SYNTHESIS OF NITROGEN-CONTAINING HETEROCYCLES BY THE IMINO DIELS-ALDER REACTION

Steven M. Weinreb* and Jeremy I. Levin
Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Abstract — This review describes the major advances reported during the past fifteen years on synthesis of heterocyclic compounds using imino dienophiles in the Diels Alder [4+2]-cycloaddition reaction.

CONTENTS

A. Introduction
B. Survey of imino dienophiles
   1. N-Sulfonyl imines
   2. N-Acyl imines
      a. Acyclic
      b. Cyclic
   3. Iminium salts and imines
   4. Miscellaneous imino compounds
   5. Intramolecular cycloadditions of imino compounds
C. Regiochemistry — summary and rationale
D. Stereochemistry — summary and rationale
E. Conclusion

A. INTRODUCTION

The [4+2]-cycloaddition of a conjugated diene with an imine was first reported by Alder in 1943.¹ In 1967 a review covering the literature to 1964 was published on this subject.² In the present review, we describe the work done in this field over the past fifteen years, with particular emphasis on the regiochemical and stereochemical course of the reaction.

A variety of imino compounds are known to undergo the Diels-Alder cycloaddition.² In general, imines bearing electron withdrawing groups are the most effective dienophiles, but simple iminium compounds are occasionally useful. Uncharged alkyl imines are usually unreactive. The
cycloaddition can be either thermal or acid catalyzed, and often is a sluggish reaction as compared to a similar "all carbon" case. Imino dienophiles are inherently unsymmetrical, and with unsymmetrical dienes can, in principle, give a mixture of regioisomers. However, the additions show high regioselectivity, and some good predictive generalizations can now be made on the basis of recent work (see Section C). Similarly, these cycloadditions often show excellent stereo-selectivity, although detailed stereochemical investigations have been somewhat limited to date (see Section D).

B. SURVEY OF IMINO DIENOPHILES

1. N-Sulfonyl imines

In 1964, Albrecht and Krause 3 first examined the thermal cycloaddition of sulfonyl imines 1a,b (derived from tolenesulfonylchloride and chloral or fluoral) with 2,3-dimethyl butadiene to form adducts 2a,b. These workers also reported high yield additions of imines 1a,b to both cyclo-

\[
\begin{align*}
&\text{CHCX}_3 + \text{C}_6\text{H}_6 \xrightarrow{\Delta} \text{C}_6\text{H}_6 \\
&\text{Ts} & \text{Ts} \\
&\text{N} & \text{N} \\
&\text{CHCX}_3 & \text{C}_6\text{H}_6 \\
&1a \text{ } \text{X} = \text{Cl} & 1a \text{ } \text{X} = \text{Cl} \\
&1b \text{ } \text{X} = \text{F} & 2b \text{ } \text{X} = \text{F}
\end{align*}
\]

hexadiene and cyclopentadiene, but they did not characterize the products stereochemically. More recently, Krow, et al. 4 reinvestigated these cases, and found that on addition of imine 1a to cyclopentadiene the endo adduct 3a predominates over the exo adduct 1a as the kinetic product (78/22). On the other hand, in the case of fluoroimine 1b, the exo-adduct 3b is favored kinetically over 4b by 57/43. Similarly, 1b and cyclohexadiene gave a kinetic product ratio of exo-5 to endo-6 of 44/56. Krow has offered a mechanistic rationale to explain these results but
sufficient experimental data is not currently available concerning the reacting geometry (E or Z) of these imines and of the "endo" orienting preferences of tosyl vs trihaloalkyl to fully explain this outcome.\textsuperscript{4,21}

Two groups have examined the thermal cycloaddition of imine 1\textsubscript{A} with a variety of unsymmetrical acyclic dienes 7-13,\textsuperscript{5,6} and in each case only a single orientational isomer (14-20) was found. This regioselectivity has been rationalized on the basis of a dipolar transition state for the imino Diels-Alder reaction\textsuperscript{5} (see Section C).

Speckamp and coworkers\textsuperscript{6,7} investigated the addition of imine 1\textsubscript{A} to the more complicated dienes 21 and 22, and found that with diene 21 only adduct 23 was formed. However, with diene 22, a 1.5:1 mixture of stereoisomers 24 and 25 was isolated and characterized. In both cases only a
single regioisomeric series was formed. A rationale similar to that first offered by Krow was proposed to explain the stereochemical outcome of this cycloaddition.

Albrecht and Kresse have described synthesis of imine 28 and its addition in refluxing benzene to 2,3-dimethylbutadiene (26) and isoprene (27) to form adducts 29 and 30, respectively, in unspecified yields. Imine 28 was also added successfully to cyclopentadiene and cyclohexadiene, to produce adducts of indeterminate stereochemistry.

Condensation of diene 21 with imine 28 in benzene at 0° gave a 100% yield of adducts 31 and 32 in a 3:1 ratio. At higher reaction temperatures, the combined yield was lower and double bond isomers were also formed. Stereochemistry was not elucidated. Adducts such as 29–32 have been converted to pyridines by treatment with base, although yields are not spectacular.

2. N-Acyl imines
   a. Acyclic

Simple acyclic N-acylimino dienophiles, such as 34, first reported by Merten and Müller, have been used extensively during the past fifteen years. These imines are most commonly generated
in situ from readily available biscarbamates \(^\text{31}\) upon heating with a catalytic amount of boron trifluoride etherate.

Cava et al.\(^\text{12}\) described an approach to isoquinuclidines via BF\(_3\) catalyzed condensation of cyclohexadiene with bis-carbamates \(^\text{35}\) and \(^\text{37}\) to produce adducts \(^\text{36}\) and \(^\text{38}\), respectively, in fair yields. The stereochemistry of \(^\text{38}\) was not established at the time, but has been recently reinvestigated in detail by Krow and coworkers,\(^\text{13}\) who found that \(^\text{38}\) was actually a mixture of exo and endo (80/20) stereoisomers. They also prepared some aryl-substituted\(^\text{13,20}\) adducts \(^\text{39}\) via the same cycloaddition and stereochemical results are outlined in Scheme I. In addition, these workers looked at the effects of other Lewis acids upon the exo/endo ratio and the effects of using carbamate esters other than ethyl. In general, the exo products were favored by about 3\text{-}4/1. The
mechanistic rationale(s) given$^{13b}$ to explain these results involves a stepwise cycloaddition of a protonated E-acylimine to the diene.$^{13b}$

Krow$^{14a}$ and Hobson$^{14b}$ have examined the additions of $^{33}$ and $^{37}$ to 1,3-cycloheptadiene, and obtained [4+2]-adducts in poor yield along with products of electrophilic substitution of the diene,$^{17}$ such as $^{40}$. Addition of $^{35}$ to cyclopentadiene and 1,3-cyclooctadiene gave no Diels-Alder products. In addition, the stereochemistry of cycloaddition of $^{35}$ and $^{37}$ with some menthadienes has been investigated in some detail.$^{15}$

Quan et al.$^{16}$ reported acid catalyzed addition of the interesting pyridyl-bis-carbamate $^{41}$ to butadiene ($^{42}$), 2,3-dimethylbutadiene ($^{43}$) and chloroprene ($^{44}$) to give adducts $^{45}$ to $^{47}$, respectively, in mediocre yields. The other possible regioisomer from chloroprene cycloaddition was not detected. Adduct $^{45}$ was converted to the tobacco alkaloid anatabine by hydrolytic removal of the carboethoxy group.

Sasaki$^{18}$ has described a homo-Diels-Alder reaction of diene $^{48}$ with bis-carbamate $^{35}$ under Lewis acid catalysis to yield compound $^{49}$ in moderate yield. Attempts at similar additions with some other imino dienophiles were unsuccessful.

A synthesis of the hydrogenation product $^{51}$ of the alkaloid cannivonine ($^{52}$) has been claimed using the endo adduct $^{51}$, formed in minor amount from addition of bis-carbamate $^{50}$ to cyclohexadiene.$^{19a}$ However, there is now considerable doubt as to the actual structures of both cannivonine and dihydrocannivonine.$^{19b}$
The trichloromethyl imine 54 has been synthesized\textsuperscript{20} and used\textsuperscript{4b,13b,14a,21} in Diels-Alder reactions. Acid catalyzed addition of 54 to butadiene, 2,3-dimethylbutadiene and isoprene gave adducts 55-57 in 55, 78 and 75\% yields, respectively. Only a single regioisomer was found in the isoprene case. With cyclopentadiene and cyclohexadiene, exo/endo stereoisomeric mixtures are obtained\textsuperscript{4b,21} (58-61), with exact ratios being dependent upon reaction conditions, although endo isomers predominate as in the case of imine 1a.
Acylimines of type 62 have found application in cycloaddition reactions.\textsuperscript{13,22,23,25} Imines of this kind are usually generated from methoxyglycinate\textsuperscript{24} by treatment with BF$_3$-etherate in situ. Addition of 62a and 62b to 1,3-cyclohexadiene produces approximately a 2/1 ratio of exo isomers 63 and 64 to endo isomers 65 and 66, respectively.\textsuperscript{13b,25}

\[ \text{NCO}_2\text{Et} \quad \text{CHCR} \quad 62a \quad R = \text{CH}_3 \]

\[ \text{NCO}_2\text{Et} \quad \text{CHCR} \quad 62b \quad R = \text{OEt} \]

\[ \text{NCO}_2\text{Et} \quad \text{COR} \quad 63 \quad R = \text{CH}_3 \]

\[ \text{NCO}_2\text{Et} \quad \text{COR} \quad 64 \quad R = \text{OEt} \]

\[ \text{NCO}_2\text{Et} \quad \text{COR} \quad 65 \quad R = \text{CH}_3 \]

\[ \text{NCO}_2\text{Et} \quad \text{COR} \quad 66 \quad R = \text{OEt} \]

Baxter and Holmes, in an approach to the alkaloid prosopine, have added imine 62 to cyclohexadiene and obtained a 4/1 mixture of exo/endo isomers 68 and 69 in a total yield of 35\%.\textsuperscript{23}

\[ \text{NCO}_2\text{CH}_2\text{O} \quad \text{CHCO}_2\text{Et} \quad 67 \]

\[ \text{BF}_3\cdot\text{Et}_2\text{O} \quad \text{H} \quad \text{NCO}_2\text{Et} \quad \text{CH}_2\text{COR} \quad 68 \]

\[ \text{NCO}_2\text{Et} \quad \text{COR} \quad 69 \]

Plieninger, et al., have described synthesis of the highly functionalized acylimine 72 by condensation of phosphine imine 70 with diethyl mesoxalate (71).\textsuperscript{26} A more convenient synthesis of the related imine 74 has been developed by Johnson starting from acetylamino malonate 73.\textsuperscript{27}

\[ \text{O}_3\text{P} \quad \text{NCO}_2\text{Et} \quad 70 \]

\[ \text{O} \quad \text{CO}_2\text{Et} \quad \text{CO}_2\text{Et} \quad 71 \quad 57\% \rightarrow \text{NCO}_2\text{Et} \quad \text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \quad 72 \]

\[ \text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \quad 73 \]

\[ \text{Br}_2 \quad \text{Collidine} \quad \text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \quad 74 \]

Imine 72 is quite reactive towards cyclopentadiene, producing adduct 75 (62\%) on heating in THF. However, other dienes reacted more sluggishly with 72 and required heating at 10\textsuperscript{4} atm. Some
of the cycloadditions reported are outlined below in Scheme II. Cycloadditions with imine 72 reportedly afforded only single regioisomers in those cases where unsymmetrical dienes were used as reacting partners. Imine 74 has also been used successfully in Diels-Alder cycloadditions. 27

The use of cyclic N-acylimines as dienophiles has received attention recently. 28 Readily available methoxyhydantoin (76) 29 upon heating or on treatment with an acid lose the elements of

\[ R = \begin{align*}
(a) & \quad C_6H_5 \\
(b) & \quad CH_2C_6H_5 \\
(c) & \quad p-Cl-C_6H_4
\end{align*}\]
methanol to generate imines such as 77 which can be trapped with conjugated dienes. Ben-Ishai and Goldstein have investigated addition of 77 to a large number of dienes and a few representative examples are listed in Scheme III. These cycloadditions were found to be regiospecific in those cases tried with unsymmetrical dienes (except for isoprene addition) as can be seen in the Scheme. The addition is also stereoselective and only endo stereoisomers were detected, although the hydantoin proton has a tendency to epimerize in some of the adducts after cycloaddition has occurred.

\[ \text{Scheme III} \]

\[ \text{Diagram of cycloadditions with percentages} \]
A series of highly substituted unsymmetrical dienes \( 78 \) to \( 82 \) has been investigated in the thermal reaction with methoxyhydantoin \( 76^c \). Ratios of the two possible orientational isomers are given in Scheme IV. In all cases, only endo stereoisomers were found as depicted in the structures.

In an independent study, Evin, Lam and Blyskal\(^{31} \) reported preparation, in situ, of imines \( 86-88 \) via chlorination and dehydrochlorination of hydantoin \( 83-85 \), respectively. The trapping
of these imines with several dienes was investigated, and some of the results are outlined below:

\[ 86 + \begin{array}{c} \text{cyclopentadiene} \\ \text{25°} \end{array} \xrightarrow{\text{OH}} \begin{array}{c} \text{H} \\ \text{N} \\ \text{O} \\ \text{CH}_3 \end{array} \]

\[ 87 + \begin{array}{c} \text{cyclopentadiene} \\ \text{25°} \end{array} \xrightarrow{\text{OH}} \begin{array}{c} \text{N} \\ \text{O} \\ \text{N} \\ \text{CH}_3 \end{array} \quad \text{68%} \]

\[ 88 + \begin{array}{c} \text{cyclopentadiene} \\ \text{25°} \end{array} \xrightarrow{\text{OH}} \begin{array}{c} \text{CO}_2\text{CH}_3 \\ \text{N} \\ \text{O} \\ \text{N} \\ \text{CH}_2\text{O} \end{array} \quad \text{79%} \]

\[ 87 + \begin{array}{c} \text{cyclohexene} \\ \text{40°} \end{array} \xrightarrow{\text{OH}} \begin{array}{c} \text{N} \\ \text{O} \\ \text{N} \\ \text{CH}_3 \end{array} \quad \text{70%} \]

\[ 87 + \begin{array}{c} \text{1,3-butadiene} \\ \text{40°} \end{array} \xrightarrow{\text{OH}} \begin{array}{c} \text{N} \\ \text{O} \\ \text{N} \\ \text{CH}_3 \end{array} \quad \begin{array}{c} \text{75%} \\ \text{total yield} \end{array} \quad \text{1:1} \]

\[ 88 + \begin{array}{c} \text{1,3-butadiene} \text{OCH}_3 \\ \text{25°} \end{array} \xrightarrow{\text{OH}} \begin{array}{c} \text{CH}_3\text{O}_2\text{C} \\ \text{N} \\ \text{O} \\ \text{N} \\ \text{CH}_2\text{O} \end{array} \quad \text{72%} \]
As in the cases reported by Ben-Ishai,\textsuperscript{28} these cycloadditions show excellent regio- and stereo-selectivity in all cases except those using isoprene as the diene component. The regiochemical results in these hydantoin cycloadditions have been rationalized on the basis of the involvement of a dipolar transition state\textsuperscript{30,31} (see Section C).

In a series of several papers, Ben-Ishai and coworkers have looked at the Diels-Alder cycloadditions of many different types of cyclic acylimines.\textsuperscript{32-36} Some representative examples are outlined below:

\begin{equation}
\begin{array}{c}
\text{Heterocycles, Vol 12, No 7, 1979}

\text{As in the cases reported by Ben-Ishai, these cycloadditions show excellent regio- and stereo-selectivity in all cases except those using isoprene as the diene component. The regiochemical results in these hydantoin cycloadditions have been rationalized on the basis of the involvement of a dipolar transition state (see Section C).}

\text{In a series of several papers, Ben-Ishai and coworkers have looked at the Diels-Alder cycloadditions of many different types of cyclic acylimines. Some representative examples are outlined below:}

\begin{align*}
\text{HCl} & \quad \text{H} & \quad \text{H} & \quad \text{H} \\
\text{+} & \quad \text{+} & \quad \text{+} & \quad \text{+} \\
\text{\textsubscript{OEt}} & \quad \text{\textsubscript{OEt}} & \quad \text{\textsubscript{OEt}} & \quad \text{\textsubscript{OEt}} \\
\text{\textsubscript{OH/RT}} & \quad \text{\textsubscript{OH/RT}} & \quad \text{\textsubscript{OH/RT}} & \quad \text{\textsubscript{OH/RT}} \\
\text{52%} & \quad \text{52%} & \quad \text{52%} & \quad \text{52%} \\
\text{(ref. 32)} & \quad \text{ref. 32)} & \quad \text{ref. 32)} & \quad \text{ref. 32)} \\
\end{align*}

\begin{align*}
\text{OCH}_3 & \quad \text{OCH}_3 & \quad \text{OCH}_3 & \quad \text{OCH}_3 \\
\text{\textsubscript{NH}} & \quad \text{\textsubscript{NH}} & \quad \text{\textsubscript{NH}} & \quad \text{\textsubscript{NH}} \\
\text{\textsubscript{OH}} & \quad \text{\textsubscript{OH}} & \quad \text{\textsubscript{OH}} & \quad \text{\textsubscript{OH}} \\
\text{\textsubscript{OH/RT}} & \quad \text{\textsubscript{OH/RT}} & \quad \text{\textsubscript{OH/RT}} & \quad \text{\textsubscript{OH/RT}} \\
\text{53%} & \quad \text{53%} & \quad \text{53%} & \quad \text{53%} \\
\text{\textsubscript{A}} & \quad \text{\textsubscript{A}} & \quad \text{\textsubscript{A}} & \quad \text{\textsubscript{A}} \\
\text{77%} & \quad \text{77%} & \quad \text{77%} & \quad \text{77%} \\
\text{\textsubscript{OH/TFA}} & \quad \text{\textsubscript{OH/TFA}} & \quad \text{\textsubscript{OH/TFA}} & \quad \text{\textsubscript{OH/TFA}} \\
\text{\textsubscript{ref. 33)} & \quad \text{\textsubscript{ref. 33)} & \quad \text{\textsubscript{ref. 33)} & \quad \text{\textsubscript{ref. 33)} \\
\end{align*}

\begin{align*}
\text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\text{\textsubscript{NH}} & \quad \text{\textsubscript{NH}} & \quad \text{\textsubscript{NH}} & \quad \text{\textsubscript{NH}} \\
\text{\textsubscript{OEt}} & \quad \text{\textsubscript{OEt}} & \quad \text{\textsubscript{OEt}} & \quad \text{\textsubscript{OEt}} \\
\text{\textsubscript{OH/TFA}} & \quad \text{\textsubscript{OH/TFA}} & \quad \text{\textsubscript{OH/TFA}} & \quad \text{\textsubscript{OH/TFA}} \\
\text{41%} & \quad \text{41%} & \quad \text{41%} & \quad \text{41%} \\
\text{\textsubscript{A}} & \quad \text{\textsubscript{A}} & \quad \text{\textsubscript{A}} & \quad \text{\textsubscript{A}} \\
\text{77%} & \quad \text{77%} & \quad \text{77%} & \quad \text{77%} \\
\text{\textsubscript{OH/TFA}} & \quad \text{\textsubscript{OH/TFA}} & \quad \text{\textsubscript{OH/TFA}} & \quad \text{\textsubscript{OH/TFA}} \\
\text{\textsubscript{ref. 33)} & \quad \text{\textsubscript{ref. 33)} & \quad \text{\textsubscript{ref. 33)} & \quad \text{\textsubscript{ref. 33)} \\
\end{align*}

\begin{align*}
\text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\text{\textsubscript{NH}} & \quad \text{\textsubscript{NH}} & \quad \text{\textsubscript{NH}} & \quad \text{\textsubscript{NH}} \\
\text{\textsubscript{OEt}} & \quad \text{\textsubscript{OEt}} & \quad \text{\textsubscript{OEt}} & \quad \text{\textsubscript{OEt}} \\
\text{\textsubscript{OH/TFA}} & \quad \text{\textsubscript{OH/TFA}} & \quad \text{\textsubscript{OH/TFA}} & \quad \text{\textsubscript{OH/TFA}} \\
\text{41%} & \quad \text{41%} & \quad \text{41%} & \quad \text{41%} \\
\text{\textsubscript{A}} & \quad \text{\textsubscript{A}} & \quad \text{\textsubscript{A}} & \quad \text{\textsubscript{A}} \\
\text{77%} & \quad \text{77%} & \quad \text{77%} & \quad \text{77%} \\
\text{\textsubscript{OH/TFA}} & \quad \text{\textsubscript{OH/TFA}} & \quad \text{\textsubscript{OH/TFA}} & \quad \text{\textsubscript{OH/TFA}} \\
\text{\textsubscript{ref. 33)} & \quad \text{\textsubscript{ref. 33)} & \quad \text{\textsubscript{ref. 33)} & \quad \text{\textsubscript{ref. 33)} \\
\end{align*}

\begin{align*}
\text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\text{\textsubscript{NH}} & \quad \text{\textsubscript{NH}} & \quad \text{\textsubscript{NH}} & \quad \text{\textsubscript{NH}} \\
\text{\textsubscript{OEt}} & \quad \text{\textsubscript{OEt}} & \quad \text{\textsubscript{OEt}} & \quad \text{\textsubscript{OEt}} \\
\text{\textsubscript{Et_2O}} & \quad \text{\textsubscript{Et_2O}} & \quad \text{\textsubscript{Et_2O}} & \quad \text{\textsubscript{Et_2O}} \\
\text{\textsubscript{BF_3-Et_2O}} & \quad \text{\textsubscript{BF_3-Et_2O}} & \quad \text{\textsubscript{BF_3-Et_2O}} & \quad \text{\textsubscript{BF_3-Et_2O}} \\
\text{R.T.} & \quad \text{R.T.} & \quad \text{R.T.} & \quad \text{R.T.} \\
\text{86%} & \quad \text{86%} & \quad \text{86%} & \quad \text{86%} \\
\text{\textsubscript{ref. 35)} & \quad \text{\textsubscript{ref. 35)} & \quad \text{\textsubscript{ref. 35)} & \quad \text{\textsubscript{ref. 35)} \\
\end{align*}

\begin{align*}
\text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\text{\textsubscript{NH}} & \quad \text{\textsubscript{NH}} & \quad \text{\textsubscript{NH}} & \quad \text{\textsubscript{NH}} \\
\text{\textsubscript{OEt}} & \quad \text{\textsubscript{OEt}} & \quad \text{\textsubscript{OEt}} & \quad \text{\textsubscript{OEt}} \\
\text{\textsubscript{Et_2O}} & \quad \text{\textsubscript{Et_2O}} & \quad \text{\textsubscript{Et_2O}} & \quad \text{\textsubscript{Et_2O}} \\
\text{\textsubscript{BF_3-Et_2O}} & \quad \text{\textsubscript{BF_3-Et_2O}} & \quad \text{\textsubscript{BF_3-Et_2O}} & \quad \text{\textsubscript{BF_3-Et_2O}} \\
\text{\textsubscript{A}} & \quad \text{\textsubscript{A}} & \quad \text{\textsubscript{A}} & \quad \text{\textsubscript{A}} \\
\text{42%} & \quad \text{42%} & \quad \text{42%} & \quad \text{42%} \\
\text{\textsubscript{ref. 36)} & \quad \text{\textsubscript{ref. 36)} & \quad \text{\textsubscript{ref. 36)} & \quad \text{\textsubscript{ref. 36)} \\
\end{align*}

\end{equation}
More recently, azaquinones have received additional attention as Diels-Alder dienophiles (see entry 3 above). Compounds of type \( \text{90} \), generated by thermal rearrangement of 1,2-bis-azidoquinones \( \text{89} \), react rapidly with a number of dienes to produce \([4+2]\)-adducts in high yield.

Some representative examples of this cycloaddition are outlined below. Stereochemistry was not determined in these cases, nor were unsymmetrical dienes tried. Interestingly, the rate of addition of azaquinones to dienes is about 10 times faster than the analogous addition of dehydrohydantoins (77).
3. Iminium salts and imines

The cycloaddition of conjugated dienes with simple alkyl imines and iminium salts has received no systematic investigation to date and only a few isolated examples have been reported since the last review.²

Middleton and Krespan³ described cycloaddition of hexafluoroacetone imine (91) to 2,3-dimethylbutadiene (100°/18 hr) to produce adduct 92 in good yield. Apparently the free base is the reactive species in this case.

Bohlmann and coworkers⁴ have added several imines to ethyl 2,4-pentadienoate (94). Thus, dihydroquinoline 93 and diene 94 on heating at 130° produced tricyclic compound 96, presumably via the unconjugated intermediate 95. Similarly, imines 97 and 98 added to diene 94 to afford adducts 99 and 100, respectively, in fair yields. However, some other substituted imines were found to react as enamines with diene 94. Adduct 99 was further transformed into the quinolizidine alkaloid lupanine (101).
Wiegrebe has condensed diene \( \text{103} \), generated in situ from the dibromomethylphenanthrene \( \text{102} \), with imines \( \text{104} \) and \( \text{105} \) to produce adducts \( \text{106} \) and \( \text{107} \), respectively, in 10% yields.

In the above two investigations, it is not completely clear from the experimental conditions described whether the reacting dienophile is in the iminium form or is the free base.

Kametani and coworkers have examined the thermolytic cycloaddition reactions of several imines with o-quinodimethanes, produced in situ from substituted benzocyclobutenes. These reactions proceeded with a high degree of regioselectivity and in good yield. Some examples follow:
In work similar to that originally described by Bohme, et al., Russian workers found that iminium salts, generated from aminals by treatment with acetyl chloride, added to isoprene to afford adducts. These adducts were not characterized but were directly rearranged with base to dienes of type, and it appears that the cycloadditions are regioselective since only one diene was isolated in each case.
The rather exotic iminium salt 117 has been added to 2,3-dimethylbutadiene to afford adduct 118 in excellent yield. The free base corresponding to 117 was unreactive toward cycloaddition.

Cycloaddition of cumulene 119 to several conjugated dienes has been described. Cyclic dienes such as cyclopentadiene and cyclohexadiene give good yields of [4+2]-adducts 120 and 121.
respectively. 2,3-Dimethylbutadiene and 119 yields a mixture of [4+2]-adduct 122 and [2+2]-adduct 123. However, with butadiene, piperylene and isoprene only [2+2]-adducts were formed from cumulene 119.

4. Miscellaneous imino compounds

The synthesis, configuration and reactivity of isonitroso malonate derivatives 124-141 have been investigated extensively by Fleury and coworkers.45-50 Scheme V shows the results of the [4+2]-cycloadditions of these dienophiles to cyclopentadiene.48 In general, the adducts formed have

<table>
<thead>
<tr>
<th>R_1</th>
<th>R_2</th>
<th>R_3</th>
<th>Yield of Adduct</th>
<th>t°C</th>
<th>Reaction Time (h)</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN</td>
<td>CN</td>
<td>SO_2 C_7 H_7</td>
<td>88</td>
<td>20</td>
<td>12</td>
<td>Et_2 O</td>
</tr>
<tr>
<td>CN</td>
<td>CN</td>
<td>COC_6 H_4 pNO_2</td>
<td>90</td>
<td>20</td>
<td>24</td>
<td>Et_2 O</td>
</tr>
<tr>
<td>CN</td>
<td>CN</td>
<td>COC_6 H_5</td>
<td>80</td>
<td>20</td>
<td>48</td>
<td>Et_2 O</td>
</tr>
<tr>
<td>CN</td>
<td>CO_2 Et</td>
<td>SO_2 C_7 H_7</td>
<td>55</td>
<td>80</td>
<td>3</td>
<td>C_6 H_6</td>
</tr>
<tr>
<td>CN</td>
<td>CO_2 Et</td>
<td>SO_2 CH_3</td>
<td>51</td>
<td>80</td>
<td>3</td>
<td>C_6 H_6</td>
</tr>
<tr>
<td>CN</td>
<td>CO_2 Et</td>
<td>COC_6 H_4 pNO_2</td>
<td>65</td>
<td>80</td>
<td>4</td>
<td>C_6 H_6</td>
</tr>
<tr>
<td>CN</td>
<td>CO_2 Et</td>
<td>COC_6 H_5</td>
<td>0</td>
<td>80</td>
<td>8</td>
<td>C_6 H_6</td>
</tr>
<tr>
<td>CN</td>
<td>CO_2 Me</td>
<td>SO_2 C_7 H_7</td>
<td>57</td>
<td>80</td>
<td>4</td>
<td>C_6 H_6</td>
</tr>
<tr>
<td>CN</td>
<td>CO_2 Me</td>
<td>SO_2 CH_3</td>
<td>50</td>
<td>80</td>
<td>4</td>
<td>C_6 H_6</td>
</tr>
<tr>
<td>CN</td>
<td>CO_2 Me</td>
<td>COC_6 H_4 pNO_2</td>
<td>62</td>
<td>80</td>
<td>4</td>
<td>C_6 H_6</td>
</tr>
<tr>
<td>CN</td>
<td>CO_2 Me</td>
<td>COC_6 H_5</td>
<td>0</td>
<td>80</td>
<td>8</td>
<td>C_6 H_6</td>
</tr>
<tr>
<td>CN</td>
<td>CONH_2</td>
<td>SO_2 C_7 H_7</td>
<td>42</td>
<td>60</td>
<td>20</td>
<td>acetone</td>
</tr>
<tr>
<td>CN</td>
<td>CONH_2</td>
<td>SO_2 CH_3</td>
<td>39</td>
<td>70</td>
<td>36</td>
<td>dioxane</td>
</tr>
<tr>
<td>R_1</td>
<td>R_2</td>
<td>R_3</td>
<td>Yield of Adduct</td>
<td>t°C</td>
<td>Reaction Time (h)</td>
<td>Solvent</td>
</tr>
<tr>
<td>-----</td>
<td>-----</td>
<td>---------------</td>
<td>-----------------</td>
<td>-----</td>
<td>------------------</td>
<td>---------</td>
</tr>
<tr>
<td>CN</td>
<td>CONH₂</td>
<td>COC₆H₄pNO₂</td>
<td>20</td>
<td>70</td>
<td>48</td>
<td>dioxane</td>
</tr>
<tr>
<td>CN</td>
<td>CONH₂</td>
<td>COC₆H₅</td>
<td>0</td>
<td>80</td>
<td>48</td>
<td>dioxane</td>
</tr>
<tr>
<td>CO₂Et</td>
<td>CO₂Et</td>
<td>SO₂C₇H₇</td>
<td>0</td>
<td>60</td>
<td>72</td>
<td>acetone</td>
</tr>
<tr>
<td>CO₂Et</td>
<td>CO₂Et</td>
<td>SO₂CH₃</td>
<td>0</td>
<td>60</td>
<td>72</td>
<td>acetone</td>
</tr>
<tr>
<td>CO₂Et</td>
<td>CO₂Et</td>
<td>COC₆H₄pNO₂</td>
<td>0</td>
<td>60</td>
<td>72</td>
<td>acetone</td>
</tr>
</tbody>
</table>

Scheme V

group R₂ endo (OR₃ is exo in the transition state, presumably) although endo-exo equilibration does often occur. The reactivity sequence for R₁,R₂ -CN >> CO₂R > CONH₂ and for R₃ = -SO₂C₇H₇ > -SO₂CH₃ > COC₆H₄pNO₂ > COC₆H₅.

Other dienes have not been investigated as thoroughly as has cyclopentadiene, but it has been reported⁵⁰ that piperylene adds to 124 to afford 142. Of potential synthetic utility is the thermal

![Reaction Scheme](image)

elimination of HCN and p-toluenesulfonic acid from 142 to yield cyanopyridine 143. Compound 124 also adds to cyclohexadiene and 2,3-dimethylbutadiene,⁴⁹ but is unreactive towards 3-vinylindene.⁵¹

Indolones of type 144 add readily to dienes to afford adducts of the Diels-Alder variety.⁵²

![Indolone](image)

Addition of 144 to cyclopentadiene and 1,4-dimethylbutadiene gave compounds 145 and 146, respectively, in unspecified yields. Stereochemistry was not determined. Addition of isoprene to
144 gave a single adduct for which structure 147 was suggested solely on mechanistic grounds.

5. Intramolecular cycloadditions of imino compounds

Only a single published example of this sort of reaction exists to date.53 Oppolzer has described thermal cyclization of oxime 148 to form a mixture of stereoisomeric products 149 and 150, presumably occurring via an intermediate o-quinodimethane.54

In recent work,55 diene 151 has been thermally cyclized to the indolizidine lactam 152, which was converted to the alkaloid δ-coniceine (153).
C. Regiochemistry - Summary and Rationale

Unlike the "all carbon" Diels-Alder reaction,\textsuperscript{56} no systematic study exists concerning the regiochemistry of the imino cycloaddition. However, there is enough fragmentary information now available about these additions with unsymmetrical dienes to make a few reasonable generalizations, particularly in the cases of N-sulfonyl and N-acyl imines. Although mechanistic information is scarce, several authors have suggested\textsuperscript{5,13b,30,31} that the regiochemical outcome for these cyclizations, whether thermal or acid catalyzed, can be rationalized most satisfactorily by invoking a polar reaction transition state or intermediate. For example, in thermal reactions one can consider four possible forms A-D. Forms A and B would lead to regioisomer 154, and C and D would afford the alternative regioisomer 153. From the available data, it appears that B and D are only applicable in those cases where groups X and Y are both electron withdrawing (i.e., imines \textsuperscript{72, 74, 124 to 141}, and perhaps 90). In virtually all other cases discussed in Part B, only pair A and C need be considered when rationalizing product regiochemistry. One must next consider the carbonium ion stabilizing ability of diene substituents R\textsubscript{1}, R\textsubscript{2}, R\textsubscript{3} and R\textsubscript{4}. It is known that C-1 and C-4 diene substituents have a greater accelerating effect on [4+2]-cycloadditions than do C-2 and C-3 substituents.\textsuperscript{57} There is some hint from the available data that this effect may be magnified in imino Diels-Alder additions.\textsuperscript{30,58} Thus for any given cycloaddition, one can readily identify the form (A-D) from which the major product is best derived.\textsuperscript{59} A similar model would seem to hold for prediction of the major product in acid catalyzed cycloadditions.
D. Stereochemistry - Summary and Rationale

As pointed out by Krow\textsuperscript{13-15,25} lone pair inversion in both reactant imines and in the Diels-Alder adducts of these imines introduces stereochemical problems not found in the "all carbon" [4+2]-cycloaddition. For example, when using acyclic imines, one cannot \textit{a priori} be sure whether the reacting dienophile has the E or Z geometry and thus predictive application of the "Alder rule of endo-addition"\textsuperscript{60} becomes difficult. Although data is still quite sparse, a few generalizations can be made regarding the stereochemistry of the imino Diels-Alder reaction.

Cyclic N-acyl imines (e.g., \textsuperscript{77, 85-88}) cannot undergo nitrogen lone pair inversion and thus the endo-addition rule\textsuperscript{60} is easy to apply. A transition state model such as \textsuperscript{156} would reasonably explain the observed high endo stereoselectivity (\textsuperscript{157}) observed in these examples.\textsuperscript{28,30,31}
In general, acyclic imino compounds do not show quite the same high degree of stereoselectivity as do the cyclic compounds, and exo/endo mixtures are usually formed. Available evidence points towards a protonated (or Lewis acid complexed) E-imine $^{158}$ as the reacting species in acid catalyzed cycloadditions of imines of type $^{1, 28, 34, 56}$ and $^{62, 13b, 25}$ In general, the group $(Y)$

attached to nitrogen seems to act most effectively as the endo director, thus leaving group $X$ as the exo substituent in the cycloaddition product. Two exceptions to this generalization are imines $^{1a}$ and $^{54}$ ($X = CCl_3$) where endo products predominate. A rationale based upon steric arguments has been postulated for these last cases.$^{4b, 7}$

A complete and detailed understanding of the mechanism of the imino Diels-Alder reaction is still lacking and the above generalizations should be considered strictly empirical at this time.

E. Conclusion

Although the imino Diels-Alder reaction has been known for over thirty-five years, it has received only a fraction of the attention paid to the "all carbon" cycloaddition.$^6$ This neglect is somewhat surprising considering that the cycloaddition is a method for carbon-carbon bond formation which shows good regio- and stereoselectivity. Clearly, this reaction has the potential for construction of a variety of nitrogenous heterocycles, but has not yet found wide application. Perhaps the increased understanding of the parameters governing the reaction which has developed during the past fifteen years will correct this situation.
Acknowledgement. We are grateful to the National Science Foundation, National Institutes of Health and A. P. Sloan Foundation for financial support.

References


27. Professor Francis Johnson, SUNY-Stony Brook, personal communication.
HETEROCYCLES Vol 12 No 7 1979

58. Isoprene cycloadditions in many cases give mixtures of regioisomers, whereas piperylene usually gives a single isomer.
59. The addition product of imine \( \text{H}_2 \) with isoprene is thus anomalous.
61. Fewer than 100 papers exist on this subject!

Received, 22nd March, 1979