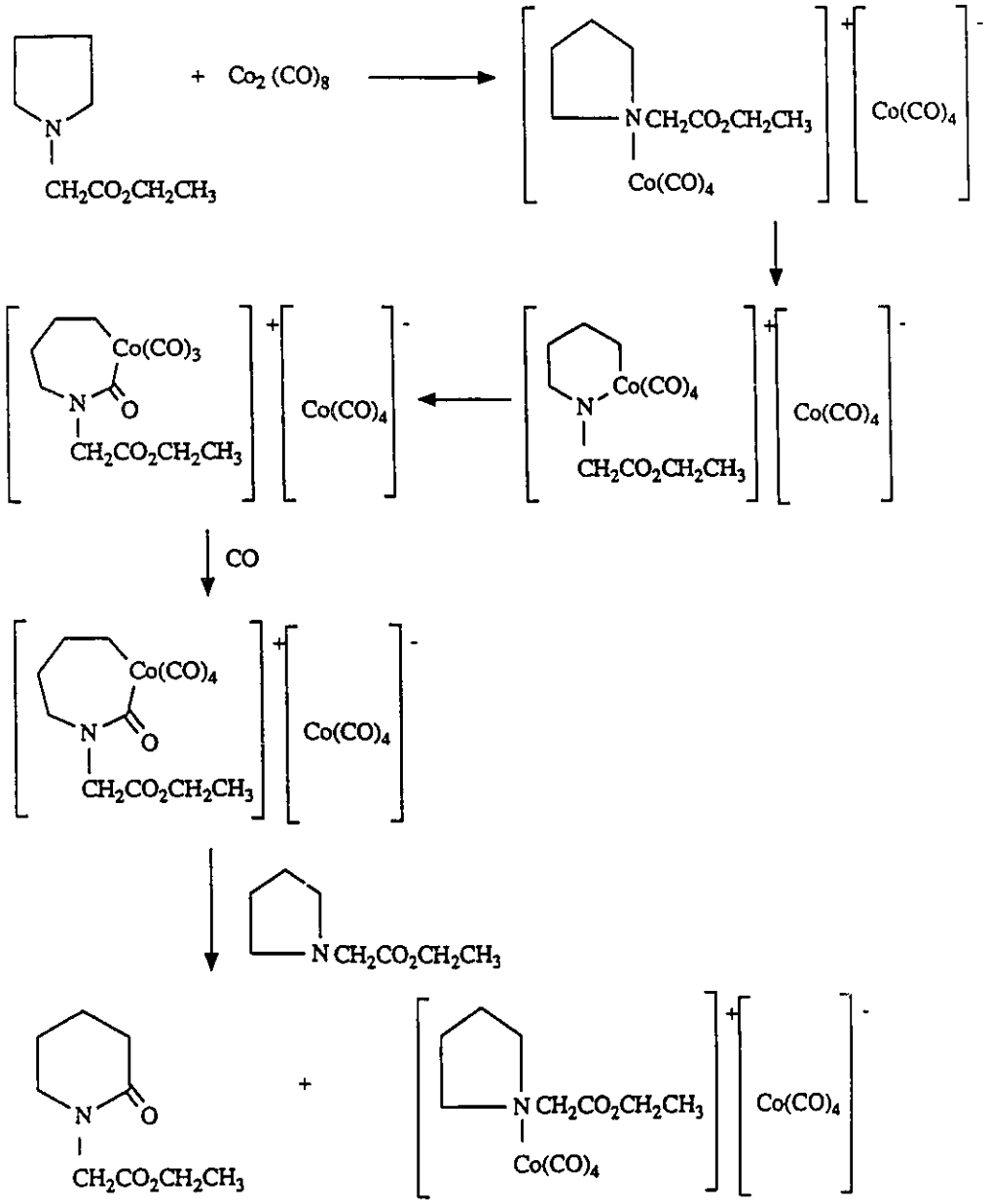
a) 54 atm of carbon monoxide; benzene solution 0,11M of pyrrolidine.

b) percentages obtained from GC data.

effect some other reaction of the pyrrolidine. Dicobalt octacarbonyl induced the conversion of the pyrrolidine into its piperidin-2-one. The use of both dicobalt octacarbonyl and triruthenium dodecacarbonyl as catalysts is superior to that of either metal complex. For example, while 17% of the piperidin-2-one (**114**) was obtained after four days at 200°C, using an 8:1 ratio of pyrrolidine:dicobalt octacarbonyl, 46% of **114** was isolated under the same reaction conditions except for the use of an 8:1:1 ratio of pyrrolidine:dicobalt octacarbonyl:triruthenium dodecacarbonyl (similar results were obtained with a ratio 8:1:0,5). These results demonstrate that a mixture of dicobalt octacarbonyl and triruthenium dodecacarbonyl is a better choice than dicobalt octacarbonyl alone. However the ratio of cobalt to ruthenium is not critical. Similar observations were made at 230°C. Indeed, use of a 4:1:0, 4:1:0,25 and 4:1:0,5 ratio afforded respectively 30%, 55% and 67% of **114** after two days. The use of a 1:0,5 ratio of dicobalt octacarbonyl:triruthenium dodecacarbonyl as catalyst afforded a slightly higher product yield than a 1:0,25 mixture. At 250°C there is no significant ruthenium effect. A 1:1 catalytic mixture of dicobalt octacarbonyl: chloro(1,5-cyclooctadiene)rhodium dimer afforded a lower yield of **114** than dicobalt octacarbonyl, at 200°C.

The dicobalt octacarbonyl induced carbonylation with ring expansion of ethyl 1-pyrrolidine acetate might be explained by a mechanism similar to the one proposed for the carbonylation of azetidines:

Scheme 5.1

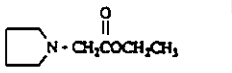
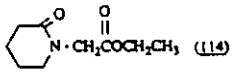
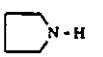
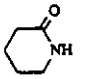
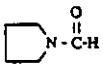
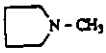
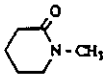
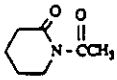
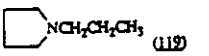
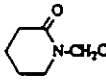
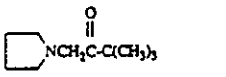
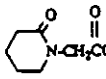
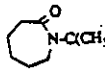
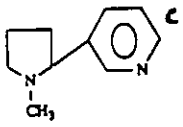
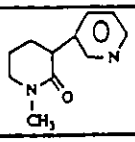
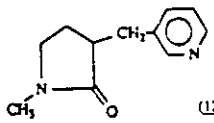


What is the role of triruthenium dodecacarbonyl which, alone, does not catalyse the carbonylation of **113**? It may be that $Ru_3(CO)_{12}$ forms a new complex with dicobalt octacarbonyl which is a more active catalyst than dicobalt octacarbonyl? It is also conceivable that $Ru_3(CO)_{12}$ prevents the decomposition of some cobalt complex. Finally $Ru_3(CO)_{12}$ may assist, in some way, one of the steps leading to the formation of a piperidin-2-one. For now, the only certainty is that the bimetallic system allows one to obtain better yields of ethyl piperidin-2-one acetate. It should be noted that this is not the first time that a mixture of dicobalt octacarbonyl and triruthenium dodecacarbonyl is found to be superior to either the cobalt or the ruthenium complex alone. Indeed, this behaviour has been observed, for example, during the carbonylation with ring expansion of oxetanes[163].

A study of the behaviour of other pyrrolidines was made, and the results are listed in Table 15.

Pyrrolidine afforded only traces of piperidin-2-one (**115**). It was converted almost exclusively into 1-formylpyrrolidine (**116**). The carbonylation of the nitrogen-hydrogen bond occurred, albeit at a reduced rate, at 140°C. It was also achieved using dicobalt octacarbonyl alone. Of course, no reaction occurred without a catalyst. These results show that the carbonylation of the nitrogen-hydrogen bond is more facile than the carbonylation with ring expansion of pyrrolidines.

Table 15 Carbonylation of Pyrrolidines Under the General Reaction Conditions[a]

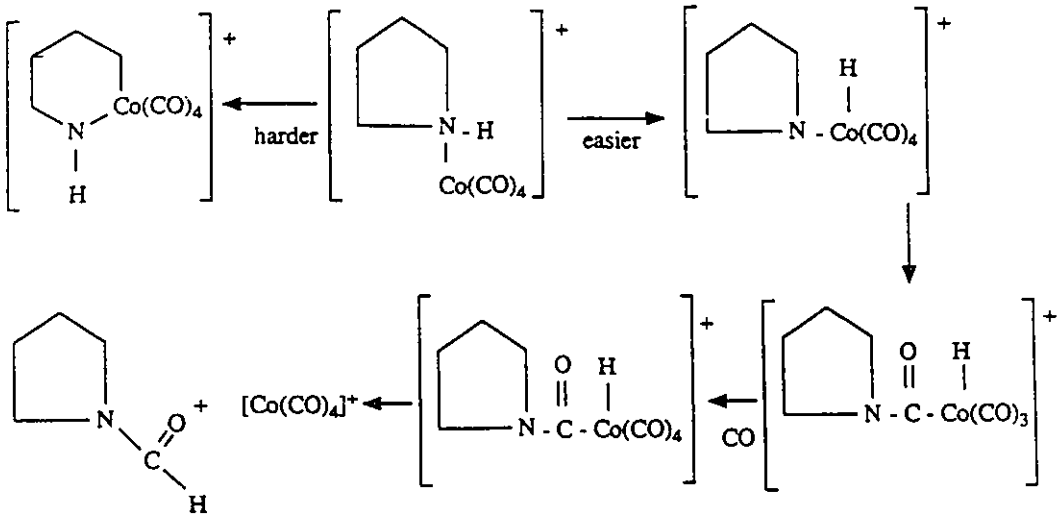
Pyrrolidine	Product	Isolated Yield (%)
	 (114)	59
	 (115)	traces[b]
	 (116)	78
	 (117)	14[b]
	 (118)	traces[b]
 (119)	 (120)	23
 (121)	 (122)	9
	 (123)	59
 [c]	 (124)	22
	 (125)	8

a) Reaction conditions: benzene, 225-230°C, 2 or 3 days, 0,11M pyrrolidine, 4:1:0,5 ratio of pyrrolidine: dicobalt octacarbonyl: triruthenium dodecacarbonyl, 54 atm of carbon monoxide.

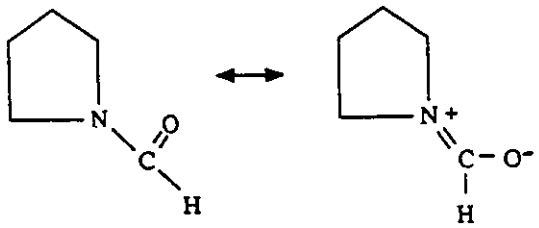
b) GC yields

c) 6,6:1:0,5 ratio of pyrrolidine: dicobalt octacarbonyl: triruthenium dodecacarbonyl.

Scheme 5.2



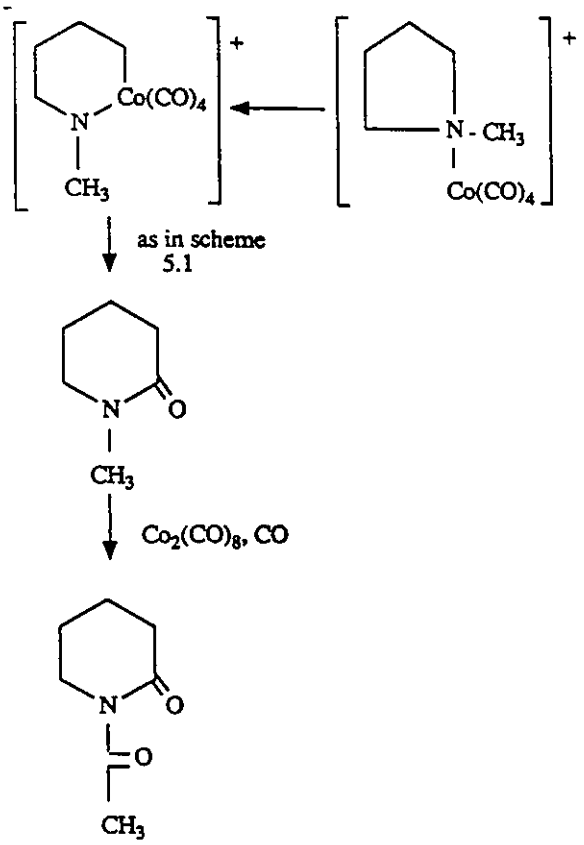
It is interesting to note that 1-formylpyrrolidine does not carbonylate with ring expansion under the reaction conditions. This is probably due to the fact that the lone pair of electrons of the nitrogen is not completely "free" because of the formyl group:



The nitrogen is less basic and consequently does not easily coordinate to cobalt. This result is reminiscent of the lack of reactivity of 1-p-tosylazetidine (see chapter 4).

The results obtained with 1-methylpyrrolidine were surprising. Only 14% of 1-methylpiperidin-2-one (**117**) was formed, while cleavage of the nitrogen-carbon (CH_3) bond occurred affording traces of 1-acetyl-piperidin-2-one (**118**). The formation of those products might be explained by Scheme 5.3.

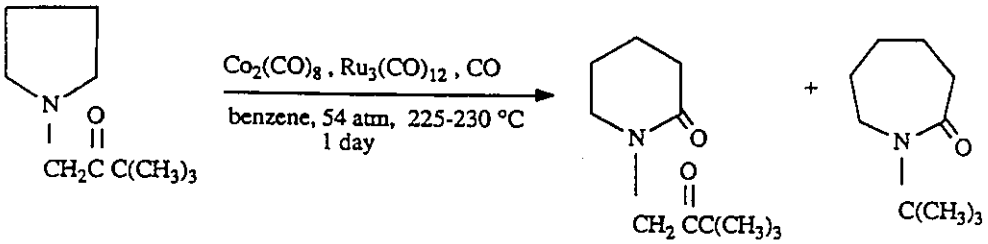
Scheme 5.3



While 1-propylpyrrolidine **(119)** was slow to react, 47% of it was converted after two days affording 23% of 1-propylpiperidin-2-one **(120)**. The percent conversion was the same after three days showing that the catalyst had been destroyed in less than two days.

It was thought that the lower reactivity of 1-propylpyrrolidine compared to ethyl 1-pyrrolidine acetate might be an indication of the importance of the ester group. In some manner, this group facilitates reaction. 1-Pyrrolidinyl-3,3-dimethyl-2-butanone **(121)** was synthesized

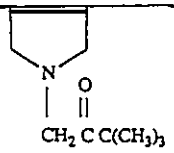
in order to see if a ketone group β to the nitrogen would also increase the reactivity of pyrrolidines. The results were unexpected as only 9% of 1-piperidinone-3,3-dimethyl-2-butanone **(122)** was obtained, the major product (59%) being 1-t-butylhexahydroazepin-2-one **(123)**.



122 123

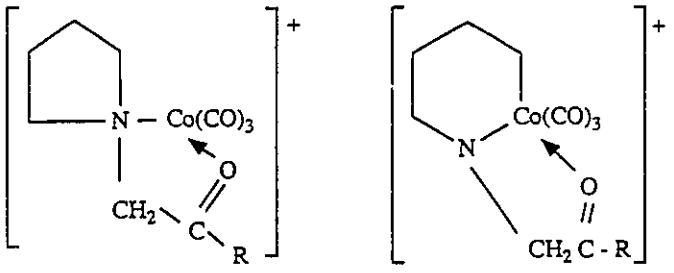
No reaction occurred at 100°C. Likewise, only the pyrrolidine was recovered when a nitrogen atmosphere was used instead of carbon monoxide. Use of dicobalt octacarbonyl as catalyst resulted in the formation of 37% of 1-piperidinone-3,3-dimethyl-2-butanone, after 24 hours. No 1-t-butylhexahydroazepin-2-one was obtained. On the other hand none of these products were formed using triruthenium dodecacarbonyl alone. The results are summarized in Table 16. The presence of the carbonyl group effectively increased the reactivity of the pyrrolidine. The reaction was complete after 24 instead of 48 hours at 225-230°C. Moreover, 37% is a fair yield of piperidin-2-one, when one considers that only dicobalt octacarbonyl was used as the catalyst. How can one rationalize the fact that a carbonyl group β to the nitrogen facilitates carbonylation with ring expansion of pyrrolidines? Perhaps this carbonyl group stabilizes some intermediate complex by coordinating to cobalt. For example, as in complex **127** and **128**:

Table 16 Influence of the Catalyst on the Carbonylation of 1-Pyrrolidinyl-3,3-dimethyl-2-butanone[a]

 :	$Co_2(CO)_8$:	$Ru_3(CO)_{12}$	Conversion of 121 (%)[b]	Isolated Yield (%) 122	123
4 :	1 :	0,5	100	9	59
4 :	1 :	0	100	37	0
4 :	0 :	0,5	30	0	0

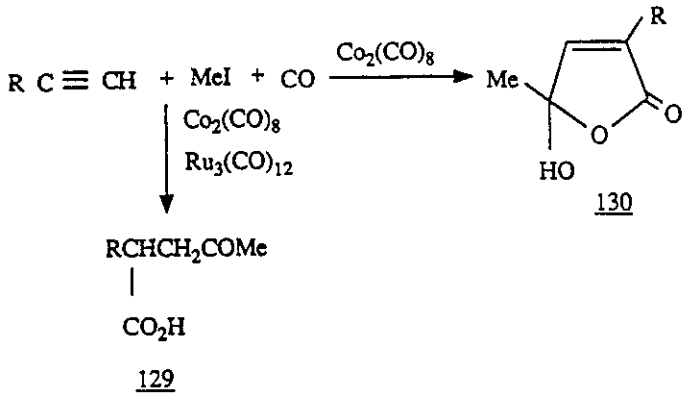
a) 54 atm of carbon monoxide; 225-230°C; 24 hours; benzene solution 0,11 M of pyrrolidine.

b) percent conversion by GC.



127 128

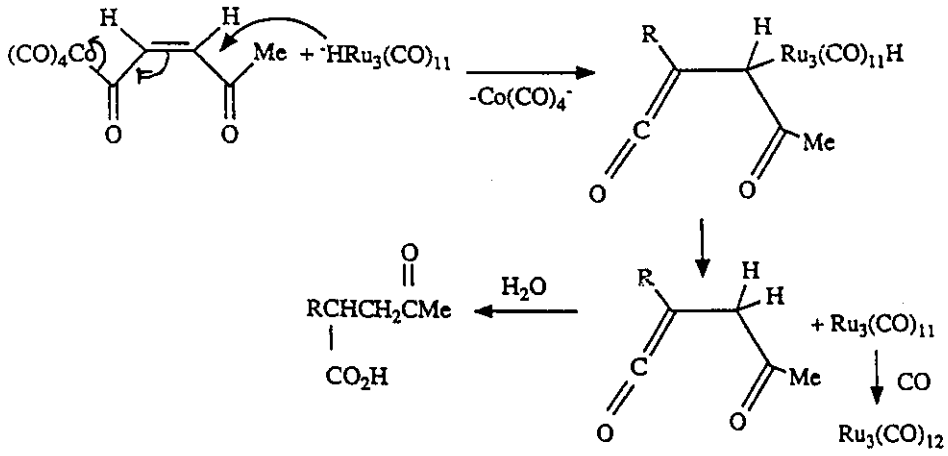
An important observation is that the formation of 1-t-butylhexahydroazepin-2-one requires both dicobalt octacarbonyl and triruthenium dodecacarbonyl. In other words, it is a genuine bimetallic catalysed reaction. This kind of catalysis has been observed before in the formation of γ-ketoacids **(129)** by the phase transfer catalysed reaction of alkynes with carbon monoxide and methyl iodide in the presence of catalytic amounts of cobalt and ruthenium carbonyl complexes[164]. With dicobalt octacarbonyl alone but-2-enolides **(130)** were obtained while triruthenium dodecacarbonyl was unable to afford carbonylated products.



129 130

The following mechanism was proposed for the formation of γ-keto-acids.[164]

Scheme 5.4



Here, a bimetallic complex was not formed. Rather, the cobalt and the ruthenium complexes were each working on their own.

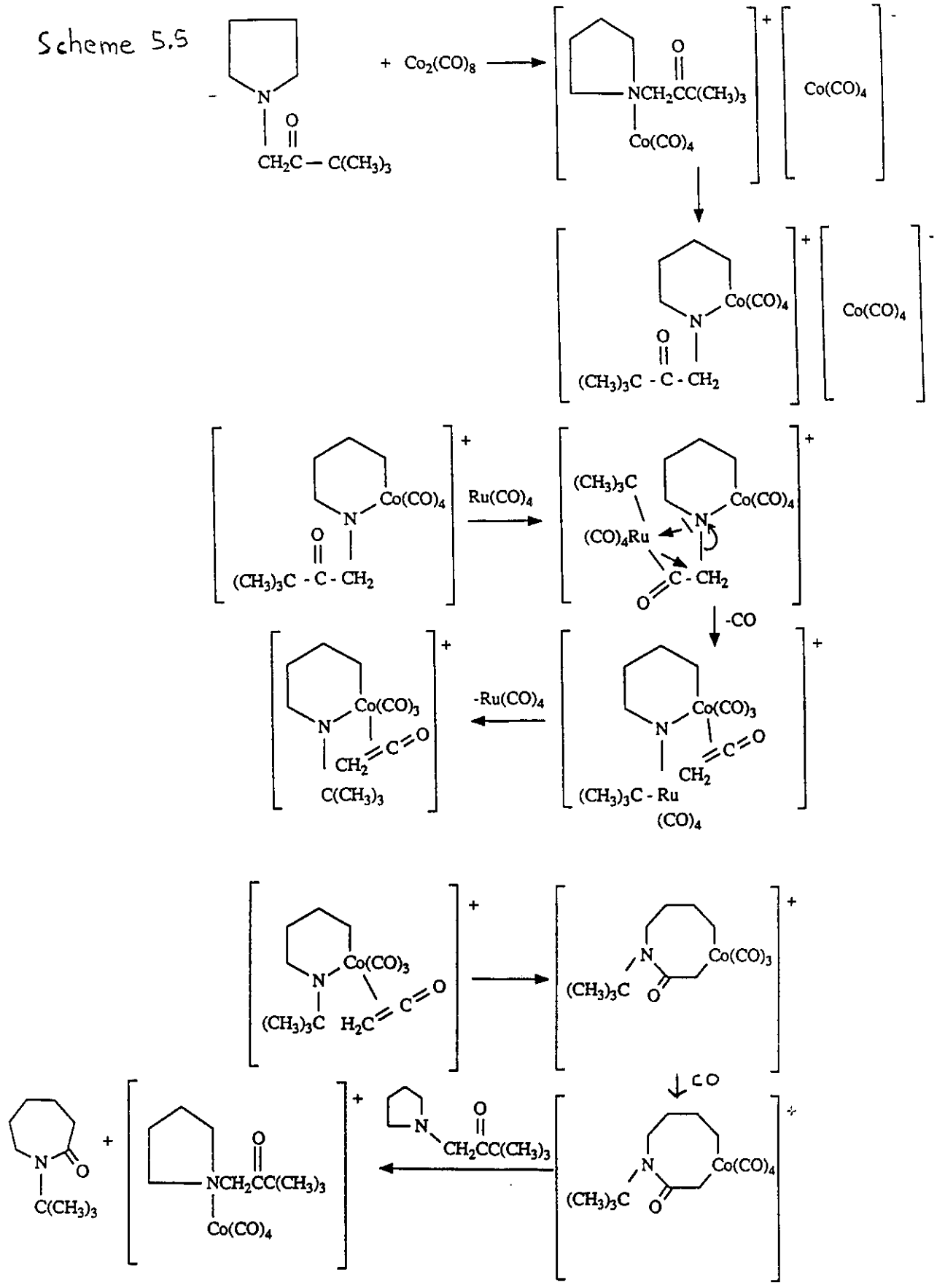
By which mechanism do dicobalt octacarbonyl and triruthenium dodecacarbonyl catalyse the conversion of 1-pyrrolidinyl-3,3-dimethyl-2-butanone to 1-t-butylhexahydroazepin-2-one **(123)**? In order to obtain **123** the cleavage of the t-butyl carbon-carbonyl carbon must occur. This cleavage can not be induced photochemically (the reaction mixture is in the dark) nor thermally (the thermolysis of ketones occurs at higher temperatures, usually 500°C[165]; the 1-pyrrolidinyl-3,3-dimethyl-2-butanone was recovered when heated for one day at 225°C and under 54 atm of carbon monoxide). The role of triruthenium dodecacarbonyl may be to induce this cleavage. Indeed it is known that group VIII metals of the second and third row are able to decarbonylate a variety of organic compounds under mild conditions. Acyl metal derivatives are probably intermediates which then revert to alkyl metal carbonyls[166].

Under our reaction conditions (225°C, 54 atm CO), ruthenium pentacarbonyl may be formed. This process is known to occur under carbon monoxide pressure (eg. 150°C, 100 atm)[167]. Moreover, at the end of the reaction, the benzene placed between the glass and the walls of the autoclave contained triruthenium dodecacarbonyl.

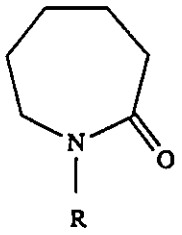
$$\frac{1}{3}\ Ru_3(CO)_{12} \underset{}{\overset{\Delta}{\rightleftharpoons}} [\,Ru(CO)_4\,] \overset{+CO}{\underset{-CO}{\rightleftharpoons}} Ru(CO)_5$$

Scheme 5.5 represents a possible pathway leading to the formation of 1-t-butylhexahydroazepin-2-one. This mechanism is, of course, only speculative.

Scheme 5.5



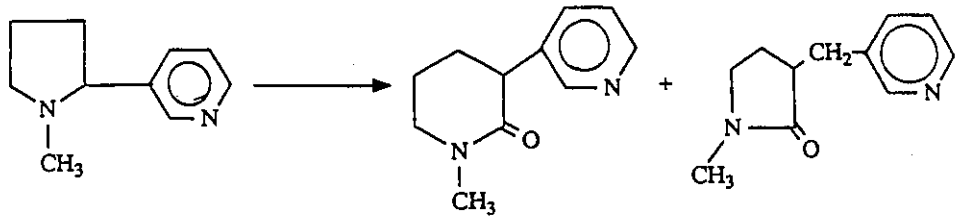
The carbon-NMR of 1-t-butylhexahydroazepin-2-one shows that there is a strong effect of the nitrogen substituent on the chemical shifts of the carbons of hexahydroazepin-2-one. Indeed, the chemical shifts reported for hexahydroazepin-2-one[143], 1-methylhexahydroazepin-2-one[143] and for 1-t-butylhexahydroazepin-2-one are shown below:



R	δ (ppm)					
	C_2	C_3	C_4	C_5	C_6	C_7
t-Bu	174,56	31,22	17,93	47,06	40,45	39,17
Me	176,01	36,93	23,41	29,91	27,70	51,43
H	179,78	36,87	23,28	29,78	30,62	42,65

Finally it was of interest to know how nicotine would react under the carbonylation conditions. By analogy with the behaviour of 1-methyl-2-phenylazetidine, one would anticipate that insertion would occur into the nitrogen-carbon bond bearing the pyridinyl group. If so,

since nicotine is optically pure, the question arises as to whether the carbonylation is enantiospecific. It was found that the carbonylation reaction afforded 22% of 1-methyl-3-pyridinylpiperidin-2-one **(124)** and 8% of 1-methyl-3-methylpyridinylpyrrolidin-2-one **(125)**. Both products were obtained in racemic form.

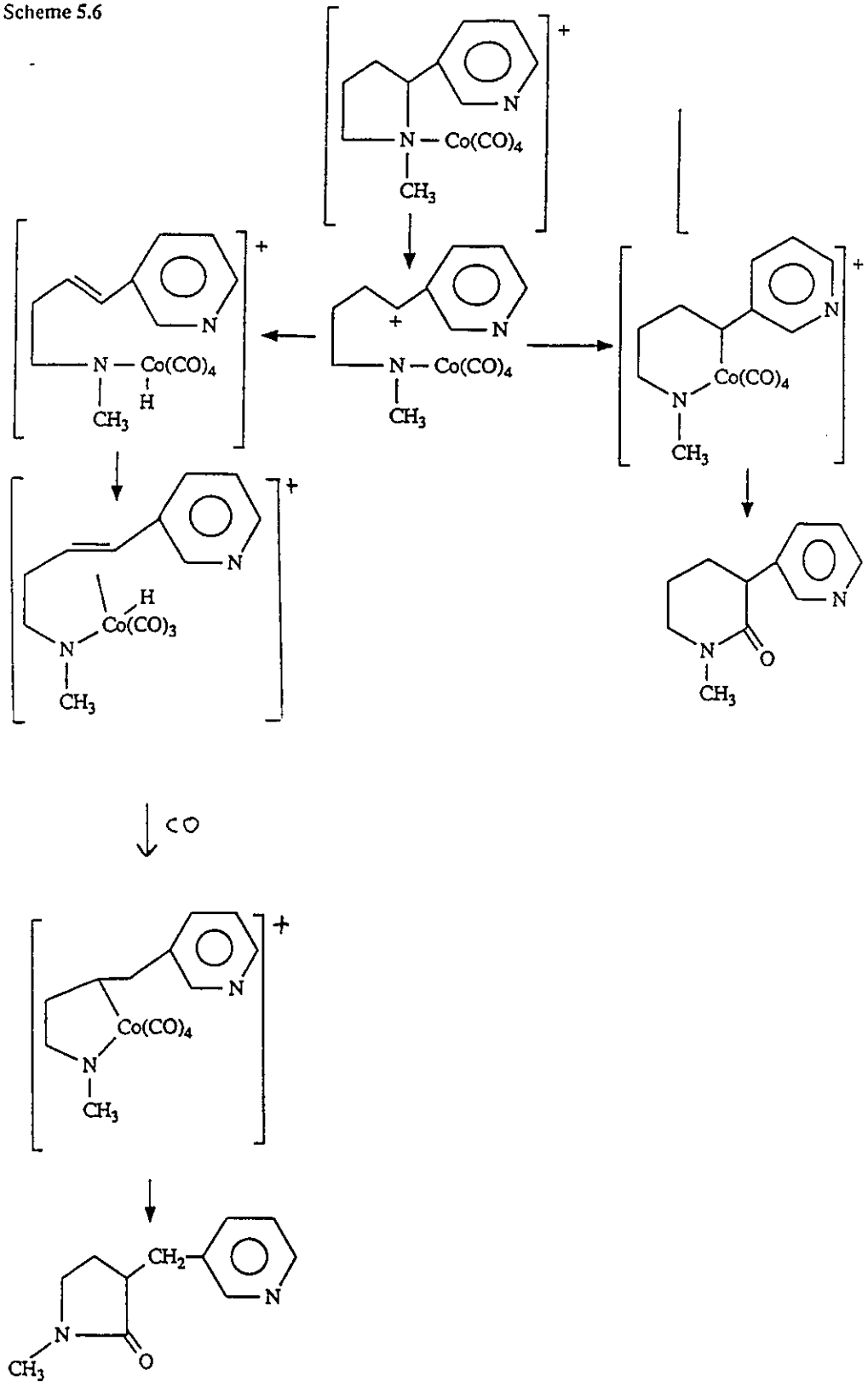


124
22%

125
8%

As expected the carbon monoxide inserts into the nitrogen-carbon bond bearing the pyridinyl group. The fact that 1-methyl-3-pyridinyl-piperidin-2-one is obtained as a racemic mixture and that 1-methyl-3-methylpyridinylpyrrolidin-2-one is formed might be explained by the mechanism described in scheme 5.6.

Scheme 5.6



The formation of the carbocation is particularly facile owing to the stabilization by resonance. Such cation formation leads to the loss of the chiral center.

Our investigation of the metal catalysed chemistry of pyrrolidine has revealed that pyrrolidines can be converted into piperidin-2-ones in the presence of $Co_2(CO)_8$. Usually, higher yields are achieved using both dicobalt octacarbonyl and triruthenium dodecacarbonyl as catalysts. However, triruthenium dodecacarbonyl alone is unable to induce the carbonylation reaction.

5.3 Experimental Data

5.3.1 General Comments

The general comments of chapter four also apply here. Pyrrolidine, 1-methylpyrrolidine, ethyl 1-pyrrolidine acetate and nicotine were purchased from Aldrich Chemical Co., and were used without further purification.

5.3.2 Synthesis of 1-Pyrrolidinyl-3,3-dimethyl-2-butanone

Pyrrolidine (4,2 ml; 51 mmol) was added at 0°C and under nitrogen to a solution of n-butyl lithium (24,5 ml of a 2,5M solution in hexane; 61 mmol) and dry ether (80 ml). The mixture was stirred for three hours at room temperature and then added, dropwise, at 0°C, to 1-bromo-3,3-dimethyl-2-butanone (8,0 ml; 61 mmol) diluted in dry ether (2 ml) (N_2 atm). The mixture was stirred overnight at room temperature. The ether solution was washed twice with 25 ml portions of water, dried over magnesium sulfate and concentrated by rotary evaporation. Distillation of the crude product under reduced pressure (34-38°C; 0,3 mm Hg) gave 84% of pure **121.**

121:

IR (benzene): ν CO = 1722 cm^{-1}

^1H NMR ($CDCl_3$) δ 1,13 (S; 9H, $(CH_3)_3C$); 1,78-1,81 (m; 4H, CCH_2CH_2C); 2,61-2,64 (m; 4H, $2CH_2\underline{CH_2}N$); 3,59 (S; 2H, NCH_2CO)

^{13}C NMR ($CDCl_3$): δ 23,67 ($C\underline{CH_2}\underline{CH_2}C$); 26,53 [$(\underline{CH_3})_3C$]; 43,34 [$(CH_3)_3\underline{C}$]; 53,94 ($2CH_2\underline{CH_2}N$); 59,76 ($N\underline{CH_2}CO$); 211,82 (CO)

Mass spec.: m/e 169 [M]+; 84 [M-$(CH_3)_3CCO$]+

5.3.3 Synthesis of 1-Propylpyrrolidine

1-propylpyrrolidine[168] **(119)** was prepared following the procedure described in 5.3.2 except that iodopropane was used instead of 1-bromopinacolone. The product was purified by silica gel column chromatography first using pentane and then mixtures of pentane and ether as eluant.

119:

^1H NMR ($CDCl_3$) δ 0,70-2,06 (m; 9H, CCH_2CH_2C and CH_2CH_3); 2,13-2,87 (m; 6H, $3CH_2N$)

^{13}C NMR ($CDCl_3$): δ 12,23 (CH_3); 22,34 ($\underline{CH_2}CH_3$); 23,47 ($NCH_2\underline{CH_2}\underline{CH_2}CH_2N$); 54,24 ($N\underline{CH_2}CH_2CH_2\underline{CH_2}N$); 58,70 ($N\underline{CH_2}CH_2CH_3$)

Mass spec.: m/e 113 [M]+; 84 [M-CH_2CH_3]+

lit[169] b.p.: 130-135°C

5.3.4 General Procedure for the Carbonylation of Pyrrolidines

The pyrrolidine (1,10 mmol), dicobalt octacarbonyl (0,094g; 0,277 mmol), triruthenium dodecacarbonyl (0,088g; 0,138 mmol), dry benzene (10 ml) and a small magnetic stirring bar were placed in an autoclave containing a glass liner. Dry benzene (ca 1,5 ml) was used to fill the space between the glass and the lower part of the autoclave. The autoclave was purged twice with carbon monoxide and loaded with 54 atm of the gas. The reaction mixture was stirred vigorously for 2 to 3 days at 225-230°C (oil bath temperature). After cooling to room temperature, the pressure was released and the autoclave was opened. The orange-brown solution was allowed to stand for 12 hours in air, and a brown solid was formed. The mixture was filtered through Celite and the

filtrate was concentrated by rotary evaporation. The crude residue was purified by preparative thin layer chromatography (alumina) using an appropriate mixture (usually 1:1) of ether-hexane as eluant. The products were identified by infrared, proton and carbon magnetic resonance, and by mass spectrometry. Piperidin-2-one, 1-formylpyrrolidine and 1-methylpiperidin-2-one were identified by comparison of spectral data with authentic samples purchased from Aldrich Co.

5.3.4.1 Carbonylation of Ethyl 1-Pyrrolidine Acetate

5.3.4.1.1 Using the general procedure

The reaction was stopped after two days. Purification on alumina plates, using ether-hexane (1:1) as eluant afforded ethyl 1-piperidin-2-one acetate (114) in 59% yield.

114:

IR (benzene): ν CO = 1658 cm^{-1} (NC=O); 1750 cm^{-1} (OC=O)

^1H NMR ($CDCl_3$) δ 1,26 (t, J = 7,1Hz; 3H, CH_3); 1,81-1,86 (m; 4H, $NCH_2\underline{CH_2}\underline{CH_2}$); 2,41 (m; 2H, CH_2CON); 3,34 (m; 2H, $CH_2\underline{CH_2}N$); 4,08 (S; 2H, NCH_2CO); 4,17 (quartet, J = 7,1Hz; 2H, OCH_2)

^{13}C NMR ($CDCl_3$): δ 14,22 (CH_3); 21,40 ($\underline{CH_2}CH_2CO$); 23,21 ($\underline{CH_2}CH_2N$); 32,11 ($\underline{CH_2}CON$); 48,67 and 49,23 ($2CH_2N$); 61,13 (OCH_2); 169,00 (NCO); 170,36 (CO)

Mass spec.: m/e 185 [M]+; 112 [M-$CO_2CH_2CH_3$]+

5.3.4.1.2 Variation in reaction conditions

Many reactions were tried in order to obtain the best conditions for the carbonylation reaction described in 5.3.4. Decane was used as

internal standard in order to follow the reactions by gas chromatography. We studied the influence of the following parameters:

Concentration

Several reactions were carried out at 195-200°C without triruthenium dodecacarbonyl, using a 10:1 ratio of pyrrolidine to dicobalt octacarbonyl. After two days the reactions were controlled by gas chromatography. Using a 0,42M pyrrolidine concentration only 5,5% of piperidin-2-one was obtained although all the pyrrolidine had reacted. When the concentration of pyrrolidine was 0,11M, only 58% of the reactant underwent conversion, affording 13% of piperidin-2-one. Similar results were obtained when the solution was 0,053M.

Temperature

The effect of the temperature was studied for different ratios of pyrrolidine to dicobalt octacarbonyl to triruthenium dodecacarbonyl (2:1:0; 4:1:0; 8:1:0 and 4:1:0,5). The ethyl 1-piperidin-2-one acetate was not obtained at 140°C. From 200 to 250°C, the carbonylation with ring expansion occurred. At 200°C the reaction was slow and at 250°C it was fast but the catalyst was rapidly destroyed. For example, use of an 8:1 ratio of pyrrolidine to dicobalt octacarbonyl led to 51% conversion of the pyrrolidine and to the formation of 21% of piperidin-2-one (after one day at 250°C). After three days, 96% of the pyrrolidine had reacted but no more piperidin-2-one had been formed. Under the same reaction conditions at 200°C, it took four days to convert 67% of pyrrolidine, yielding 17% of piperidin-2-one. Using a ratio 4:1:0,5 of pyrrolidine: $Co_2(CO)_8$: $Ru_3(CO)_{12}$, at 250°C, complete conversion of the

pyrrolidine occurred after one day, affording 31% of piperidin-2-one. At 230°C, it took two days to convert 84% of the pyrrolidine yielding 67% of the piperidin-2-one. At 200°C the reaction was slightly slower. It took four days to convert 85% of the pyrrolidine, affording 60% of piperidin-2-one.

5.3.4.2 Carbonylation of Pyrrolidine

5.3.4.2.1 Using the general procedure

The reaction was stopped after two days. Only traces of piperidin-2-one (**115**) were observed by gas chromatography. The major product was 1-formylpyrrolidine (**116**). It was isolated in 78% yield.

115:

GC Mass spec.: m/e 99 [M]+; 56 [M-HNCO]+

lit[170] b.p.: 94°C (0,9 mm Hg)

116:

IR (benzene): ν CO = 1675 cm^{-1}

^1H NMR ($CDCl_3$): δ 1,75-2,10 (m; 4H, $CH_2\underline{CH_2}\underline{CH_2}CH_2$); 3,22-3,67 (m; 4H, $2CH_2N$); 8,20 (broad S; 1H, HCO)

^{13}C NMR ($CDCl_3$): δ 24,27 and 24,94 ($CH_2\underline{CH_2}\underline{CH_2}CH_2$); 43,15 and 46,06 ($2CH_2N$); 160,76 (CO)

Mass spec.: m/e 99 [M]+; 70 [M-HCO]+

lit[171] b.p.: 213-14°C

5.3.4.2.2 Variation in Reaction Conditions

Temperature

At 140°C the reaction occurred but was slower in that 22% of 1-formylpyrrolidine was obtained after one day.

Catalyst

A reaction was done without triruthenium dodecacarbonyl and using half the amount of dicobalt octacarbonyl (8:1 ratio of pyrrolidine to dicobalt octacarbonyl). 55% of 1-formylpyrrolidine was obtained after two days.

No reaction occurred in the absence of metal catalysts.

5.3.4.3 Carbonylation of 1-Methylpyrrolidine

The reactions were conducted as described in 5.3.4 but using decane as internal standard. After one or three days the reactions were stopped with a brown oil formed in the bottom of the glass. The benzene solution was light brown. The brown oil contained alot of carbonylated product and of metal carbonyls, as determined by infrared spectroscopy.

The solution and the brown oil were concentrated by rotary evaporation. Chloroform was added to the residue, and gas chromatography, after filtration, gave 7% of 1-methylpiperidin-2-one (**117**) (after one day). This product was obtained in 14% yield after three days. Traces of another compound, having a molecular weight of 141, were also observed. It might be 1-acetylpiperidin-2-one (**118**).

117:

IR (benzene): ν CO = 1650 cm^{-1}

^1H NMR ($CDCl_3$) δ 1,67-2,10 (m; 4H, $CH_2\underline{CH_2}\underline{CH_2}CH_2$); 2,37 (m; 2H, $\underline{CH_2}CO$); 2,95 (S; 3H, NCH_3); 3,28 (m; 2H, $\underline{CH_2}N$)

^{13}C NMR ($CDCl_3$): δ 21,53 ($\underline{CH_2}CH_2CO$); 23,21 ($NCH_2\underline{CH_2}$); 32,27 ($\underline{CH_2}CO$); 34,62 (NCH_3); 49,94 (NCH_2); 169,69 (NCO)

Mass spec.: m/e 113 [M]+; 85 [M-CO]+

lit[143] b.p.: 105-106°C (12 mm Hg)

118:

GC Mass spec.: m/e 141 [M]+; 126 [M-CH_3]+; 98 [M-CH_3CO]+

lit[172] b.p.: 109°C (9 mm Hg)

5.3.4.4 Carbonylation of 1-Propylpyrrolidine

The reaction was carried out following procedure 5.3.4 but in the pesence of decane. After two days, 47% of 1-propylpyrrolidine reacted, purification affording 1-propylpiperidin-2-one (**120**) in 23% yield.

120:

IR (benzene): ν CO = 1650 cm^{-1} (lit IR(CCl_4): ν CO = 1650 cm^{-1})[173]

^1H NMR ($CDCl_3$): δ 0,88 (t, J = 7,4Hz; 3H, CH_3); 1,54 (sextuplet, J = 7,5Hz; 2H, $\underline{CH_2}CH_3$); 1,74-1,78 (m; 4H, $CH_2\underline{CH_2}\underline{CH_2}CH_2$); 2,35 (m; 2H, CH_2CO); 3,22-3,32 (m; 4H, $2CH_2N$)

^{13}C NMR ($CDCl_3$): δ 11,41 (CH_3); 20,33 ($\underline{CH_2}CH_3$); 21,52 ($\underline{CH_2}CH_2CO$); 23,39 ($\underline{CH_2}CH_2N$); 32,42 ($\underline{CH_2}CO$); 47,85 ($CH_3CH_2\underline{CH_2}N$); 48,74 ($CH_2CH_2\underline{CH_2}N$); 169,35 (NCO)

Mass spec.: m/e 141 [M]+; 126 [M-CH_3]+; 112 [M-CH_2CH_3]+

lit[173] b.p.: 110°C (10 mm Hg)

5.3.4.5 Carbonylation of 1-pyrrolidinyl-3,3-dimethyl-2-butanone

5.3.4.5.1 Using the general procedure

All the 1-pyrrolidinyl-3,3-dimethylbutanone reacted after 24 hours. Purification afforded 9% of 1-piperidinone-3,3-dimethyl-2-butanone (**122**) and 59% of 1-t-butyl-hexahydroazepin-2-one (**123**) [174].

122:

IR (benzene): ν CO = 1650 cm^{-1} (NC=O); 1722 cm^{-1} ($C_2C=O$)

^1H NMR ($CDCl_3$): δ 1,18 (S, 9H, $(CH_3)_3C$); 1,80-1,85 (m; 4H, $CH_2\underline{CH_2}\underline{CH_2}CH_2$); 2,39 (m; 2H, CH_2CON); 3,22 (m; 2H, $CH_2\underline{CH_2}N$); 4,29 (S; 2H, NCH_2CO)

^{13}C NMR ($CDCl_3$): δ 21,49 ($\underline{CH_2}CH_2CO$); 23,22 ($\underline{CH_2}CH_2N$); 26,32 ($(\underline{CH_3})_3C$); 32,07 ($\underline{CH_2}CON$); 43,30 ($(CH_3)_3\underline{C}$); 49,21 and 51,78 ($2CH_2N$); 170,11 (NCO); 209,62 ($C_2\underline{C}O$)

Mass spec.: m/e 197 [M]+; 112 [M-$(CH_3)_3CCO$]+

123:

IR (benzene): ν CO = 1692 cm^{-1}

^1H NMR ($CDCl_3$): δ 0,92 (S; 9H, $(CH_3)_3C$); 1,34-1,43 (m; 2H, $NCH_2\underline{CH_2}$); 1,93-2,06 (m; 2H, $\underline{CH_2}CH_2CO$); 2,35 (t; 2H, CH_2CO); 3,24-3,29 (m; 2H, CH_2N); 3,35 (m; 2H, $\underline{CH_2}CH_2CH_2N$). Those assignments were confirmed by a COSY spectrum.

^{13}C NMR ($CDCl_3$): δ 17,93 ($\underline{CH_2}CH_2CO$); 29,33 ($(\underline{CH_3})_3C$); 29,80 ($(CH_3)_3\underline{C}$); 31,22 ($\underline{CH_2}CO$); 39,17 (CH_2N); 40,45 ($\underline{CH_2}CH_2N$); 47,06 ($\underline{CH_2}CH_2CH_2N$); 174,56 (NCO). Those assignments were made with the help of a HETCOR spectrum.

Mass spec.: m/e 169 [M]+; 112 [M-$(CH_3)_3C$]+; 70 [M-$(CH_3)_3CNCO$]+

5.3.4.6 Carbonylation of Nicotine

This reaction was done in a similar manner to that described in 5.3.4 (nicotine (1,20g; 7,38 mmol); dicobalt octacarbonyl (0,378g; 1,11 mmol); triruthenium dodecacarbonyl (0,357g; 0,55 mmol). After three days there was no more nicotine. The reaction was stopped, and purification by thin layer chromatography (alumina), using diethyl ether as eluant, afforded 22% of 1-methyl-3-pyridinyl-piperidin-2-one **(124)** and 8% of 1-methyl-3-methylpyridinyl-pyrrolidin-2-one **(125)**. Both products were obtained as racemic mixtures.

124:

IR (benzene): ν CO = 1650 cm^{-1}

^1H NMR ($CDCl_3$): δ 1,83-2,22 (m; 4H; $\underline{CH_2CH_2}CH$); 3,01 (S; 3H, CH_3); 3,29-3,49 (m; 2H, CH_2N); 3,65 (m; 1H, CH); 7,19-8,46 (m; 4H, aromatic protons)

^{13}C NMR ($CDCl_3$): δ 21,25 (CH_2); 30,30 (CH_2); 35,17 (CH_3); 46,31 (CH); 50,27 (CH_2N); 123,21, 135,69, 136,99, 147,81 and 149,62 (aromatic carbons); 169,53 (NCO)

Mass spec.: m/e 190 $[M]^+$; 175 $[M-CH_3]^+$; 119 $[C_5H_4NCH{=}CO]^+$; 105 $[C_5H_4CH{=}CH_2]^+$

Elemental Analysis: calculated: C 69,45 H 7,42 N 14,72

found: 69,84 7,09 14,29

125:

IR (benzene): ν CO = 1698 cm^{-1}

^1H NMR ($CDCl_3$): δ 1,57-2,08 (m; 2H; $\underline{CH_2}CH_2N$); 2,64-2,72 (m; 2H, $\underline{CH_2}$— ); 2,82 (CH_3); 2,87-3,27 (m; 3H, CH_2N and CH); 7,24-8,01 (m; 4H, aromatic protons)

^{13}C NMR ($CDCl_3$): δ 24,05 ($\underline{CH_2}CH_2N$); 29,86 (CH_3); 34,30 ($\underline{CH_2}$— ); 43,06 (CH); 47,47 (CH_2N); 123,36, 134,73, 136,41, 147,81 and 150,21 (aromatic carbons); 175,05 (NCO)

Mass spec.: m/e 190 [M]+; 147 [M-CH_3N=CH_2]+; 133 [M-CH_3NCO]+; 98 [M-$CH_2C_5H_4N$]+; 92 [$C_5H_4NCH_2$]+

References

1. Collman, J.P., Hegedus, L.S., Norton, J.R., and Finke, R.G., Principles and Applications of Organotransition Metal Chemistry, University Science Books, Mill Valley, Calif., 1987.
2. Parshall, G.W. Homogeneous Catalysis, Wiley, New York, 1980.
3. Keim, W., in Fundamental Research in Homogeneous Catalysis, 4, Graziani, M., and Giango, M., editors, Plenum Press, New York, 1984.
4. Falbe, J., and Bahrmann, H., J. Chem. Ed., 1984, 61, 961.
5. Alper, H., and des Roches, D., J. Organomet. Chem., 1976, 117, C44.
6. Dehmlow, E.V. and Dehmlow, S.S., Phase Transfer Catalysis, Verlag Chemie, Weinheim, 1980.
7. a) Freedman, H.H., Pure & Appl. Chem., 1986, 58, 857.
   b) Starks, C.M., J. Am. Chem. Soc., 1971, 93, 195.
8. Alper, H., Adv. Organomet. Chem., 1981, 19, 183.
9. Cassar, L., Ann. N.Y. Acad. Sci., 1980, 333, 208.
10. Knowles, W.S., Sabacky, M.J., and Vineyard, B.D., Adv. Chem. Ser., 1974, 132, 274.
11. Miyashita, A., Yasuda, A., Takaya, H., Toriumi, K., Ito, T., Souchi, T., and Noyori, R., J. Am. Chem. Soc., 1980, 102, 7932.
12. Noyori, R., Ohta, M., Hsiao, Y., Kimamura, M., Ohta, T.and Takaya, H., J. Am. Chem. Soc., 1986, 108, 7117.
13. Takaya, H., Ohta, T., Sayo, N., Kumobayashi, H., Akutagawa S., Inoue, S., Kasahara, I., and Noyori, R., J.Am. Chem. Soc., 1987, 109, 1596.
14. Knowles, W.S., Acc. Chem. Res., 1983, 16, 106.

15. Katsuki, T. and Sharpless, K.B., J. Am. Chem. Soc., 1980, 102, 5974.

16. Pino, P., Consiglio, G., Botteghi, C., and Salomon C., Adv. Chem. Ser., 1974, 132, 295.

17. Calet, S., Ph.D. Thesis, Paris, 1987.

18. Tkatchenko, I., in Comprehensive Organometallic Chemistry, 8, Wilkinson, G., Stone, F. and Abel, E., editors, Pergamon Press, Oxford, 1982.

19. Wojcicki, A., Adv. Organomet. Chem., 1973, 11, 87.

20. Connor, J.A., Topics Curr. Chem., 1977, 71, 71.

21. Hodoli, H.A. and Shriver, D.F., Inorg. Chem., 1979, 18, 1236.

22. Rosenthal, A. and Wender I., in Organic Syntheses via Metal Carbonyls, 1, Wender I. and Pino P. editors, Wiley, New York, 1968.

23. Mullen, A. in New Syntheses with Carbon Monoxide, Falbe J. editors, Springer Verlag, Berlin, 1980.

24. Thomson, D.T., and Whyman, R., in Transition Metals in Homogeneous Catalysis, Schrauzer G.N. editors, Dekker, New York, 1971.

25. Bird, C.W., Transition Metal Intermediates in Organic Synthesis, Logos Press/Academic Press, New York, 1967.

26. Pino, P., Piacenti F. and Bianchi M., in Organic Synthesis via Metal Carbonyls, 2, Wender I., and Pino P. editors, Wiley, New York, 1977.

27. Jolly, P.W., and Wilke, G., The Organic Chemistry of Nickel, 2, Academic Press, New York, 1970.

28. Rempel, G.L., Teo, W.K., James, B.R. and Plackett, D.V., Adv. Chem. Ser., 1974, 132, 166.

29. Alper, H. and Hartstock, F.W., J. Chem. Soc., Chem. Commun., 1985, 1141.

30. Alper, H., Vasapollo, G., Hartstock, F.W., Mlekuz, M., Smith, D.J.H., and Morris, G.E., Organometallics, 1987, 6, 2391.

31. Falbe, J., Carbon Monoxide in Organic Synthesis, Spinger Verlag, Berlin, 1970.

32. Mullen, A., in New Syntheses with Carbon Monoxide, Falbe J. editors, Springer Verlag, Berlin, 1980.

33. Falbe, J., and Korte, F., Chem. Ber., 1965, 98, 1928.

34. Falbe, J., and Korte, F., Angew. Chem. Int. Ed. Engl., 1962, 1, 266.

35. Hegedus, L.S., and D'Andrea, S., J. Org. Chem., 1988, 53, 3113.

36. Hegedus, L.S., and McGuire, M.A., J. Am. Chem. Soc., 1982, 104, 5538.

37. Alper, H., and Amaratunga S., Can. J. Chem., 1983, 61, 1309.

38. Murahashi, S., and Horiie, S., J. Am. Chem. Soc., 1956, 78, 4816.

39. Horiie, S. and Murahashi, S., Bull. Chem. Soc. Japan, 1960, 33, 88.

40. Takahashi, H., and Tsuji, J., J. Organomet. Chem., 1967, 10, 511.

41. Hegedus, L.S., and Kramer, A., Organometallics, 1984, 3, 1263.

42. Alper, H., Israël J. Chem., 1981, 21, 203.

43. Hidai, M., Orisaku, M., and Uchida, Y., Chem. Lett., 1980, 753.

44. Aumann, R., and Ring, H., Angew. Chem. Int. Ed. Engl., 1977, 16, 50.

45. Kamiya, Y., Kawato, K., and Ohta, H., Chem. Lett., 1980, 1549.

46. Alper, H. Arzoumanian, H., Petrignani, J.F. and Saldana-Maldonado, M., J. Chem. Soc., Chem. Commun., 1985, 340.

47. Alper H., and Mahatantila C.P., Organometallics, 1982, 1, 70.

48. Alper, H., and Sakakibara, T., J. Chem. Soc., Chem. Commun., 1979, 458.

49. Alper, H. Urso, F., and Smith, D.J.H., J. Am. Chem. Soc., 1983, 105, 6737.

50. Klein, D.P., Hayes, J.C., and Bergman, R.G., J. Am. Chem. Soc., 1988, 110, 3704.

51. Chamchaang, W., and Pinhas, A.R., J. Chem. Soc., Chem. Commun., 1988, 710.

52. Roberto, D., and Alper, H., Organometallics, 1984, 3, 1767.

53. Alper, H., and Hamel, N., Tetrahedron Lett., 1987, 28, 3237.

54. Saldana-Maldonado, M., Ph.D. thesis, Aix-Marseille III, 1987.

55. Heck, R.F., in Organic Synthesis via Metal Carbonyls, 1, Wender I., and Pino, P. editors, Wiley, New York, 1968.

56. Heck, R.F., J. Am. Chem. Soc., 1963, 85, 1460.

57. Abendroth, H.J., and Henrich, G., Angew. Chem., 1959, 71, 283.

58. Paulsen, S.R., Belg. Patent 588,352, 1959.

59. Schmitz, E., Angew. Chem., 1959, 71, 127.

60. Schmitz, E., in Advances in Heterocyclic Chemistry, 2, Academic Press, New York, 1963.

61. Schmitz, E., Dreiringe mit zwei Heteroatomen, Springer-Verlag, Berlin and New York, 1967.

62. Schmitz, E., in Advances in Heterocyclic Chemistry, 24, Academic Press, New York, 1979.

63. Heine, H.W., in Small Ring Heterocycles, Hassner, A. editor, 42 part 2, Wiley, New York, 1983.

64. Schmitz, E., in Comprehensive Heterocyclic Chemistry, 7, Part 5, Katritzky, A.R., Rees C.N., and Lwowski W. editors, Pergamon Press, Oxford, 1984.

65. Schulz, M., and West, G., J. Prakt. Chem., 1970, 312, 161.

66. Dorn, H., and Otto, A., Chem. Ber., 1968, 101, 3287.

67. Heine, H.W., Baclawski, L.M., Bonser, S.M., and Wachob, G., J. Org. Chem., 1976, 41, 3229.

68. Somogyi, L., Chem. Ber., 1986, 119, 2963.

69. Lehman, L.S., Backawski, L.M., Harris, S., Heine, H.W., Springer, J.P., VanderHewel, W.J.A., and Arison, B.H., J. Org. Chem., 1981, 46, 320.

70. Izydore, R.A., and McLean, S., J. Am. Chem. Soc., 1975, 97, 5611.

71. Schulz, M., and West, G., J. Prakt Chem., 1974, 316, 999.

72. Komatsu, M., Ohshiro, Y., and Agawa, T., Tetrahedron Lett., 1972, 3999.

73. Komatsu, M., Nishikaze, N. Sakamoto, M., Ohshiro, Y., and Agawa, T., J. Org. Chem., 1974, 39, 3198.

74. Agawa, T., Ohshiro, Y., and Komatsu, M., Japan Kokai 75, 117, 765 (1975); Chem. Abstr., 1976, 84, 59159w.

75. Schmitz, E., and Habish, D., Chem. Ber., 1962, 95, 680.

76. Sosnovsky, G., and Lukszo, J., J. Cancer Res. Clin. Oncol., 1984, 107, 217.

77. Paget, C.J., and Davis C.S., J. Med. Chem., 1964, 7, 626.

78. Roberts, R.M., Gilbert, J.C., Rodewald, L.B., and Wingrove A.S., An Introduction to Modern Experimental Organic Chemistry, Holt, Rinehart and Winston Inc., New York, 1969.

79. Schmitz, E., Horig, C., and Gründemann, C., Chem. Ber., 1967, 100, 2093.

80. Bergmann, E., Zimkin, E., and Pinchas, S., Recueil de travaux de chimie des Pays Bas, 1952, 71, 169.

81. Westphal, O., and Burlet W., Angew. Chem., 1945, 58, 77.

82. Nabeya, A., Tamura Y., Kodama, T., and Fwakura, Y., J. Org. Chem., 1973, 38, 3758.

83. Aylward, J.B., J. Chem. Soc., C, 1970, 10, 1494.

84. Knapp, S., Toby, B.H., Sebastian, M., Krogh-Jespersen, K., and Potenza, J.A., J. Org. Chem., 1981, 46, 2490.

85. Condon, F.E., Org. Magn. Reson., 1974, 6, 517.

86. Rodebaugh, R.M., and Cromwell, N.H., J. Het. Chem., 1968, 5, 309.

87. Cromwell, N.H., Bambury, R.E., and Adelfang, J.L., J. Am. Chem. Soc., 1960, 82, 4241.

88. Schmitz, E. Habish, D., and Gründemann, C., Chem. Ber., 1967, 100, 142.

89. Sternberg, H.W., Wender, I., Friede, R. and Orchin, M., J. Am. Chem. Soc., 1953, 75, 3148.

90. Alper, H. and Delledonne, D., unpublished results.

91. Bruce, M.I., and Goodall, B.L., in The Chemistry of the Hydrazo, Azo and Azoxy Groups, part 1, Patai, S. editor, John Wiley & Sons, New York, 1975.

92. Bruce, M.I., Goodall, B.L., Redhouse, A.D., and Stone, F.G.A., Chem. Commun., 1972, 1228.

93. Fahey, D.R., Chem. Commun., 1970, 417.

94. Faher, D.R., J. Organomet. Chem., 1971, 27, 283.

95. Newbold, B.T., in The Chemistry of the Hydrazo, Azo and Azoxy Groups, part 2, Patai, S., editor, John Wiley & Sons, New York, 1975.

96. Olah, G.A., J. Am. Chem. Soc., 1959, 81, 3165.

97. Jardine, I., and McQuillan, F.J., Chem. Commun., 1970, 626.

98. Lewis, G.E., and Mayfield, R.J., Aust. J. Chem., 1966, 19, 1445.

99. Röper, M., Schieren, M., and Heaton, B.T., J. Organomet. Chem., 1986, 299, 131.

100. Cox, R.A., and Buncel, E., in The Chemistry of the Hydrazo, Azo and Azoxy Groups, part 2, Patai, S. editor, John Wiley & Sons, New York, 1975.

101. Calderazzo, F., Fachinetti, G., Marchetti, F., and Zanazzi, P.F., J. Chem. soc., Chem. Commun., 1981, 181.

102. Alper, H., and Paik, H., J. Organomet. Chem., 1978, 144, C18.

103. McKillop, A., Fiaud, J.C., and Hug, R.P., Tetrahedron, 1974, 30, 1379.

104. Gladysz, J.A., Williams, G.M., Tam, W., Johnson, D.L., Parker, D.W., and Selover, J.C., Inorg. Chem., 1979, 18, 553.

105. Latosh, N.I., and Pushkareva, Z.V., Doklady Akad. Nauk S.S.S.R., 1958, 124, 98.

106. Moore, J.A., in Heterocyclic Compounds with Three and Four Membered Rings, Weissberger, A., editor, Interscience, New York, 1964.

107. Testa, E., Wittgens, A., Maffii, G., and Bianchi, G., in Research Progress in Organic-Biological and Medicinal Chemistry, 1, U. Gallo and L. Santamario, Editors, Società Editoriale Farmaceutica, Milan, 1964.

108. Cromwell, N.H., and Phillips, B., Chem. Rev., 1979, 79, 331.

109. Moore, J.A., and Ayers, R.S., in Small Ring Heterocycles, part 2, Hassner A. editor, Interscience, New York, 1983.

110. Davies, D.E. and Storr, R.C., in Comprehensive Heterocyclic Chemistry, 7, A.R. Katritsky, A.R., Rees, C., and Lwowski W. editors, Pergamon Press, New York, 1984.

111. Aue, D.H., Bowers, M.T., Webb, H.M., and McIver, R.T., J. Am. Chem. Soc., 1971, 93, 4314.

112. Aue, D.H., Webb, H.M., and Bowers, M.T., J. Am. Chem. Soc., 1975, 97, 4137.

113. Espie, J.C., and Rassat, A., Bull. Soc. Chim. France, 1971, 4385.

114. Testa, E., Fontanella, L., and Aresi, V., Justus Liebigs Ann. Chem., 1964, 673, 60.

115. Kobor, J. Szegedi Pedagog Foiskola Evk., Masodik Resz., 1967, 41, Chem. Abstr., 1969, 70, 28809 q.

116. Testa, E., Fontanella, L., and Aresi, V., Justus Liebigs Ann. Chem., 1964, 676, 160.

117. Schacht, E.H., and Goethals, E.J., Makromol. Chem., 1973, 167, 155.

118. Iwakura, Y., Nabeya, A., Nishiguchi, T., and Ichikawa, Y., J. Org. Chem., 1965, 30, 3410.

119. Iwakura, Y., Nabeya, A., Nishiguchi, T., and Ohkawa, K.H., J. Org. Chem., 1966, 31, 3352.

120. Takayoshi, M., Akiko, C., and Masaki, O., Bull. Chem. Soc. Jap., 1970, 43, 3287.

121. Perchenko, V.N., Sytov, G.A., Kalashnikova, I.S., Ledina, L.E., Shanazarova, I.M., Nametkin, N.S., and Kammeva, G.L., Koord.

Khim.,1985, 11, 161; Chem. Abstr., 1985, 103, 114945 n.

122. Ledina, L.E., Sytov, G.A., Perchenko, V.N. and Nametkin, N.S., Dokl. Akad. Nauk. SSSR, 1980, 255, 874; Chem. Abstr., 1981, 94, 166761 q.

123. Fugami, K., Morizawa, Y., Oshima, K., and Nozaki, H., Tetrahedron, 1985, 26, 857.

124. Vaughan, W.R., Klonowski, R.S., McElhinney, R.S., and Millward, B.B., J. Org. Chem.; 1961, 26, 138.

125. White, J., and McGillivray, G., J. Org. Chem.; 1974, 39, 1973.

126. Freeman, J.P., and Mondron, P.J., Synthesis, 1974, 894.

127. Rodionov, V.M., and Yavorskaya, E.V., Zhur. Obshchei Khim., 1953, 23, 983; Chem. Abst. 1954, 48, 8755.

128. Stoilova, V., Trifonov, L.S., and Orahovats, Synthesis, 1979, 105.

129. Wladislaw, B., J. Org. Chem., 1961, 26, 711.

130. Rodebaugh, R.M., and Cromwell, N.H., J. Het. Chem., 1968, 5, 309.

131. Rodebaugh, R.M., and Cromwell, N.H., J. Het. Chem., 1971, 8, 19.

132. Chen, T.Y., Hung, M.H., Chen, P.T., and Ohta, M., Bull. Chem. Soc. Japan, 1972, 45, 1179.

133. Brown, C.A., and Barton, D., Synthesis, 1974, 434.

134. Plieminger, H., and Schneider, K., Chem. Ber., 1959, 92, 1594.

135. Bernath, G., Kovacs, K., and Lang, K.L., Acta Chim. Acad. Sci. Hung; 1970, 64, 183.

136. Göndös, G., Lang, K.L., Szeghy, A., Dombi, G., and Bernath, G., J. Chem. Soc., Perkin, I., 1979, 1770.

137. Moriconi, E., and Mazzochi, P., J. Org. Chem., 1966, 31, 1372.

138. Duhamel, L., Duhamel, P., and Siret, P., Bull. Soc. Chim. France, 1973, 2460.

139a) Duhamel, P., Duhamel, L., and Siret, P., C.R. Acad. Sci. Paris, Ser. C, 1973, 276, 519.

b) Duhamel, P., Duhamel, L., Legal, J.C., and Valnot, J.Y., Bull. Soc. Chim. France, 1972, 3222.

140. Moriconi, E.J., and Meyer, W.C., J. Org. Chem., 1971, 36, 2841.

141. Mickel, S.J., Hsiao, C.N., and Miller, M.J., Org. Syntheses, 1987, 65, 135.

142. Hassner, A., and Wiegand, N., J. Org. Chem., 1986, 51, 3652.

143. Rae, I.D., Aust. J. Chem., 1979, 32, 567.

144. Franklin, N.C., Möhrle, H., and Kilian, R., Tetrahedron, 1969, 25, 437.

145. Montando, G., Caccamese, S., Librando, V., and Recca, A., J. Molec. Struct., 1975, 27, 303.

146. Rueppel, M.L., and Rapoport, H., J. Am. Chem. Soc., 1971, 93, 7021.

147. Yakushijin, K., Suzuki, R., Kawaguchi, N., Tsuboi, Y., and Furukawa, H., Chem. Pharm. Bull., 1986, 34, 2049.

148. Stewart, J.D., Fields, S.C., Kochhar, K.S., and Pinnick, H.W., J. Org. Chem., 1987, 52, 2110.

149. Malmberg, M., and Nyberg, K., Acta Chem. Scand. B, 1981, 35, 411.

150. Bryndza, H.E., Fultz, W.C., and Tam, W., Organometallics, 1985, 4, 939.

151. Ashby, J., and Griffiths, D., J. Chem. Soc. (PI), 1975, 657.

152. Liu, P.S., Marquez, V.E., Kelley, J.A., and Driscoll, J.S., J. Org. Chem., 1980, 45, 5225.

153. Kiseleva, I.N., Zobacheva, M.M., and Perekalin V.V., J. Org. Chem. USSR, 1974, 10, 2236.

154. Ponomarev, A.A., and Sedavkina, V.A., Chemistry of Heterocyclic Compounds, 1969, 5, 598.

155. Tyurenkov, I.N., Perekalin, V.V., Kovalev, G.V., Morozov, I.S., Grineva, V.S., and Kiseleva, I.N., Tr. Volgogr. Gos. Med. Inst., 1979, 31, 35; Chem. Abstr., 1981, 95, 143835 y.

156. Patent Fr. 1, 298-571, July 13, 1962; Chem. Abstr., 1963, 58, 1435h.

157. Kochhar, K.S., and Pinnick, H.W., Tetrahedron Lett., 1983, 24, 4785.

158. Smalley, R.K., in Comprehensive Heterocyclic Chemistry, 7, Part 5, A.R. Katritzky, A.R., Rees, C., and Lwowski W. Editors, Pergamon Press, Oxford, 1984.

159. Duong, T., Prager, R.H., Tippett, J.M., Ward, A.D., and Kerr, D.I., Aust. J. Chem., 1976, 29, 2667.

160. Duong, T., Prager, R.H., Tippett, J.M., Ward, A.D. and Kerr, D.I., Aust. J. Chem., 1976, 29, 2651.

161. Jones, R.A., in Comprehensive Heterocyclic Chemistry, 4, Part 3, Katritzky, A.R., Rees, C.W., Bird, C.W., and Cheeseman, G.W.H. editors, Pergamon Press, Oxford, 1984.

162. Keim, W., Behr, A., and Röper, M., in Comprehensive Organametallic Chemistry, 8, Wilkinson, G., Stone F. and Abel, E. editors, Pergamon Press, Oxford, 1982.

163. Alper, H., Calet, S., and DeWang, M., J. Org. Chem., 1989, 64, 0000.

164. Alper, H. and Petrignani, J.F., J. Chem. Soc. Chem. Commun., 1983, 1154.

165. Schubert, W.M. and Kintner, R.P., in The Chemistry of the Carbonyl Group, Patai, S., editor, Interscience Publishers, London, 1966.

166. Heck, R.F., Organotransition Metal Chemistry, A Mechanistic Approach, Maitlis, P.M., Stone, F.G., and West, R. editors, Academic Press, 1974.

167. Bruce, M.I., in Comprehensive Organometallic Chemistry, 4, Wilkinson, G., Stone, F., and Abel, E., editors, Pergamon Press, Oxford, 1982.

168. Ahmed, M.G., Hickmott, P.W., and Soelistyowati, R.D., J. Chem. Soc., Perkin Trans. II, 1978, 372.

169. Reppe, W., Justus Liebigs Ann. Chem., 1955, 596, 1.

170. Donaruma, L.G. and Huber, M.L., J. Org. Chem., 1956, 21, 965.

171. Chem. Abstr., 1959, 53 18874d
Komori, S., Okahara, M., and Shinsugi, E., Technol. Repts. Osaka Univ., 1958, 8, 497.

172. Tani, H., Oguni, N. and Araki, T., Bull. Chem. Soc. Japan, 1964, 37, 1245.

173. Wanhoff H. and Korte F., Chem. Ber., 1967, 100, 2122.

174. Chem. Abstr., 1968, 69 10105b.

Claims to Original Research

1. Carbonylation with ring expansion of 1,2,3,3-tetraalkyldiaziridines to 1,3-diazetidinones.
2. Rearrangement of 1,2-diaroyldiaziridines to 1,2,4-oxadiazolines and to oxazolines.
3. Cobalt induced formation of acetylated diazenes from diaziridines under phase transfer catalysis.
4. Cobalt induced formation of acetic acid 2-acetylhydrazides from azoarenes.
5. Cobalt induced formation of acetic acid hydrazides form azoarenes.
6. Cobalt induced formation of hydrazines from azoarenes, in presence of dimethylaminopyridine.
7. Carbonylation with ring expansion of azetidines to pyrrolidin-2-ones.
8. Carbonylation with ring expansion of 2-vinylazetidines to 1,2,6,7-tetrahydro-3H-azepin-2-ones.
9. Carbonylation with ring expansion of 2-iminylazetidines to 2,3,6,7-tetrahydro-1H-1,3-diazepin-2-ones.
10. Carbonylation and ring expansion of pyrrolidines to piperidin-2-ones.
11. Cobalt and ruthenium induced rearrangement of 1-piperidinone-3,3-dimethyl-2-butanone to 1-t-butylhexahydroazepin-2-one.