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DIELS–ALDER REACTIONS OF AZADIENES

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CONTENTS

I. INTRODUCTION

The Diels–Alder reaction has been the subject of extensive preparative,[1-14] theoretical,[15,16] and mechanistic[17] study which has contributed to the ease and predictability with which this reaction may be utilized today. The all-carbon Diels–Alder reaction is perhaps the single most powerful process for the regio- and stereospecific preparation of carbocyclic 6-membered rings, yet systems in which one or more of the atoms of the diene, or dienophile,[6] is a heteroatom have attracted less attention despite comparable preparative value. It may be the ambiguities concerning the mode of cycloaddition, the uncertainties surrounding the observed or predicted regio- or stereoselectivity, the relative lack of dependable procedures or notable applications, and the uncertainty in the question of concerted versus stepwise polar cycloaddition which have served to discourage the practicing chemist from utilizing heterodienes on a routine basis. Nevertheless, a number of significant observations have brought the potential use of heterodienes to the stage of routine application.

This review is restricted to those systems in which one or more atoms of the diene is a nitrogen atom and is designed to complement earlier reviews[1,2,5] and the recent coverage of heterodienophiles.[6] The text edited by J. Hamer[1] and the review of Needleman[7] provide excellent surveys up to 1965 and contain information on successful and unsuccessful early studies. No attempt has been made to exhaustively cover the literature since 1965.

II. 1-AZABUTADIENE SYSTEMS

Early reports of successful Diels–Alder reactions of 1-azabutadienes include only the reactions of benzoisoxazole[18] and unsaturated 3,4-dihydroisoquinolines,[19] eqns (1)–(3), and represent the early exceptions to the general observation that such systems fail to undergo [4 + 2] cycloaddition.[1,2]

eqn. 1

eqn. 2

eqn. 3
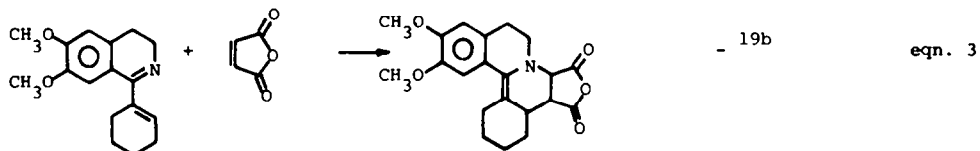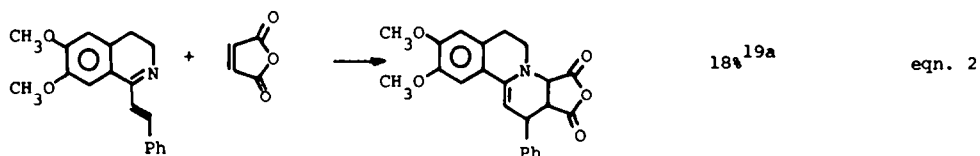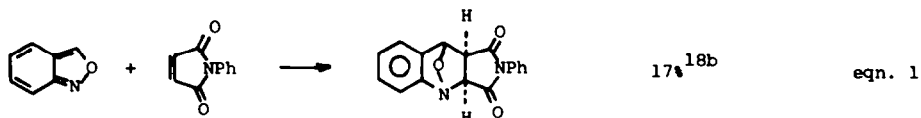
It has been known for some time that unsaturated imines participate in Diels–Alder reactions preferentially through their enamine tautomer,[20] eqn (4) and in instances where isomerization is prevented [2 + 2] cycloaddition usually intervenes, eqn (5).[21a] Exceptions to this generalization are the observations that selected imines afford [4 + 2] cycloaddition products with diphenyl ketene,[21a] eqn (5), chlorocyanoketene,[21b] eqn (6), and benzoylsulfene,[22] eqn (7).

eqn. 4 [20]

eqn. 5

eqn. 6
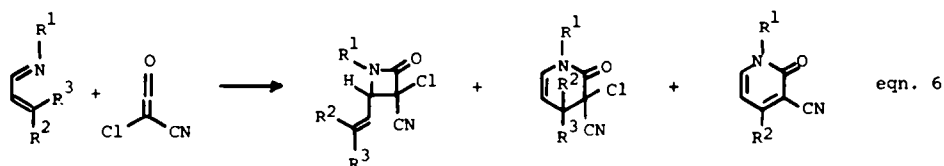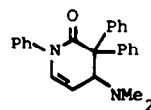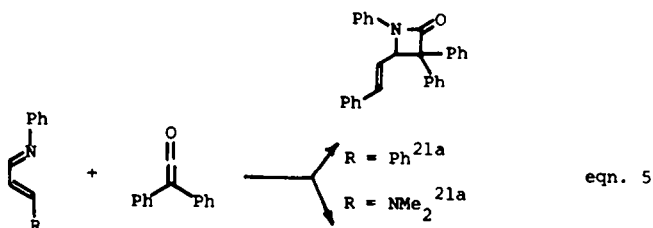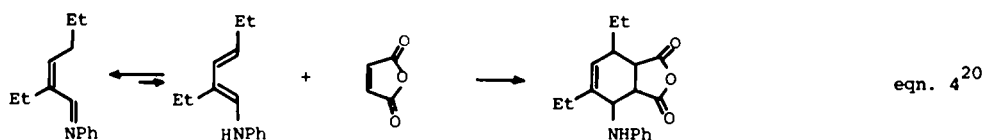
R^1	R^2	R^3			
t-Bu	Ph	H	–	56%	19% [21b]
C$_6$H$_{11}$	Ph	H	–	71%	21%
p-CH$_3$OC$_6$H$_4$	Ph	H	17%	42%	22%
t-Bu	Ph	Ph	86%	–	–
C$_6$H$_{11}$	Ph	Ph	58%	36%	–
p-CH$_3$OC$_6$H$_4$	Ph	Ph	90%	–	–

eqn. 7

$10-43\%^{22}$

R = H, Alkyl

R' = Ar, Alkyl
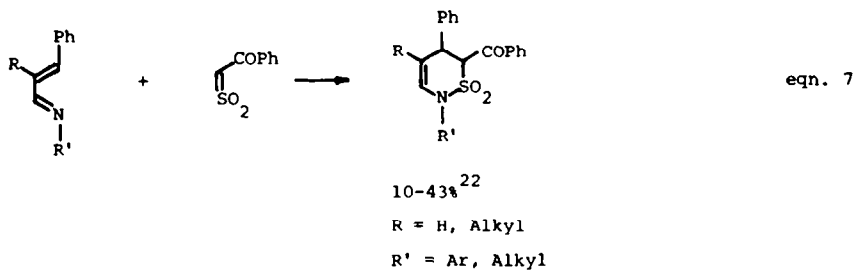
Two recent reports have described successful approaches to the use of 1-azabutadienes which have broad synthetic implications, eqns (8) and (9), Schemes 1-2. Fowler[23a] has shown that gas phase pyrolysis of N-acyl-O-a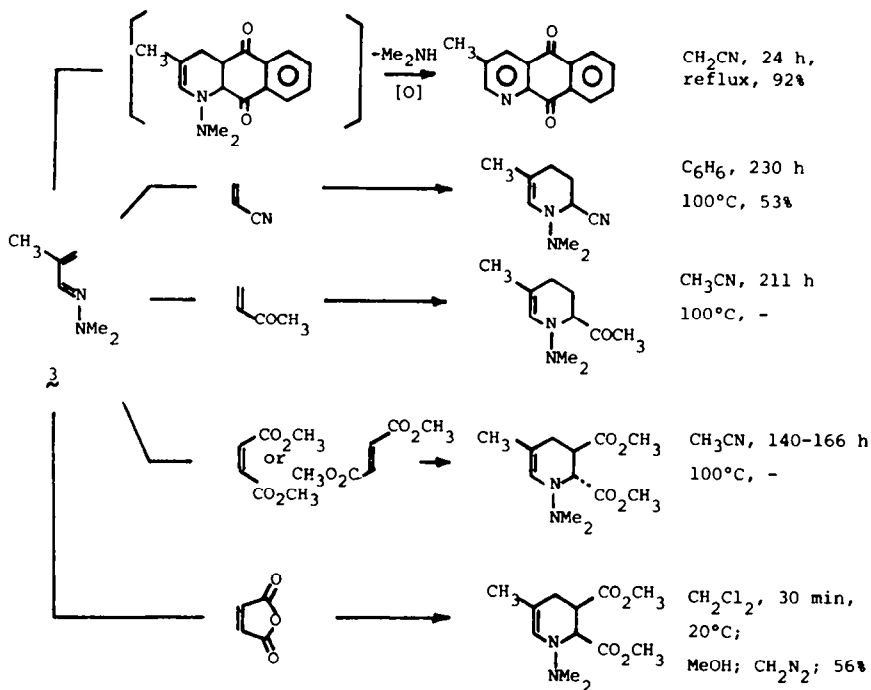cetyl-N-allylhydroxylamines generates N-acyl-1-azabutadienes which were shown to be capable of undergoing intramolecular [4 + 2] cycloaddition, eqns (8)–(9). The entropic assistance provided by the intramolecular cycloaddition, the inability of the dienes to tautomerize, and the relative stability of the product (acyl vs alkyl enamine) may account for the success of this process. This reaction has been applied to the synthesis of amide 1,[23b] a key intermediate in the total synthesis of deoxynupharidine 2, Scheme 1.[23c]

R=H,n=1,2
R=Ph,n=1

eqn. 8

$70-75\%^{23a}$

eqn. 9

$69\%^{23a}$

1 : 3 1
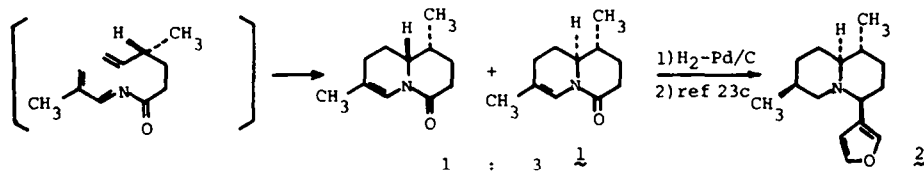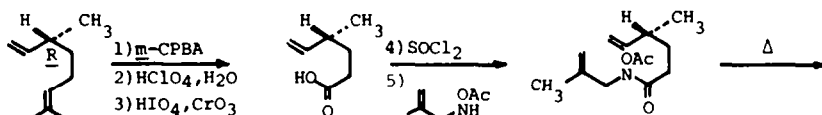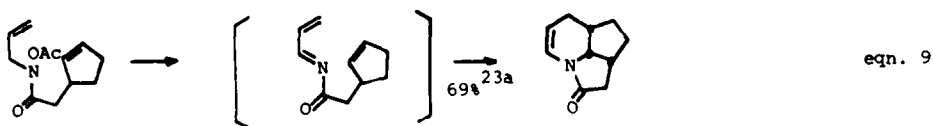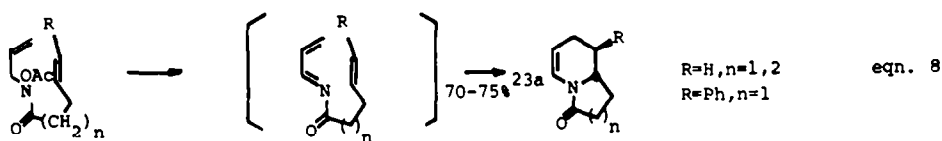
23b

Scheme 1.

In a successful effort to increase the reactivity of simple 1-azadienes toward typical electron-deficient dienophiles, Ghosez et al.[24] have reported that the α,β-unsaturated hydrazone 3 reacts regioselectively with a wide range of typical dienophiles to give the [4 + 2] cycloadducts. Reductive cleavage of the N–N bond and reduction of the C–C double bond in the adducts provided the substituted piperidines, Scheme 2. Similar reactions with α,β-unsaturated oximes failed to give [4 + 2] cycloadducts.[24] It remains to be determined whether this process is general for unsaturated hydrazones capable of tautomerization.

CH₂CN, 24 h, reflux, 92%

CH_2CN, 24 h, reflux, 92%

C_6H_6, 230 h 100°C, 53%

CH_3CN, 211 h 100°C, -

CH_3CN, 140-166 h 100°C, -

CH_2Cl_2, 30 min, 20°C; MeOH; CH_2N_2; 56%

Scheme 2.

In related work, Gompper has described the [4 + 2] cycloaddition of hydrazone **4** with diphenyl ketene, eqn (10).[25]

eqn. 10[25]
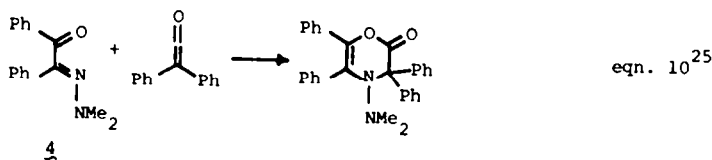
Fitton[26] has shown that 3-(aryliminomethyl)chromones **5** undergo [4 + 2] cycloaddition with dichloro- or chlorophenyl ketene **6**, whereas the isomeric 2-(aryliminomethyl)chromones **7** undergo [2 + 2] cyclo-addition with the same ketenes, eqns (11) and (12).

eqn. 11

21-85% R^5=Cl,Ph[26]

eqn. 12

R^5=Cl,Ph[26]
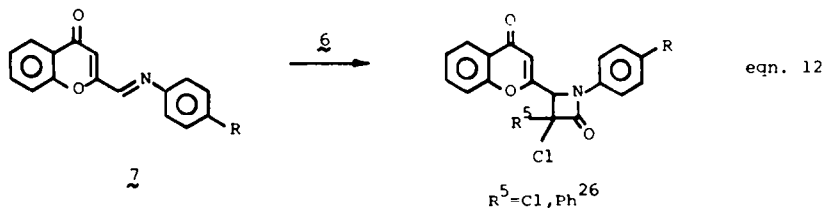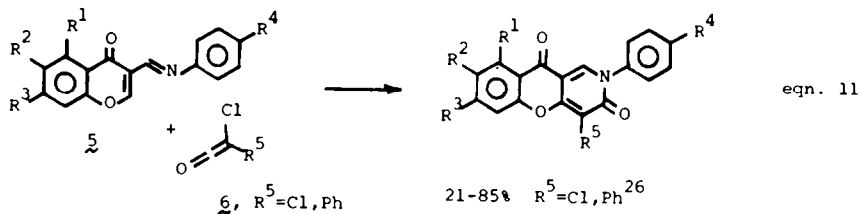
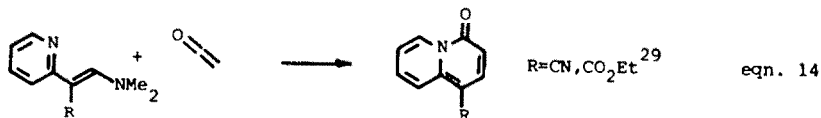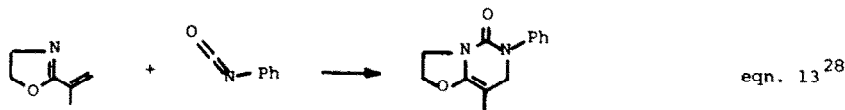$2H$-1,3-Oxazin-2-ones, e.g. **8** and **9**, have been shown to participate in a [4 + 2] cycloaddition reaction with N-aryl maleimides but failed to react with dimethyl acetylenedicarboxylate, diethyl azodicarboxylate or enamines. The reaction of **8** with ynamines took an entirely different course, Scheme 3.[27]
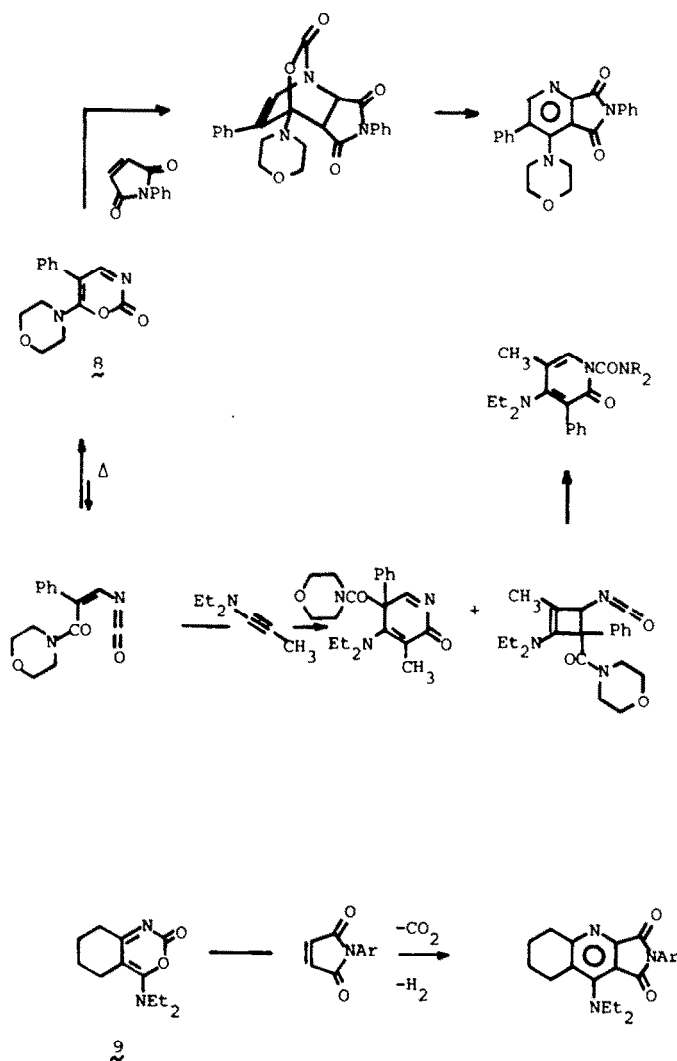
Scheme 3.[27]

Since the initial observation that certain unsaturated–heterocycles may participate in [4 + 2] cycloadditions, eqns (2) and (3), a small number of additional examples have been described, eqns (13)–(17), and require the use of reactive ketene or isocyanate dienophiles.[28-30]

eqn. 13[28]

$R=CN, CO_2Et$ [29]   eqn. 14

eqn. 15

R=H, 39%[30]
R=Cl, 48%
R=NO$_2$, 78%

+ 1:2 adduct   eqn. 16

28%[30]

or   →   1:2 adducts[30]   eqn. 17
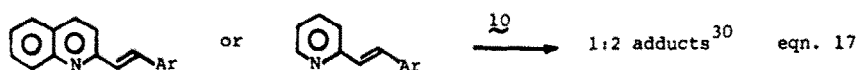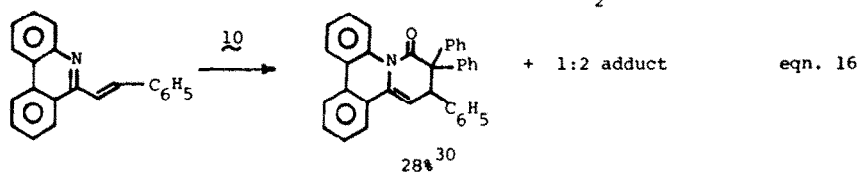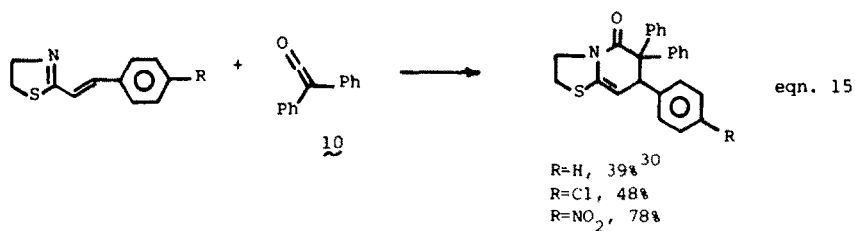
Table 1. Intermolecular Diels–Alder reaction of o-quinone methide imines

Substrate	Dienophile	Conditions	Product	
		200°C		— 31a
	Cl—CO$_2$H	hv		— 31b
	CO$_2$CH$_3$ / CO$_2$CH$_3$	hv		88% 31b
	NPh	hv, Et$_2$O 6 hr		14% 31c
—		hv, Et$_2$O 8 hr		98% 31c
	—	F$^-$, CH$_3$CN		77% 31d
		—		X=O,S 31e

Initial studies[31,32] on the generation and properties of o-quinone methide imines, Table 1, suggest that upon continued investigation they will prove useful synthetic intermediates comparable to the o-xylylenes[12b,13] and o-quinone methides.[5,12b,33]

In recent studies, Saegusa et al.[31d] have shown that [o-[(trimethylsilyl)alkylamino]-benzyl]trimethyl-ammonium halides undergo a fluoride anion induced 1,4-elimination to generate o-quinone methide N-alkylimines under mild conditions, eqn (18). Although attempts to trap the o-quinone methide imines with intermolecular dienophiles such as acrylate, fumarate, acetylenedicarboxylate and N-phenyl-maleimide failed and resulted in the formation of dimer 11, eqn (18), intramolecular Diels–Alder reactions proved useful, eqn (19). The application of this methodology to the synthesis of 9-azaestro-

$$\text{eqn. 18}$$

11

$$\text{eqn. 19}$$

n=3 53%
n=4 58%
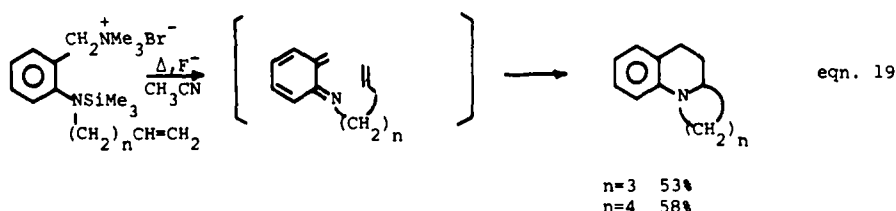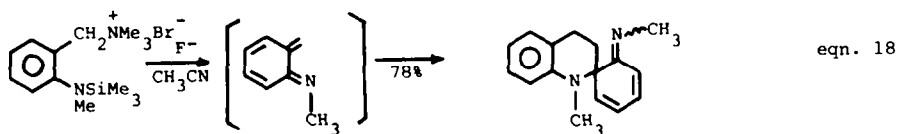
1,3,5(10)-trien-17-one (12) attests to the synthetic utility of the o-quinone methide imines, Scheme 4.[31d]
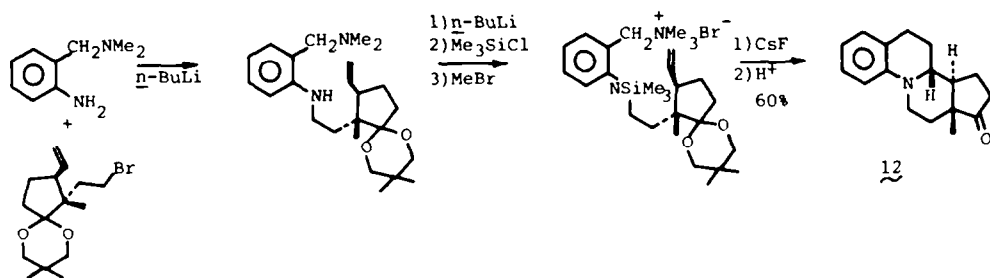
Scheme 4.

Warming benzotriazinone 13 or irradiation of carbamate 14 generated the reactive o-quinone methide ketene 15 which in the presence of phenylisocyanate affords 2-anilino-benz-3,4-oxazin-4-one (16) by way of a [4 + 2] cycloaddition reaction, eqn (20).[34]

$$\text{eqn. 20}$$
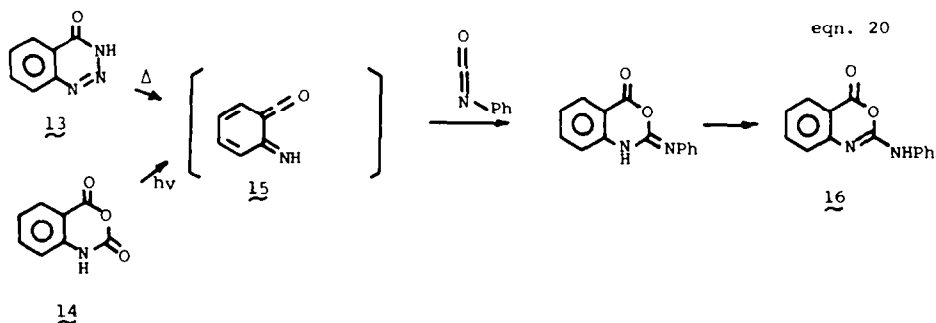
McKillop and Sayer[35] have reported that the Cu(II) complexes derived from o-nitrosophenols react smoothly with dimethyl acetylene dicarboxylate to give 1,4-benzoxozines, eqn (21).

$$\text{eqn. } 21^{35}$$
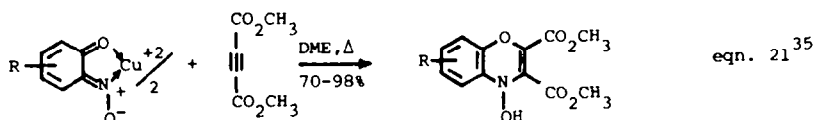
III. 2-AZABUTADIENE SYSTEMS

III.1 2-Azabutadienes

A number of [4 + 2] cycloaddition reactions of simple 2-azabutadienes have been reported and in each instance the diene is substituted with strong electron-donating groups capable of enhancing their reactivity toward typical electron-deficient dienophiles.

Thermolysis of 2-methoxy-1-azetine (**17**) afforded **18** via electrocyclic ring opening followed by a 1,5-hydride shift. Treatment of **18** with dimethyl acetylene dicarboxylate gave the pyridine product **19**, eqn (22).

$$\text{eqn. } 22$$
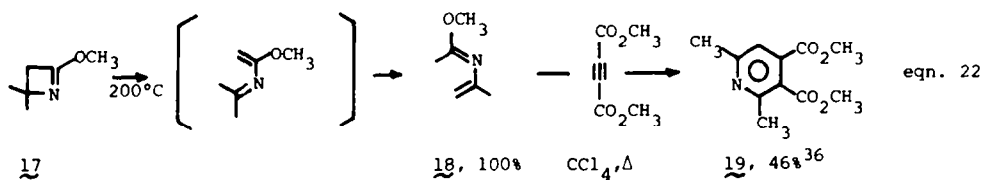
Thermolysis of 3-substituted 2-dimethylamino-1-azirines, prepared from the corresponding tertiary carboxamides, was shown to give 1-dimethylamino-2-azabutadienes which undergo regiospecific Diels–Alder reactions with a wide range of electron-deficient dienophiles,[37] Scheme 5.
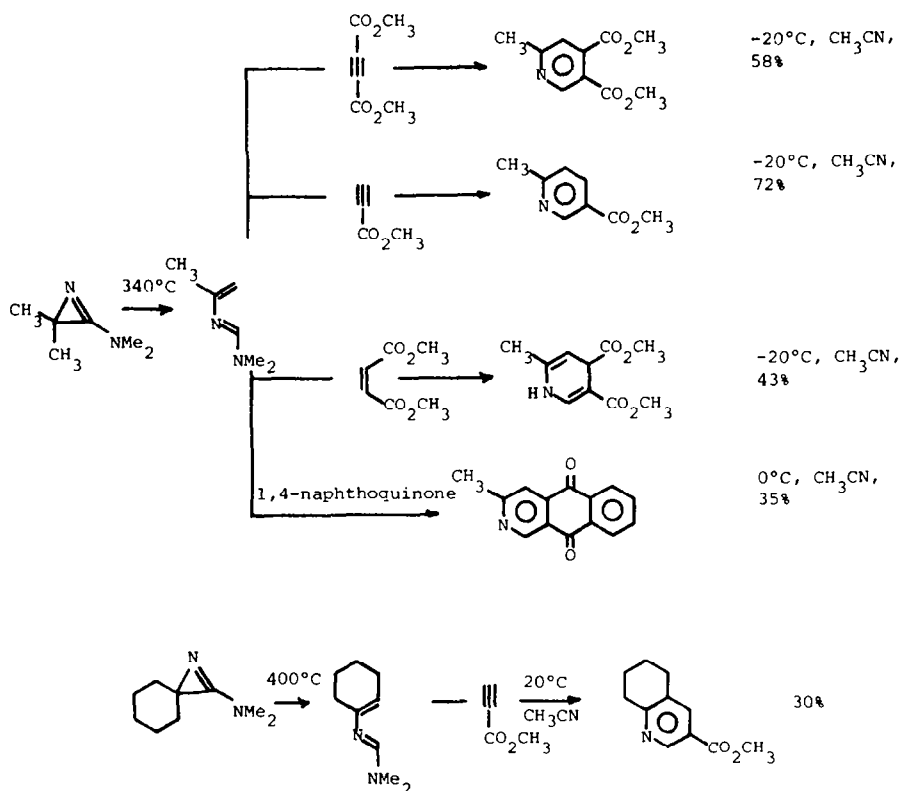
Scheme 5.[37]
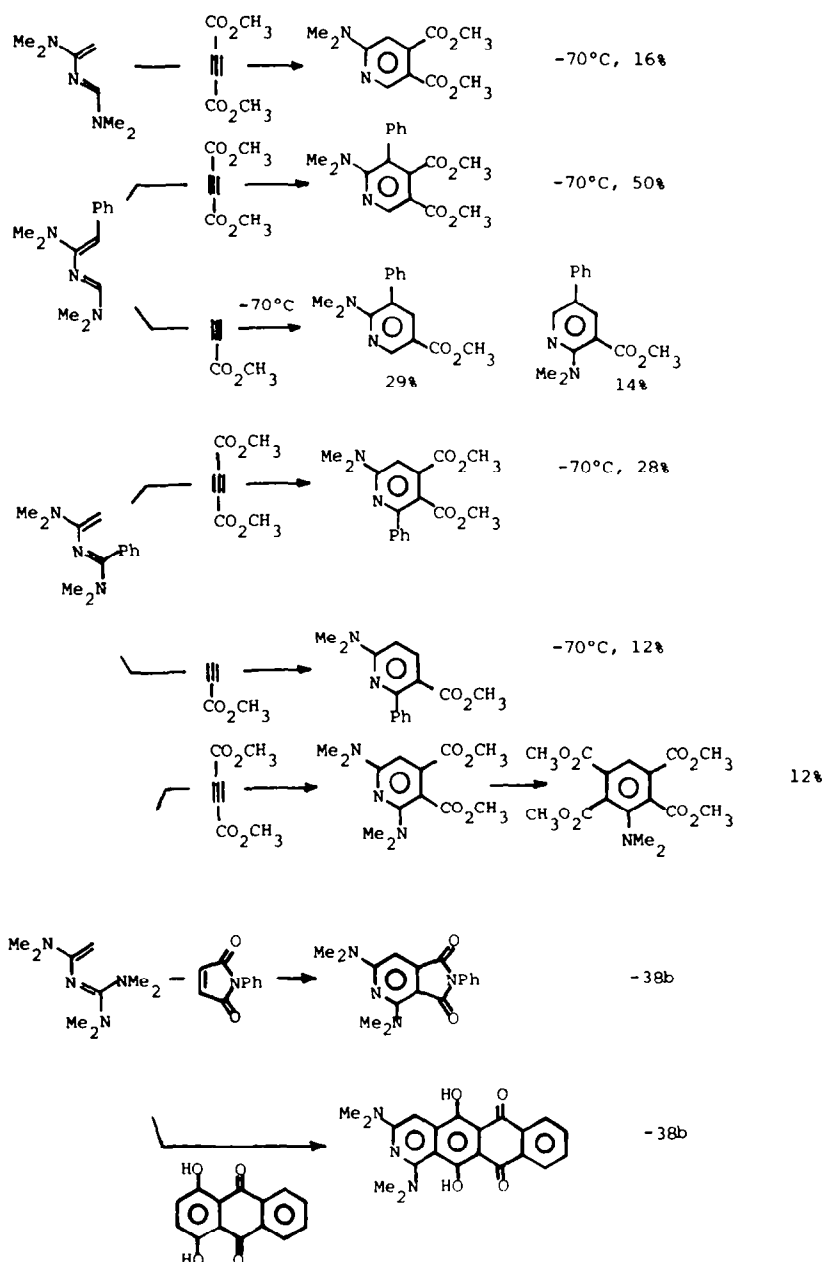
Scheme 6.[38]

A series of reactive 1,3-bis(dimethylamino)-2-azabutadienes were generated *in situ* from 1-alkyl-2-azavinamidinium salts and were found to be reactive toward electron-deficient dienophiles,[38] Scheme 6.

A simple preparation of 1,3-bis(*t*-butyldimethylsilyloxy)-2-azabutadienes from imides and their reaction with a range of typical dienophiles have been described,[39] Scheme 7. The apparent ease with which this 2-azadiene system may be generated and the facility with which **20** undergoes cycloaddition with electron-deficient dienophiles should prove exceptionally useful.

Imines generated from the reaction of aryl aldehydes with the ethyl ester of glycine react with
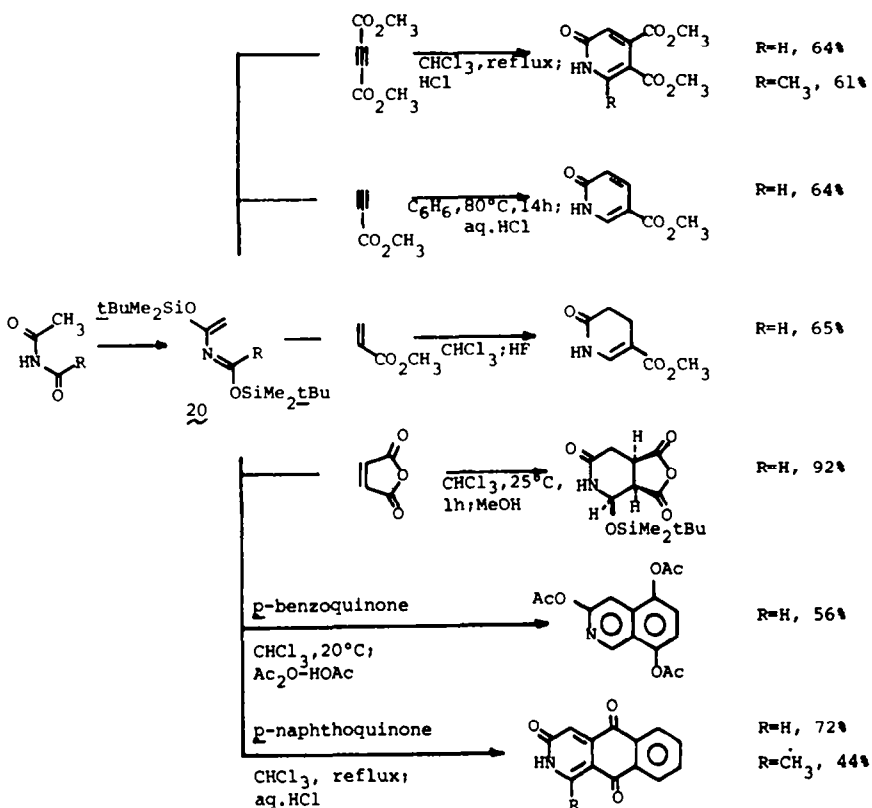
Scheme 7.[39]

dimethylformamide diethyl acetal to afford 1-aryl-4-dimethylamino-3-carboethoxy-2-azabutadienes which were shown to react with dimethyl acetylene dicarboxylate,[40] eqn (23).

eqn. 23

$$CH_3CN, \Delta$$

X=H	41%[40]
X=Cl	38%
X=CH$_3$	15%

eqn. 24

Y=OAc, X=H	neat, reflux, 7 days	83%[42a]
Y=Ph, X=H	toluene, 110°C	62%[42b]
Y=Cl, X=H	toluene, 110°C	53%[42b]
Y=CH$_3$, X=CH$_3$	neat, 100°C	34%[42b]
Y=Ph, X=CH$_3$	toluene, 110°C	9%[42b]
X=Y=H	DME, 95°C	26%[42b]
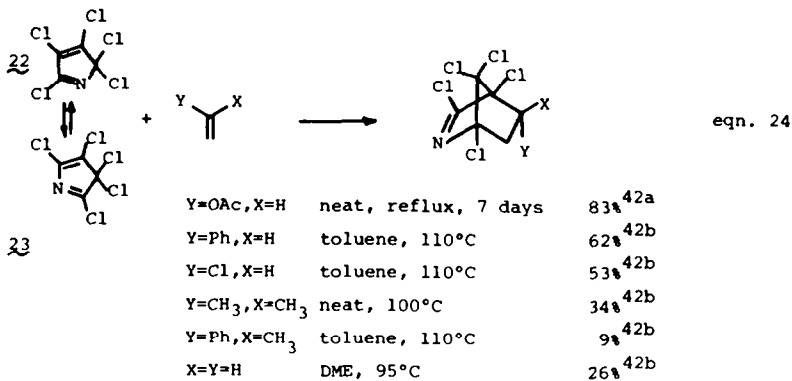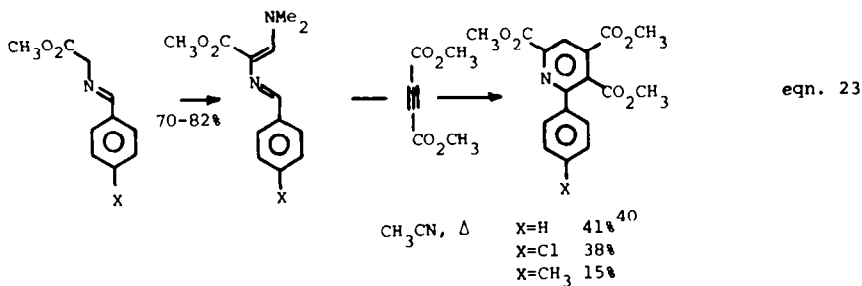
Thermolysis of 4,4-dimethyl-1-(1-phenylvinyl)-5-(1-pyrrolidinyl)-4,5-dihydro-1H-1,2,3-triazole provided **21** which was shown to react sluggishly with typical electron-deficient dienophiles,[41] Scheme 8.

The initial reports that pentachloro-1-azacyclopentadiene **22** behaves as a reactive, electron-deficient 1-azabutadiene[42c-e] have been shown to be in error.[42a,b] The system undergoes Diels–Alder reactions with reactive or electron-rich olefins as pentachloro-2-azacyclopentadiene **23**,[42a,b] eqn (24).


Scheme 8.
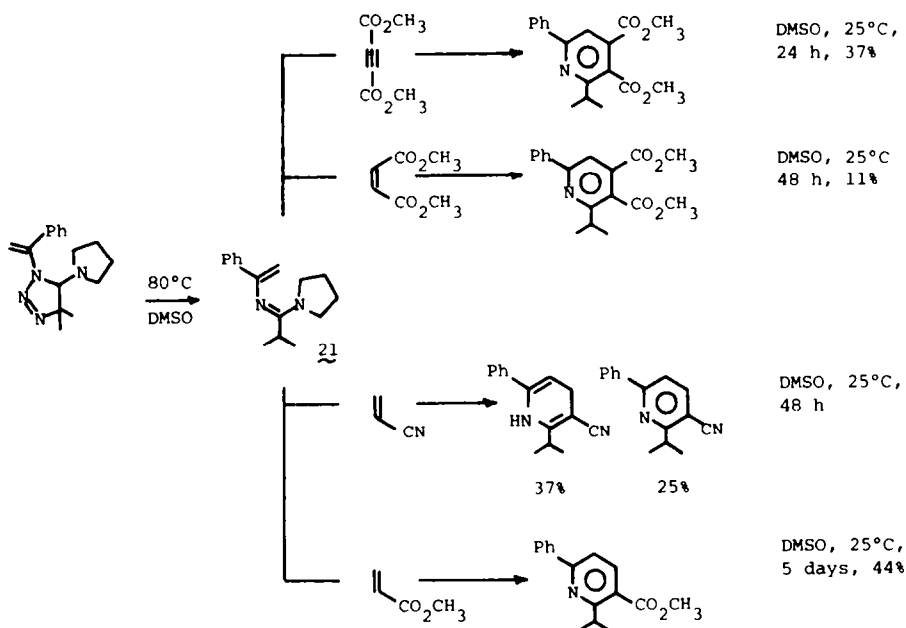
2-Substituted-4-methyl-1,3-oxazin-6-ones **24** have been shown to react exothermically with electron-rich dienophiles, e.g. 1-(diethylamino)propyne and 1-ethoxy-1-(dimethylamino)ethylene, to give the substituted 4-aminopyridines **25** and **26** respectively in high yield,[43] eqns (25) and (26). The synthetic potential of 3-aza-α-pyrones would seem to be limited only by the stability and the ease of preparation of the parent ring system.[44]

Similarly, 4H-3,1-benzoxazinones **27** may undergo a [4 + 2] cycloaddition with 1-(diethylamino)propyne but the solvent and substituent (R) play an important role in determining the course of the reaction,[45a] eqn
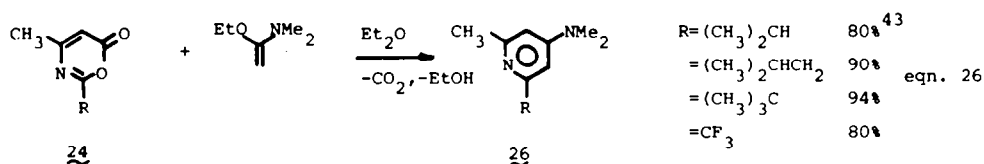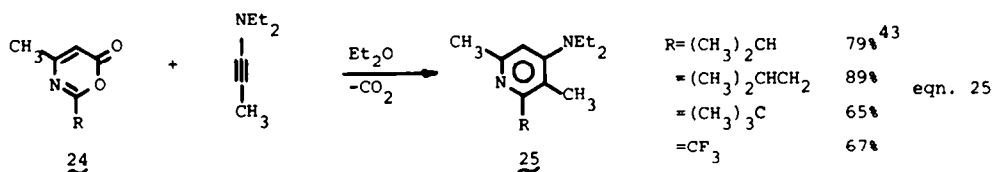
(27). The reaction of 4H-3,1-benzoxazinones **27** with enamines has been shown to take an entirely different course.[45b]


eqn. 27
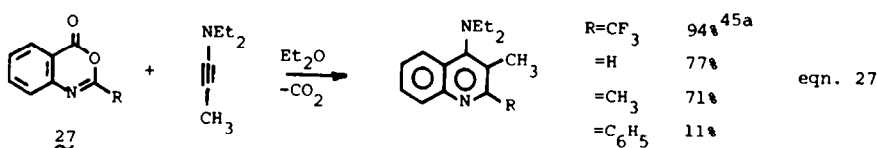
The initial observation that imines derived from aniline and aryl aldehydes react with electron-rich or reactive olefins in the presence of catalysts ($BF_3 \cdot OEt_2$ or protic acids) to give formal [4 + 2] cycloadducts continues to be investigated,[46,47] Scheme 9, and these studies have been briefly reviewed.[9] These systems fail to give Diels–Alder products with typical electron-deficient dienophiles.[1,9]
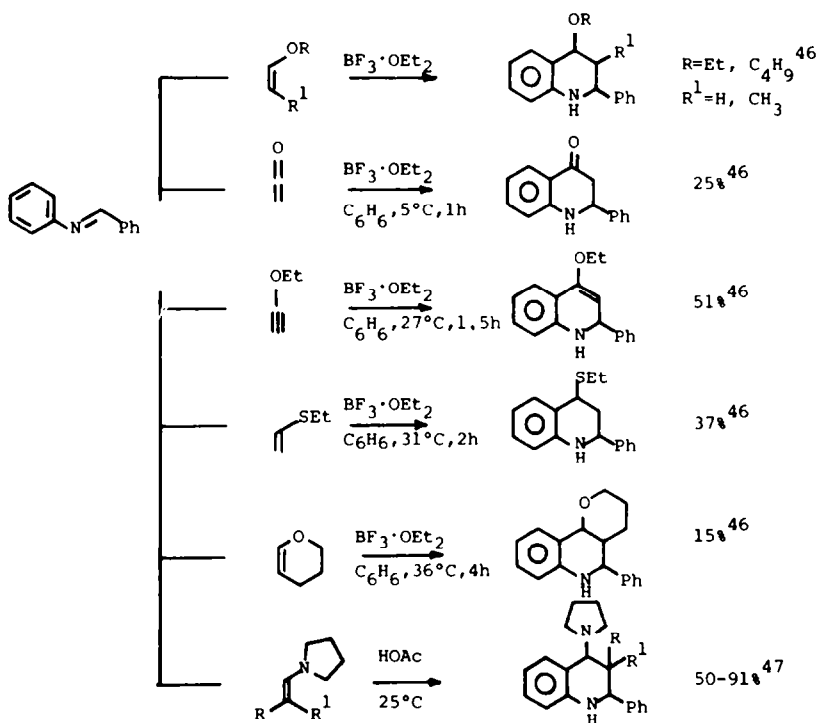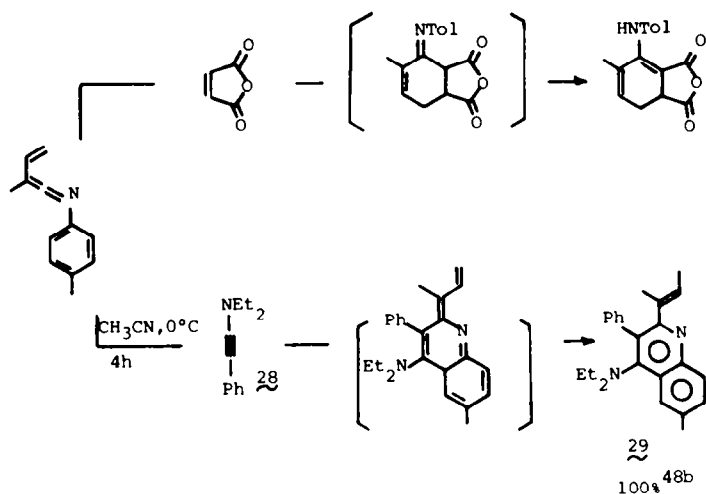

Scheme 9.

Ghosez *et al.*[48a] have shown that N-aryl ketenimines react with ynamines to give substituted quinolines, eqn (28). Solvent effects for this reaction are consistent with a polar cycloaddition.

In an extension of this observation, Ghosez has shown that a N-aryl vinylketenimine reacts with electron-deficient dienes in an all-carbon Diels–Alder reaction while its reaction with the electron-rich ynamine **28** affords quinoline **29** by cycloaddition across the azadiene system,[48b] Scheme 10.


eqn. 28

$R=R^1=CH_3$ 85%[48a]
$R=Ph, R^1=CH_3$ 67%
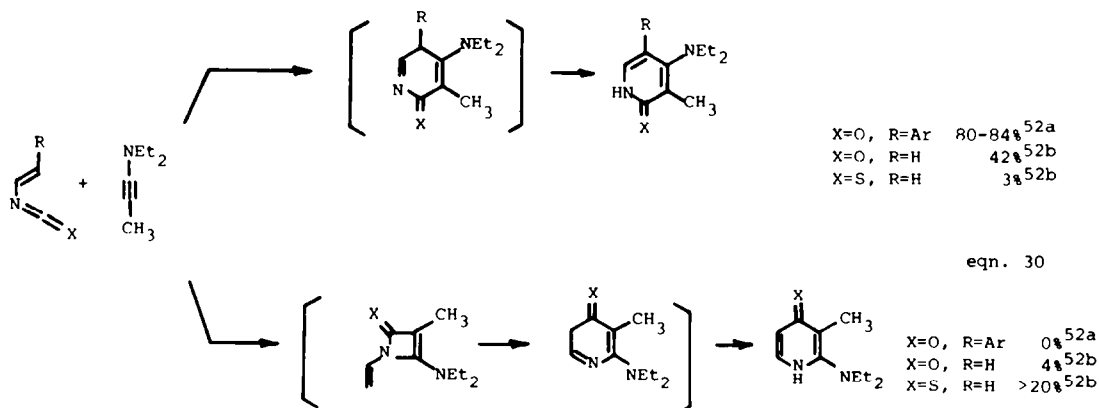$R=R^1=Ph$ 61%
$R=CH_3, R^1=Ph$ 52%
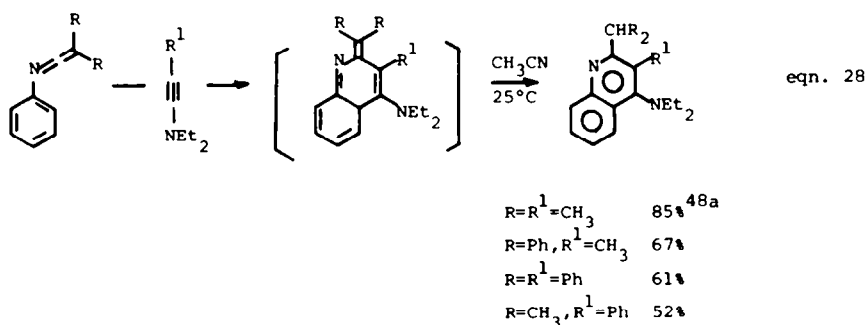
Scheme 10.

Similar observations have been made on the reactions of N-aryl ketenimines or N-aryl vinyl-ketenimines with thiobenzophenones[49] and these studies have been reviewed recently.[7d]

Phenylisocyanate and related aryl isocyanates have been reported to give [4 + 2] cycloaddition products with ynamines,[50a] benzyne[50b] and ethoxyacetylene,[51] eqn (29). The course of the reaction of ynamines with aryl isocyanates is strongly dependent on reaction conditions. Products resulting from [2 + 2] cycloaddition adducts are formed in nonpolar reaction solvents (cyclohexane) whereas [4 + 2] cycloadducts are isolated from polar reaction solvents (acetonitrile) suggesting a pronounced polar character to the Diels-Alder reaction.
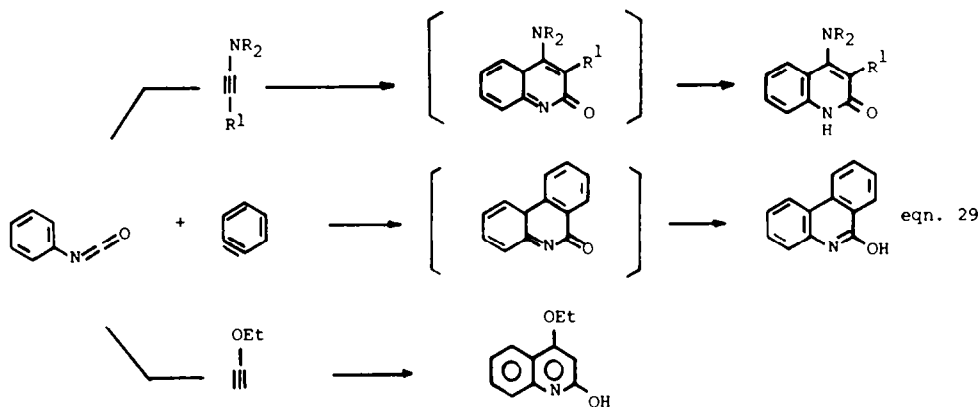
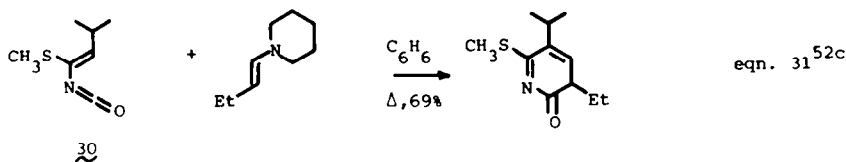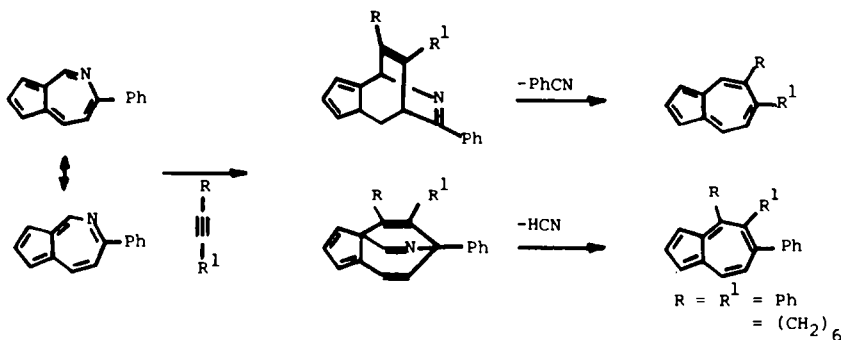

eqn. 29

Recent reports have described [4 + 2] cycloaddition reactions of vinyl isocyanates and vinyl thioiso-cyanates,[52] eqns (30) and (31).

X=O, R=Ar	80-84%	[52a]
X=O, R=H	42%	[52b]
X=S, R=H	3%	[52b]

eqn. 30

X=O, R=Ar	0%	[52a]
X=O, R=H	4%	[52b]
X=S, R=H	>20%	[52b]

$$\text{eqn. 31}^{52c}$$

A recent report has described the Diels–Alder reaction of 6-phenyl-5-azaazulene with acetylenes.[52d]
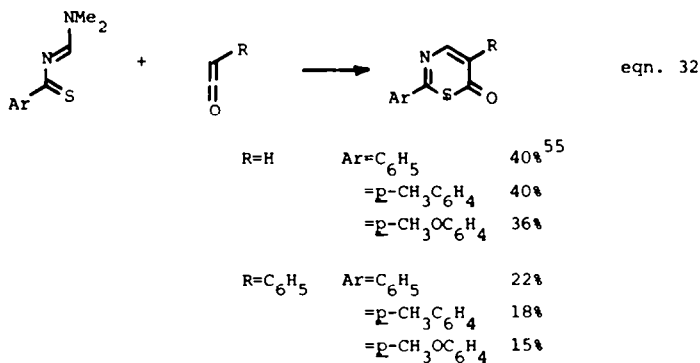

$$R = R^1 = Ph$$
$$= (CH_2)_6$$

III.2 Hetero-2-azabutadienes

A number of Diels–Alder reactions in which N-acylimines **31** act as dienes have been reported and much of this work has been reviewed.[5,53] X and Y are generally strong electron-withdrawing groups and

$$X=CCl_3, \quad Y=H$$
$$X=Y=CF_3$$

as such the N-acylimines are useful electron acceptor partners in a cycloaddition reaction. Examples of Diels–Alder reactions with vinyl ethers, enamines, olefins, sulfene, acetylenes and either the C=C or C=O bond of ketenes have been reported.[5,53] This complements the ability on many simple N-acylimines to behave as dienophiles toward typical electron-rich dienes.[6,54]

An example of N-thioacylimine participating as the 4π component of a [4 + 2] cycloaddition with ketenes has been described,[55] eqn (32).

$$\text{eqn. 32}$$

| R=H	Ar=C_6H_5	40%[55]
	=$\underline{p}$-$CH_3C_6H_4$	40%
	=$\underline{p}$-$CH_3OC_6H_4$	36%
R=C_6H_5	Ar=C_6H_5	22%
	=$\underline{p}$-$CH_3C_6H_4$	18%
	=$\underline{p}$-$CH_3OC_6H_4$	15%

Vinylnitroso compounds constitute a class of electron-deficient hetero-2-azabutadienes which have been shown to participate in a number of useful Diels–Alder reactions.[56,57,58c] The addition of electron-withdrawing substituents to the vinylnitroso system enhances their reactivity toward simple olefins,[56a,c,d] Table 2.

Table 2. Diels–Alder reactions of vinylnitroso compounds (4π component) with olefins and dienes

Vinylnitroso	Dienophile	Product
		R^1=Ph 92%[56b]
		R^1=CO$_2$Et, X=CH$_2$ 79%[56c] R^1=CO$_2$Et, X=O 46%[56c] R^1=COCH$_3$, X=O 75%[56e]
		R^1=CO$_2$Et 81%[56c] R^1=COCH$_3$ 86%[56e]
		R^1=CO$_2$Et >42%[56c]
		R^1=CO$_2$Et 100%[56c]
		R^1=CO$_2$Et, CHO 43%[56c,d] R^1=COCH$_3$ 44%[56e]
		R^1=CHO,R^2/R^3=(CH$_2$)$_6$,R^4=H 42%[56d] R^1=COCH$_3$,R^2/R^3=(CH$_2$)$_4$,R^4=H 22%[56e] R^1=CHO,R^2=R^4=Ph,R^3=H 13%[56d] R^1=COCH$_3$,R^2=R^4=Ph,R^3=H 46%[56e]
		R^1=R^2=H,R^3=Ph 90%[56a] R^1=R^2=H,R^3=pBrC$_6$H$_4$ 79%[56a] R^1=R^2=H,R^3=2-furyl 62%[56a] R^1=R^2=R^3=H 19%[56a]
		R^1=R^2=H,R^3=Ph,R^4=H 45%[56a] R^1=R^2=H,R^3=Ph,R^4=CH$_3$ 44%[56a] R^1=R^2=Cl,R^3=H,R^4=H 0%[56a]
		R^1=R^2=H,R^3=Ph 41%[56a]
		R^1=R^2=H,R^3=Ph 26%[56a] R^1=R^2=Cl,R^3=H 0%[56a]
		R^1=CH$_2$Cl 72%[58c] R^1=CH$_3$ 23% R^1=Ph 87% R^1=CN 40% R^1=H 13%
		R^1=Ph 48%[58c]

Vinylnitroso compounds may act as either the 2π or 4π component of Diels–Alder reactions with dienes,[56a] Scheme 11. In general it has been found that β-substituted vinylnitroso systems act as dienophiles,[6,58] Scheme 11—path *b*, whereas the vinylnitroso systems lacking a β-substituent behave as 4π components in their Diels-Alder reaction with dienes,[56a] Scheme 11—path *a*.
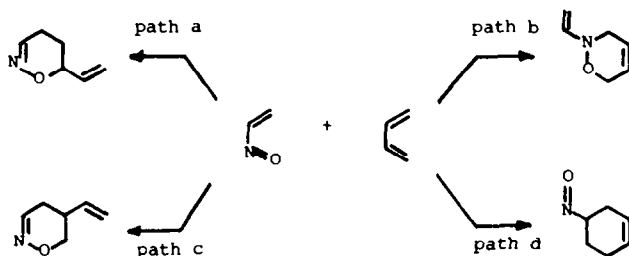
Scheme 11.

The speculation that the observed Diels–Alder reaction of vinylnitroso compounds with dienes, Scheme 11—path *a*, may actually arise from a sequence involving the all-carbon Diels–Alder reaction, Scheme 11—path *d*, followed by [3,3]-sigmatropic rearrangement to the oxazine 32, eqn (33), has not received experimental proof.
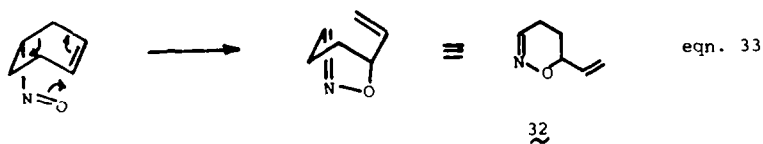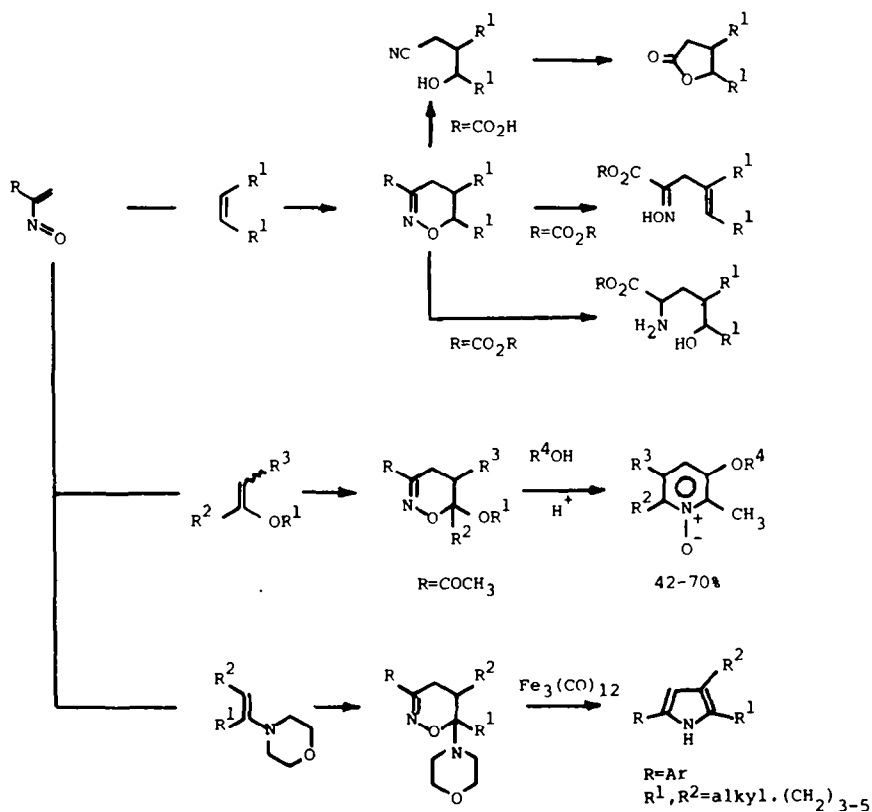

eqn. 33

32

Table 2 summarizes many of the reported Diels–Alder reactions of vinyl-nitroso compounds in which they serve as dienes.

This work has been applied to the preparation of aryl pyruvate oximes,[56a,c,e] amino acids,[56a,c] hydroxy nitriles,[56a,d] γ-lactones,[56d] pyridine N-oxides,[56f] and pyrroles,[57] Scheme 12.
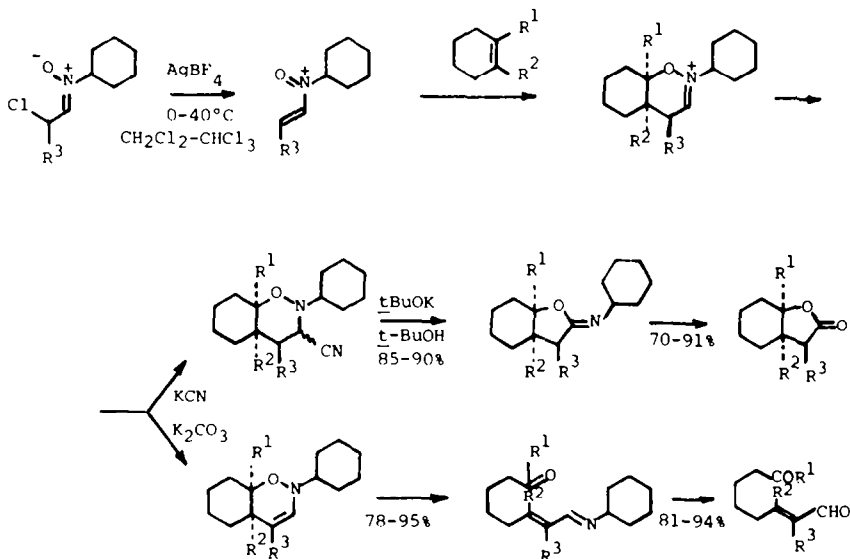

Scheme 12.

The ability for acyl nitroso compounds to behave as dependable 2π components of Diels–Alder reactions with dienes has been well established[6,59] and has found substantial utility in the synthesis of natural products. Recently, Mackay *et al.*[60] have described the isolation of 5,6-dihydro-1,4,2-dioxazine **36** (10%, $R^1 = t$-Bu) from the reaction of acyl nitroso **33** with cyclopentadiene, Scheme 13. Though this product may arise from the thermal isomerization of the oxazine **35**, Scheme 13 and eqn (34), acyl nitroso **34** gave the 5,6-dihydro-1,4,2-dioxazine **37** in excellent yield without the apparent intermediacy of the oxazine.


36, $R^1 = t$-Bu, $R^2 = R^3 = H$

37, $R^1 = p$-NO$_2$C$_6$H$_4$, $R^2 = CH_3$, $R^3 = $Ph

Scheme 13.

eqn. 34
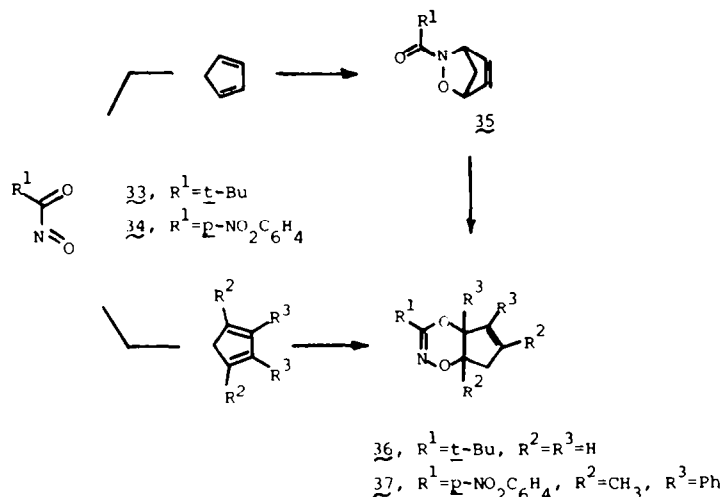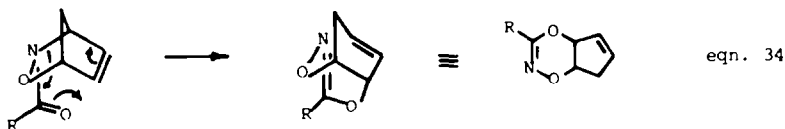
In related work, Eschenmosher *et al.*[61] have described the generation of N-vinyl-N-cycloal-kanenitrosonium ions and their reaction with olefins[61a–c] and alkynes.[61d,e] The olefin cycloadducts were utilized for the preparation of γ-lactones or dicarbonyl compounds, Scheme 14, and the alkyne adducts afforded α-methylene ketones or aldehydes directly, eqn (35).

Scheme 14.

eqn. 35

R^1=H, alkyl

R^2=alkyl

R^3=H, CH_3
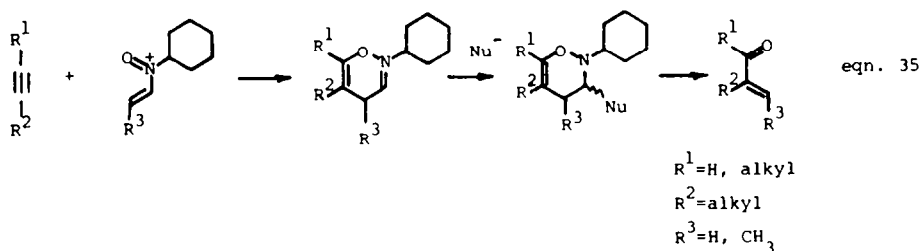
A similar sequence employing N-(2,3-epoxypropyliden)-cyclohexylamine N-oxide for the preparation of α-methylene-γ-lactones has been described,[62] Scheme 15.
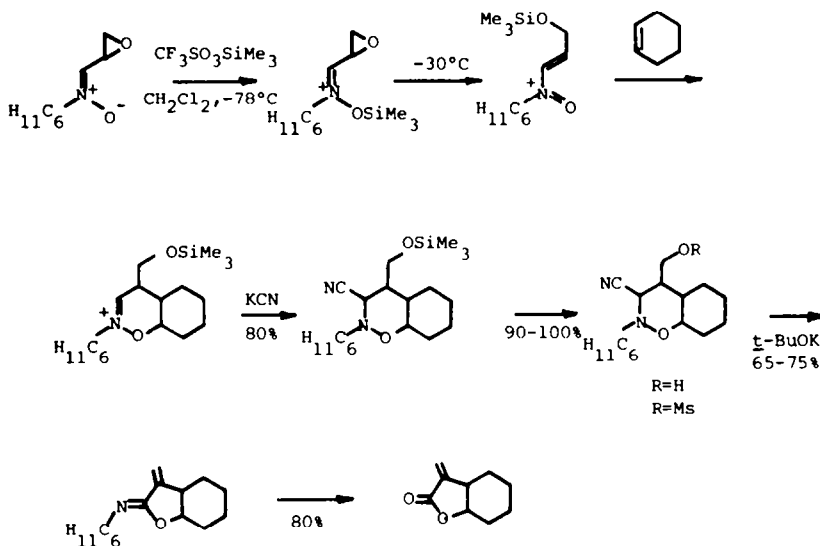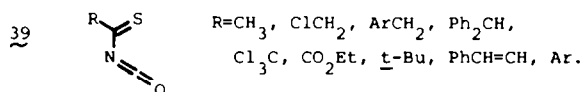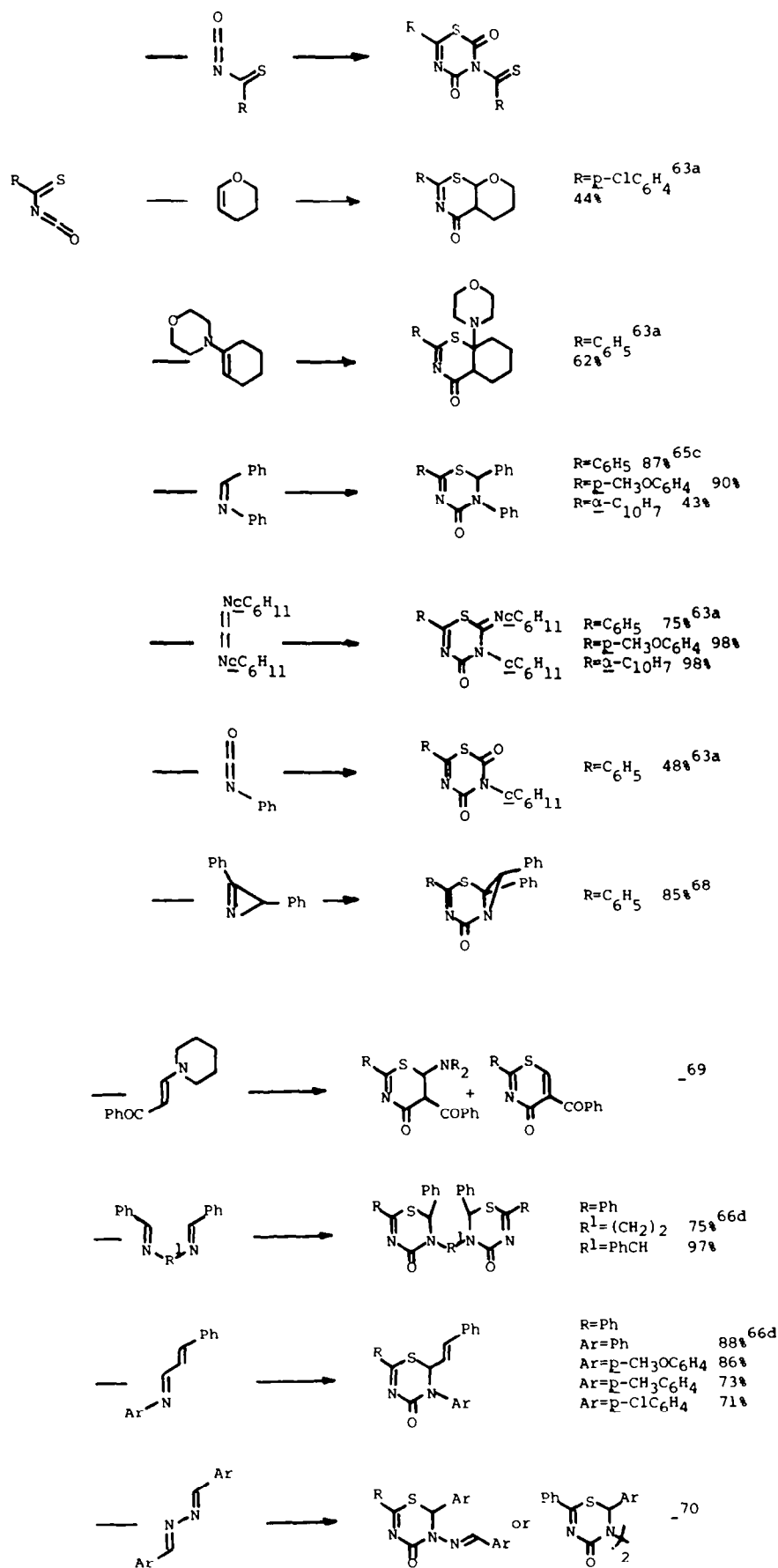

Scheme 15.

A number of heterocumulenes have been shown to function as hetero-2-azadienes in [4 + 2] cycloaddition reactions with dienophiles. Alkyl and aryl acyl isocyanates (38, X=Y=O), isothiocyanates (38, X=O, Y=S) or thioacyl isocyanates (38, X=S, Y=O) have been shown to participate in [4 + 2]
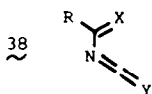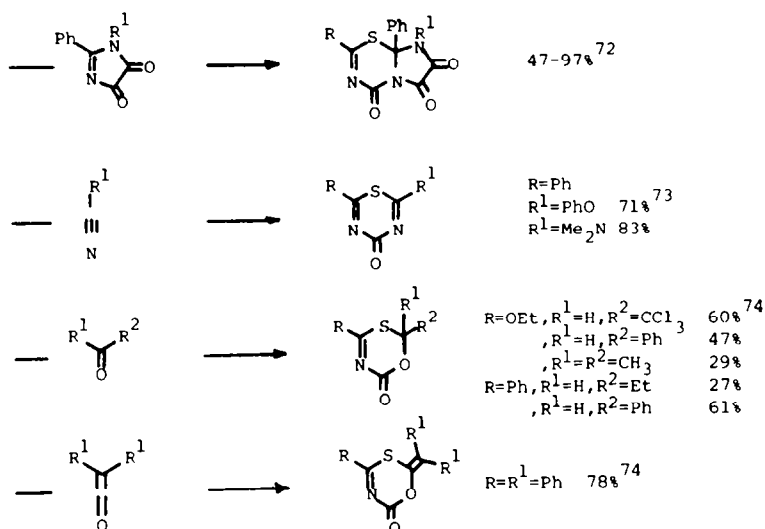

cycloaddition reactions though substantial differences in reactivity exist. Much of this work has been summarized in recent reviews.[7,5]

Thioacyl isocyanates, because of their high and dependable reactivity, compose the bulk of the work and extensive studies of their reactions with olefins,[64] e.g. norbornene, enamines,[63] dihydropyran,[63a] thioacyl isocyanates (dimerization),[65] imines,[65d,66] carbodiimides,[63a,67] the C=N bond of isocyanates,[63a] azirines,[68] β-enaminoketones,[69] the C=N bond of cinnamylidenesanilines,[66d] dianils,[66d] azines,[70] hydrazones,[71] imidazoline-4,5-dione,[72] aryl cyanates and disubstituted cyanamides,[73] the C=O bond of aldehydes,[74] acetone,[74] and ketenes[74] and alkyl/aryl iminodithiocarbonates[75] have been described. Typical examples are illustrated in Scheme 16. An extensive report by Goerdeler et al.[63d] compares the reactivity of several thioacyl isocyanates 39 toward most dienophiles and found that those substituted with strong electron-withdrawing groups are more stable and less prone to cycloaddition.


R=CH_3, $ClCH_2$, $ArCH_2$, Ph_2CH,

Cl_3C, CO_2Et, t-Bu, PhCH=CH, Ar.

R=p-ClC$_6$H$_4$ 44% [63a]

R=C$_6$H$_5$ 62% [63a]

R=C$_6$H$_5$ 87% [65c]
R=p-CH$_3$OC$_6$H$_4$ 90%
R=α-C$_{10}$H$_7$ 43%

R=C$_6$H$_5$ 75% [63a]
R=p-CH$_3$OC$_6$H$_4$ 98%
R=α-C$_{10}$H$_7$ 98%

R=C$_6$H$_5$ 48% [63a]

R=C$_6$H$_5$ 85% [68]

[69]

R=Ph
R^1=(CH$_2$)$_2$ 75% [66d]
R^1=PhCH 97%

R=Ph
Ar=Ph 88% [66d]
Ar=p-CH$_3$OC$_6$H$_4$ 86%
Ar=p-CH$_3$C$_6$H$_4$ 73%
Ar=p-ClC$_6$H$_4$ 71%

or [70]

R=Ph
R¹=PhO 71% [73]
R¹=Me₂N 83%

47-97% [72]

R=OEt,R¹=H,R²=CCl₃ 60% [74]
,R¹=H,R²=Ph 47%
,R¹=R²=CH₃ 29%
R=Ph,R¹=H,R²=Et 27%
,R¹=H,R²=Ph 61%

R=R¹=Ph 78% [74]

Scheme 16.

Similarly, aliphatic and aromatic acyl isocyanates undergo a wide range of [4 + 2] cycloaddition reactions though [2 + 2] cycloaddition and simple addition reactions are often observed. The substituent on the acyl isocyanate may determine the course of the reaction and such effects have been covered in prior reviews.[7,5] [4 + 2] Cycloadditions have been described for olefins such as norbornene and 4-vinyl pyridine, p-quinone, allenes, the C=C bond of ketenes, imines, dianils, ethylene diimines, enamines, vinyl ethers, ketene acetals, 1,2-dialkoxy-1-alkenes, carbodiimides, azirines, vinyl sulfides, and acetylenes.[7b,c] An example of the utility of such processes is the preparation of exo,cis-hydroxy acid 40 from norbornene,[76] eqn (36).

eqn. 36

40
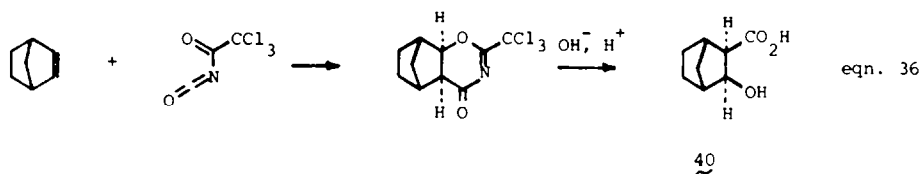
Acyl isothiocyanates have been shown to undergo [4 + 2] cycloaddition with enamines,[77] eqn (37), imines[78] and hydrazones.[79]

CHCl₃
1 h, 5°C;
30 min, reflux
49-55%

eqn. 37 [77]
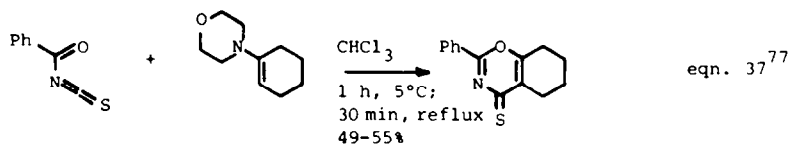
N-Sulfinylaniline 41 and related sulfinylimines may behave as 2π components of [4 + 2],[6] [2 + 2] or dipolar [3 + 2] cycloaddition reactions and, in some instances, as the 4π component of Diels–Alder reactions,[80] Scheme 17. Strained and reactive olefins, e.g. norbornene, norbornadiene, dicyclopentadiene, and cyclopentene, have been shown to react as dienophiles with N-aryl sulfinylimines. Typical products are 42–44.

Kobelt et al. have shown that 45 undergoes a Diels–Alder reaction with phenylacetylene,[81] eqn (38).

36%

eqn. 38
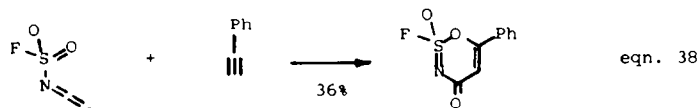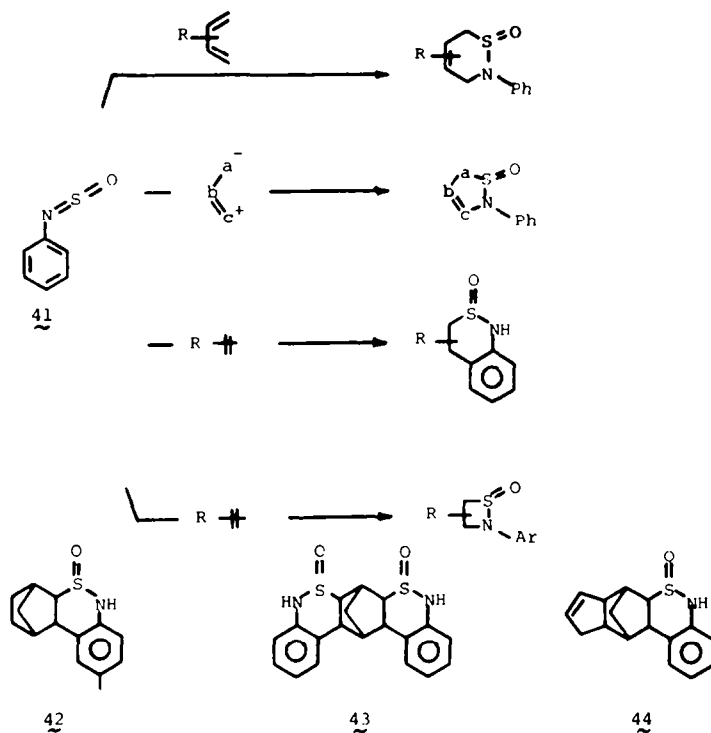
Scheme 17.

IV. 1,2-DIAZABUTADIENE SYSTEMS

IV.1 1,2-Diazabutadienes

Electron-deficient azoalkenes have been shown to react with dienes,[56a,b] Table 3, or reactive and electron-rich olefins,[82] Scheme 18. The reaction of electron-deficient azoalkenes with enamines has been shown to give [3+2][83] cycloaddition products, eqn (39), and not the originally reported [4+2] cycloaddition products.[82]
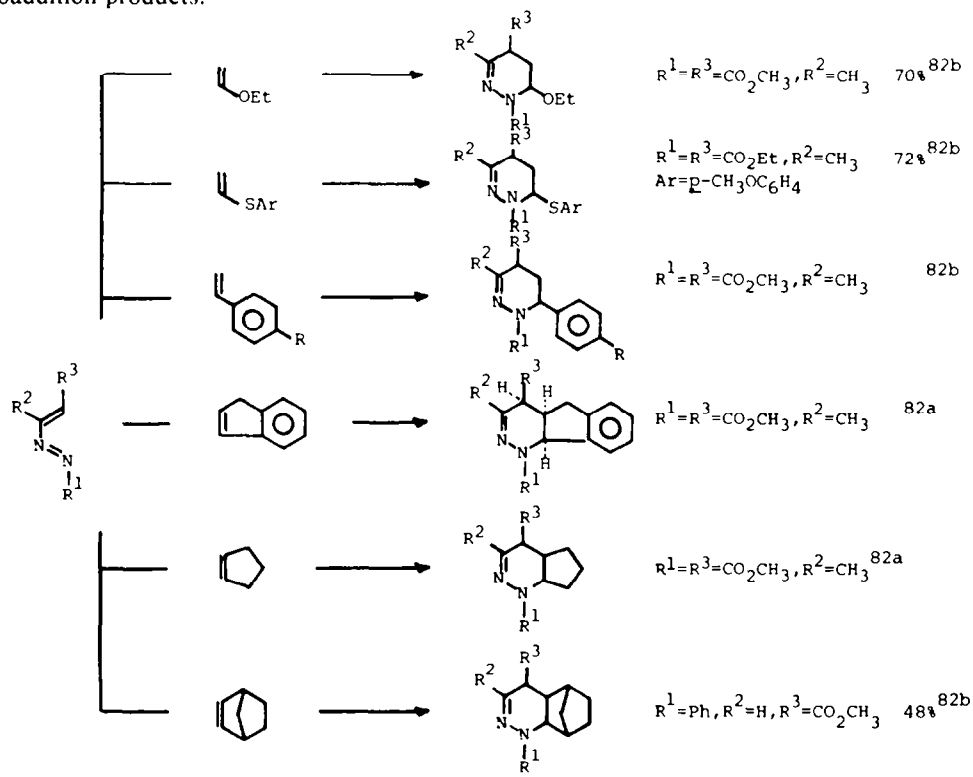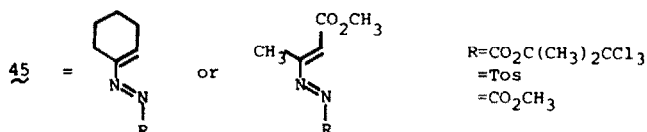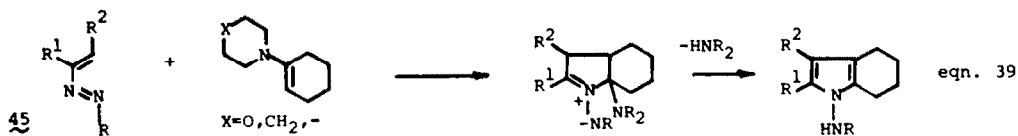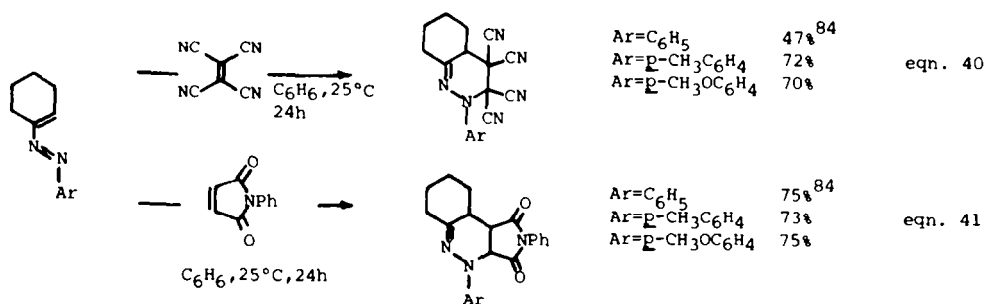

Scheme 18.[82a,b]

Table 3. Diels–Alder reactions of azoalkenes with dienes and reactive olefins[56a,b]

Vinyl Hydrazone	Dienophile	Product

$R^1=R^2=H,R^3=Ph,R^4=2,4-(NO_2)_2C_6H_3;96\%$
$R^1=R^2=H,R^3=Ph,R^4=Ts$ 72%
$R^1=R^2=H,R^3=Ph,R^4=CO_2Et$ 96%
$R^1=R^2=H,R^3=CH_3,R^4=2,4-(NO_2)_2C_6H_3;$
  78%
$R^1=H,R^2=CO_2Et,R^3=CH_3,R^4=$
  $2,4-(NO_2)_2C_6H_3;83\%$
$R^1=H,R^2=CO_2Et,R^3=CH_3,R^4=4-NO_2C_6H_4;$
  88%
$R^1=H,R^2=CO_2Et,R^3=CH_3,R^4=Ph$ 61%
$R^1=R^2=H,R^3=CH_3,R^4=Ph$ 14%

$R^1=R^2=H,R^3=Ph;$
$Ar=2,4-(NO_2)_2C_6H_3$ 67%

$R^5=H,R^2=H;$
$R^1=H,R^3=Ph,R^4=$
  $2,4-(NO_2)_2C_6H_3;$ 89%
$R^1=H,R^3=CH_3,R^4=$
  $2,4-(NO_2)_2C_6H_3;$ 22%
$R^1=CO_2Et,R^3=CH_3,R^4=Ph$ 0%
$R^5=CH_3,R^2=H;$
$R^1=H,R^3=Ph,R^4=$
  $2,4-(NO_2)_2C_6H_3;$ 87%

$R^1=R^2=H,R^3=CH_3;$
$Ar=2,4-(NO_2)_2C_6H_3$ 68%

$R^1=R^2=H,R^3=Ph;$
$Ar=2,4-(NO_2)_2C_6H_3$ 32%

$R^1=R^2=H,R^3=Ph;$
$Ar=2,4-(NO_2)_2C_6H_3$ 20%

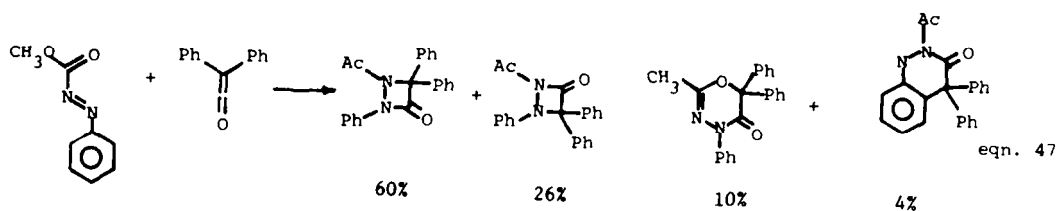eqn. 39

45 + X=O,CH$_2$,- → $-HNR_2$ →

45 = or $R=CO_2C(CH_3)_2CCl_3$
  $=Tos$
  $=CO_2CH_3$

Simple azoalkenes have been shown to react with typical electron deficient dienophiles[84] to give Diels–Alder products, eqns (40) and (41).

$$Ar=C_6H_5 \quad 47\%^{84}$$
$$Ar=\underline{p}-CH_3C_6H_4 \quad 72\%$$
$$Ar=\underline{p}-CH_3OC_6H_4 \quad 70\%$$

eqn. 40

$$Ar=C_6H_5 \quad 75\%^{84}$$
$$Ar=\underline{p}-CH_3C_6H_4 \quad 73\%$$
$$Ar=\underline{p}-CH_3OC_6H_4 \quad 75\%$$

eqn. 41

Reports of azoalkenes acting as 4π components in Diels–Alder reactions with azodicarboxylates,[85] eqns (42)–(44), thioisocyanates,[86] eqn (45), and ketenes,[87,88] eqns (46) and (47), have been published recently.

$$R^1=Ph, R^2=OCH_3 \quad 77\%^{85}$$
$$R^1=\underline{p}BrC_6H_4, R^2=OCH_3 \quad 79\%$$
$$R^1=Ph, R^2=OPh \quad 90\%$$
$$R^1=CH_3, R^2=OCH_2CCl_3 \quad 81\%$$

eqn. 42

$$R^2=OCH_3 \quad 79\%^{85}$$
$$R^2=OC(CH_3)_2CCl_3 \quad 72\%$$

eqn. 43

$$R^2=OCH_2CCl_3 \quad 80\%^{85}$$
$$R^2=Ph \quad 34\%$$

eqn. 44

$$43-90\%^{86}$$
$$R^1=CH_3, Ph$$
$$R^2=CH_3, alkyl$$
$$R^3=CONHPh, alkyl, H$$
$$R=SO_2R, COR, CO_2Et, Ph$$

eqn. 45

eqn. 46

eqn. 47
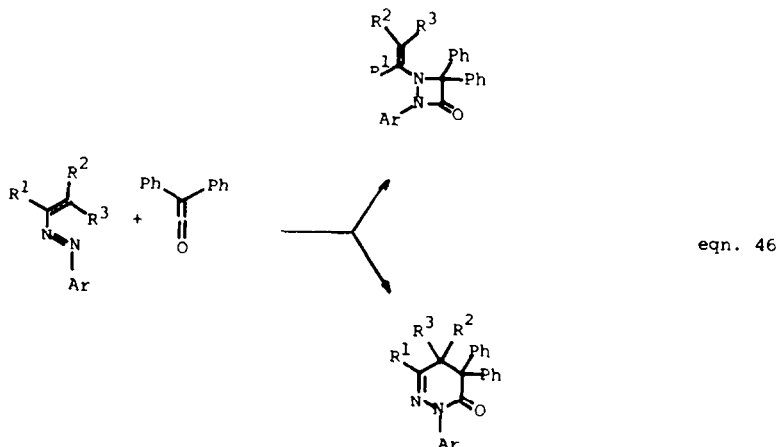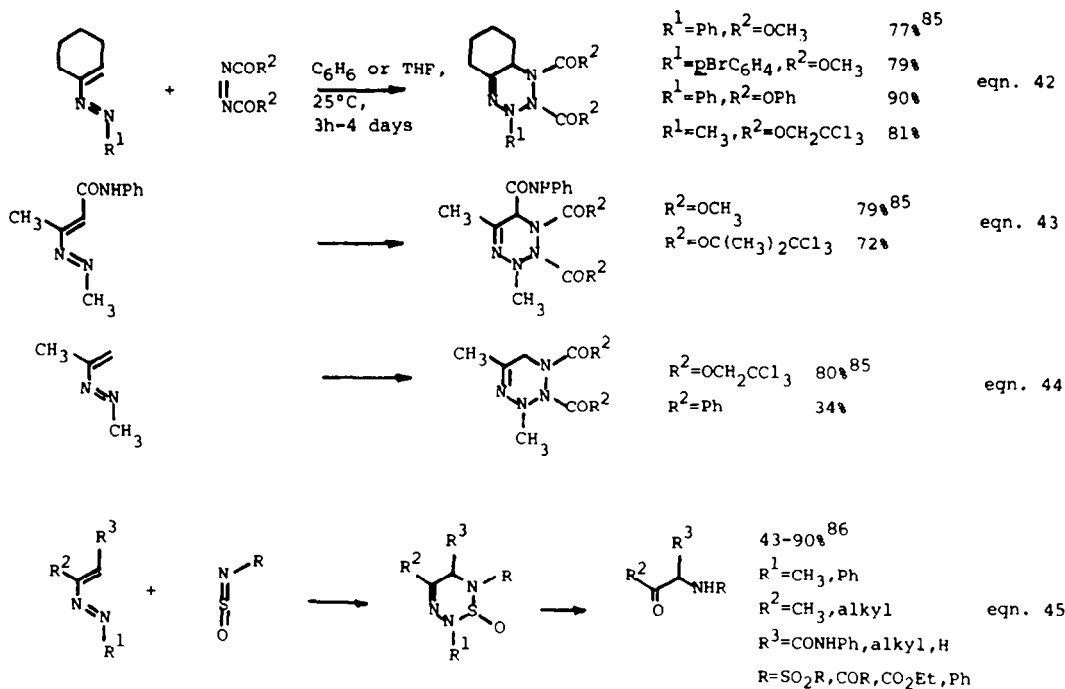
IV.2 Hetero-1,2-diazabutadienes

Azodicarboxylates are best recognized for their ability to participate as 2π components in Diels–Alder reactions with dienes and for their effective participation in ene reactions with simple olefins. However, olefins which do not contain a reactive allylic hydrogen and therefore cannot enter into an ene reaction may react with azodicarbonyl compounds by two different modes: [2 + 2] cycloaddition to
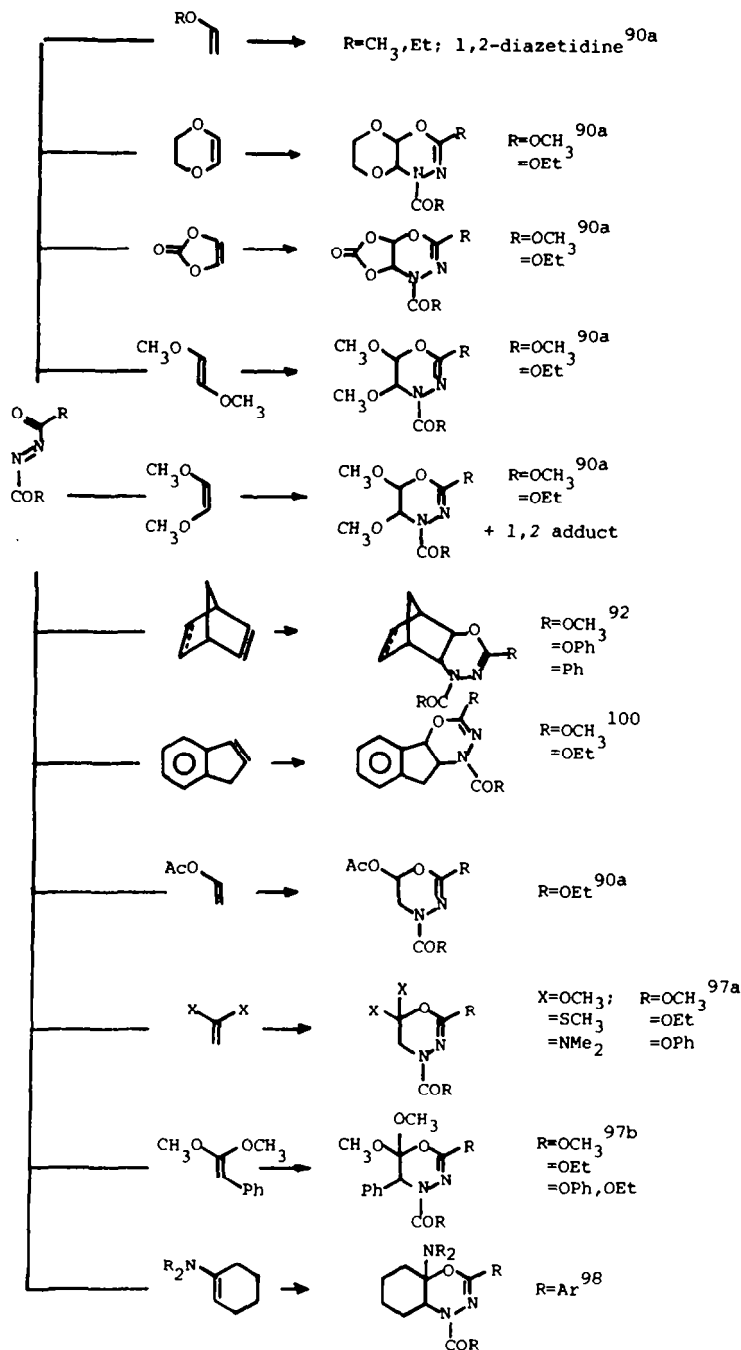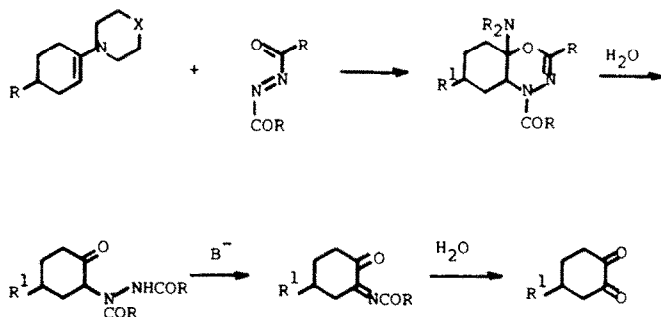

Scheme 19.

give 1,2-diazetidines and [4 + 2] cycloaddition to give 1,3,4-oxadiazines with the azodicarboxylate acting as the 4π component of the cycloaddition.[89,5] Typical 4π Diels–Alder reactions of azodicarboxylates are summarized in Scheme 19[90-100] and much of this work has been reviewed.[89,5]

The reaction of azodicarboxylates with electron-rich olefins has been extensively studied and typical substituent effects governing the course of [4 + 2] versus [2 + 2] cycloaddition are briefly summarized in Scheme 20.[91a]

>95	<5	R=OCH$_2$CCl$_3$ 85%
77	23	R=OCH$_3$ 73%
65	35	R=OEt 84%
<5	>95	R=Ph 66%
		R=OCH$_3$ Solvent
80	20	CH$_3$CN
65	35	neat
33	67	Et$_2$O
33	67	C$_6$H$_6$

X=OCH$_3$	87	13	82%
X=CH$_3$	84	16	85%
X=H	77	23	73%
X=Cl	67	33	56%
X=NO$_2$	<5	>95	40%
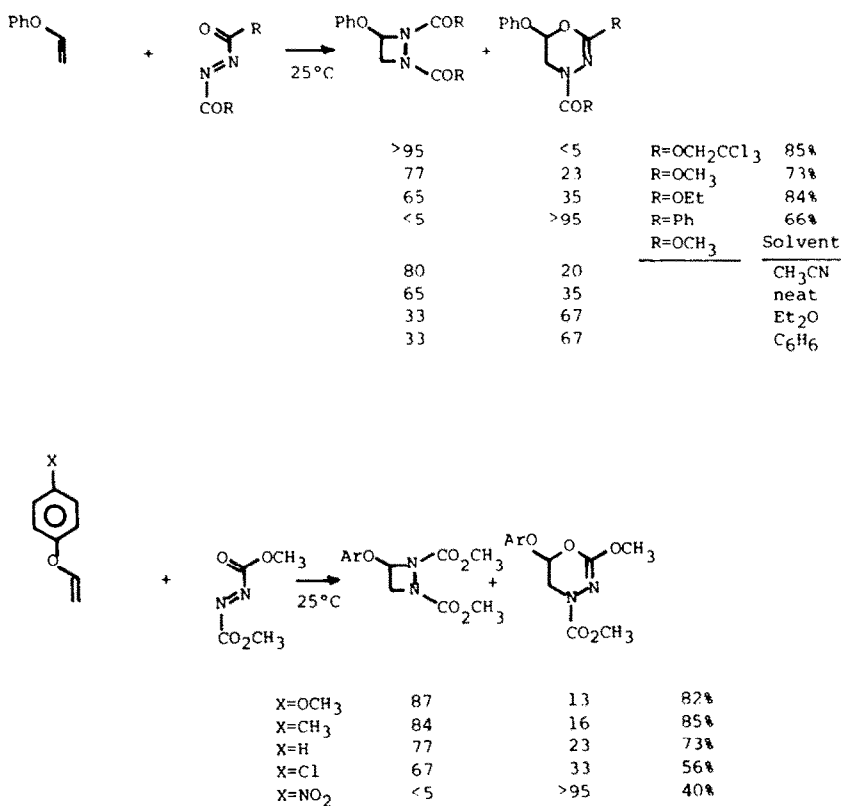
Scheme 20

The reaction of enamines with azodicarboxylates has been used for the preparation of α-diketones,[98] Scheme 21.

Scheme 21.

In a series of articles,[101] Mackay et al. have shown that the Diels–Alder adducts of azodicarboxylates and diacyl azocompounds with cyclopentadiene, cyclopentadienones, and 2,5-dimethyl-3,4-diphenyl-

cyclopentadiene give the expected diazines **47–49**, eqns (48)–(50), which may rearrange to the 1,3,4-oxadiazines **50–52**, the formal products of a 4π Diels–Alder reaction of **46** with the dienes.

eqn. 48

eqn. 49

eqn. 50
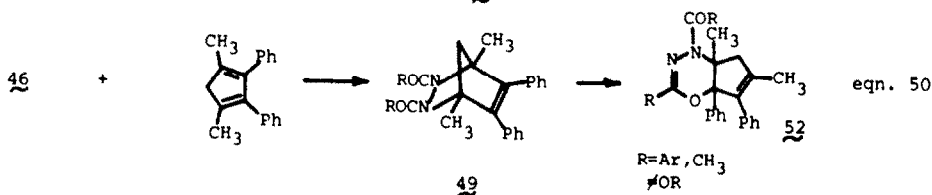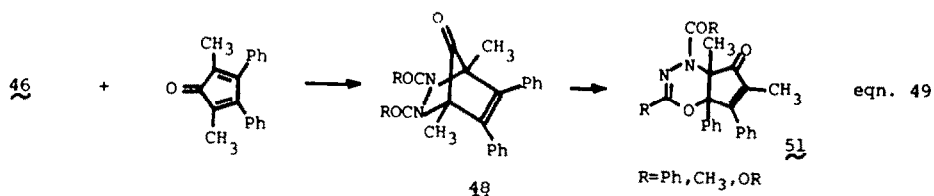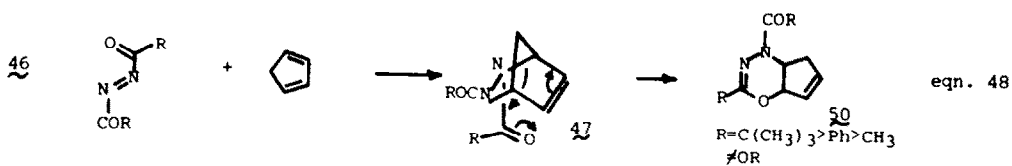
V. 1,3-DIAZABUTADIENE SYSTEMS

The reports of simple 1,3-diazabutadienes participating in [4 + 2] cycloaddition reactions are rare. Matsuda et al.[102a] have shown that **53a** reacts with isocyanates to give 1,3,5-triazine derivatives, eqn (51). The 1,3-diazabutadiene **53a** failed to react with dimethyl acetylene dicarboxylate and affords [2 + 2] cycloadducts with diphenyl ketene.

eqn. 51

R=CH$_3$	R^1=Ph	90% [102a]
R=Et	R^1=Ph	100%
R=Ph	R^1=Ph	85%
R=CH$_3$	R^1=CH$_3$	68%
R=Ph	R^1=CH$_3$	78%
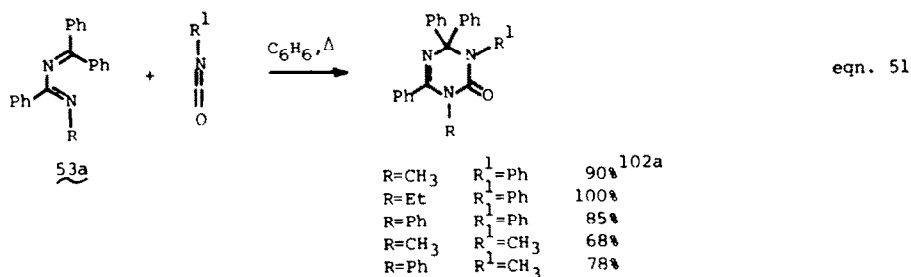
The N-silyl unsaturated urea **53b** has been shown to react with isocyanates and dimethyl acetylene dicarboxylate,[102b] Scheme 22. Nitriles are unreactive and linear adducts are obtained in the reaction of **53b** with diphenyl ketene and chloral.
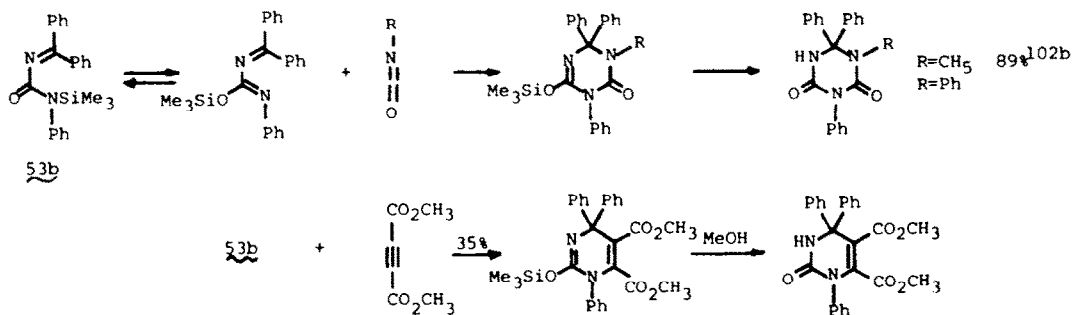
Scheme 22.

4,6-Diaryl-1,2,3,5-oxathiodiazine-2-oxides **54** react with a wide range of heterodienophiles including amidines, imidates, iminochlorides, ureas and thioureas,[103] eqn (52), and enamines,[104] eqn (53).
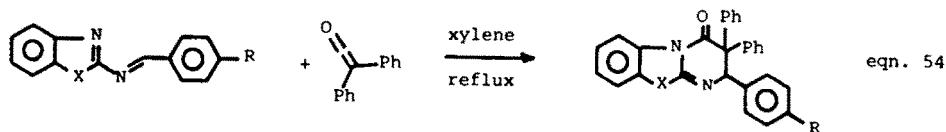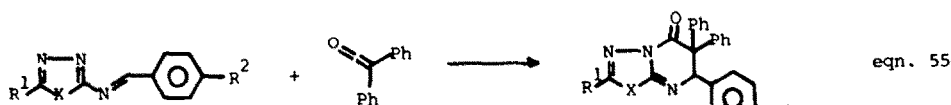
eqn. 52

$$Ar = C_6H_5, \underline{m}-CH_3C_6H_4, \underline{p}-CH_3C_6H_4$$

X	R	
X=CH$_3$	R=OEt	25–92%[103]
=C$_6$H$_5$	=OEt	
=C$_6$H$_5$	=NH$_2$	
=CCl$_3$	=Cl	
=Ar	=NHAr	
=Ar	=NHR	
=Ar	=OH	
=OH	=NH$_2$	
=NH$_2$	=NH$_2$	
=SH	=NH$_2$	

eqn. 53

(130°, 1h, 48%)
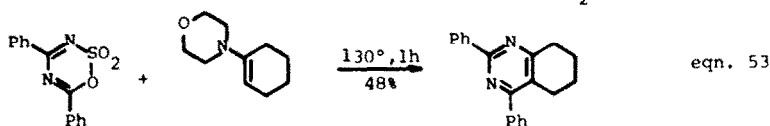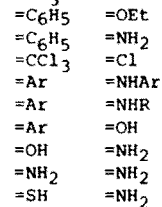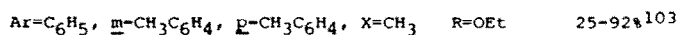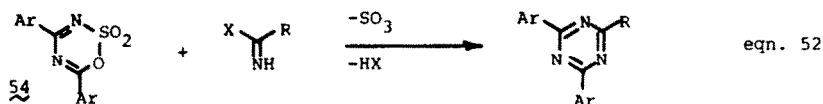
Imidoyl isothiocyanates have been shown to participate as 4π components in Diels–Alder reactions with themselves (dimerize),[105a-e] enamines[105a] and isothiocyanic acid,[105f,g] Scheme 23.
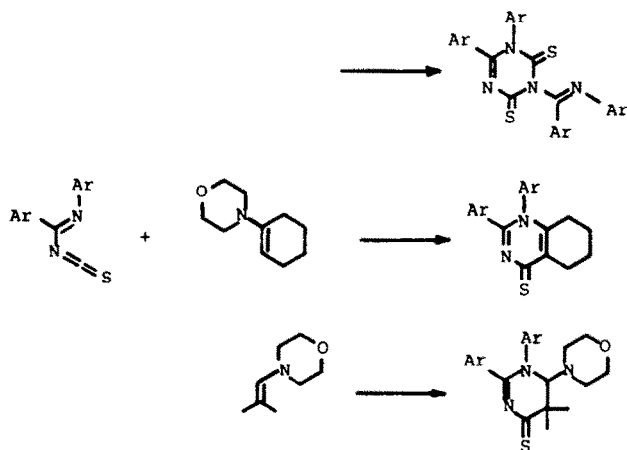
Scheme 23.

A number of reactions of reactive dienophiles with 1,3-diazabutadienes in which part of the diene system is incorporated into an aromatic or heterocycle have been described,[106-110] eqns (54)–(61).
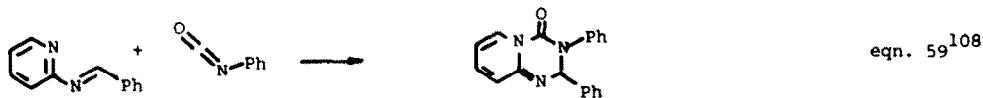
eqn. 54

(xylene, reflux)

	R	
X=O	R=NMe$_2$	50%[106]
	R=OCH$_3$	74%
	R=NO$_2$	86%
X=S	R=NMe$_2$	91%
	R=OCH$_3$	87%
	R=NO$_2$	70%
X=NH→NCOCHPh$_2$		
	R=NMe$_2$	84%
	R=OCH$_3$	81%
	R=NO$_2$	75%

eqn. 55
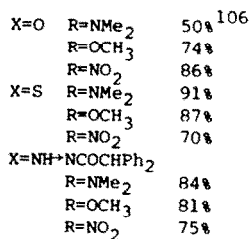
X=O	R^1=Ph	R^2=NMe$_2$	33%[106]
		=OCH$_3$	58%
		=NO$_2$	36%
X=S	R^1=H	R^2=OCH$_3$	87%
	R^1=CH$_3$	R^2=NMe$_2$	63%
		=OCH$_3$	67%
		=NO$_2$	79%
X=Se	R^1=Ph	R^2=NMe$_2$	43%
		=OCH$_3$	54%
		=NO$_2$	78%

Ar=C$_6$H$_5$
=p-CH$_3$C$_6$H$_4$ eqn. 56[107]

eqn. 57[107]

R=H,CH$_3$,Et[108]   eqn. 58

eqn. 59[108]

X=O,S[109]   eqn. 60

CHCl$_3$
reflux   eqn. 61
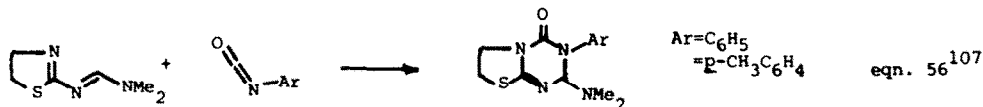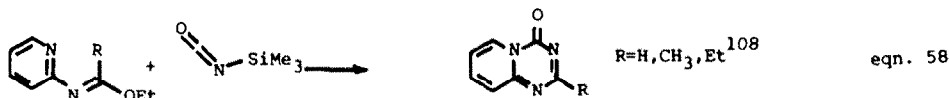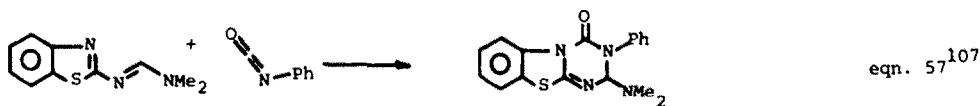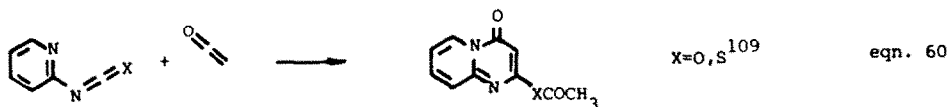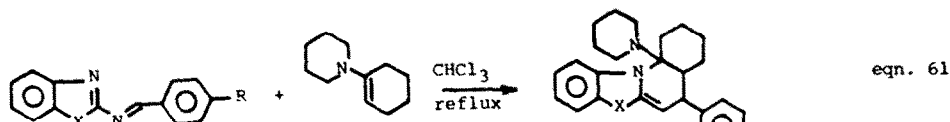
R=NO$_2$	X=O	37%[110]
R=NO$_2$	X=NH	33%
R=OCH$_3$	X=O,NH	0%

VI. 1,4-DIAZABUTADIENE SYSTEMS

There are few examples of 1,4-diazabutadienes participating in [4 + 2] cycloaddition reactions. The initial reports[111] that diphenyl or dimethyl ketene react with α-diimines to give products of a [4 + 2]

cycloaddition reaction, eqn (62), have been reinvestigated[112] and found to give β-lactams, the product of [2 + 2] cycloaddition, eqn (63).


eqn. 62

eqn. 63
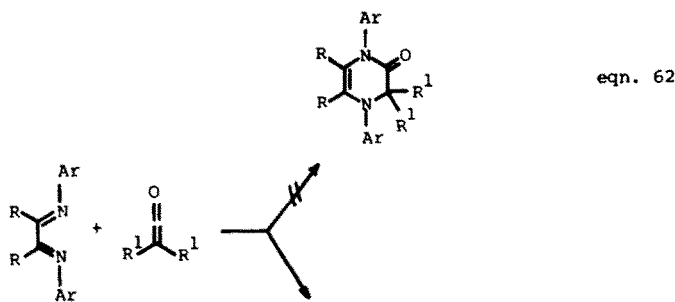
The dimerization[113] of substituted o-benzoquinone diimines, eqn (64), and their reaction with diarylketenes,[114a] eqn (65), have been reported. The solvent effects, substituent effects, and activation parameters of the reaction of 55 with diarylketenes are consistent with a moderately polar transition state with the diimines functioning as electron-deficient dienes.[114a] Similar observations have been described for the [4 + 2] cycloaddition of diiminosuccinonitrile (DISN) with electron-rich dienophiles.[114b]

eqn. 64

eqn. 65

$R^1 = COPh, SO_2Ph$
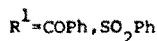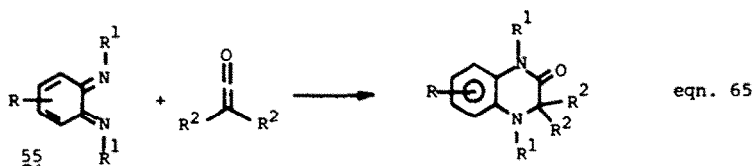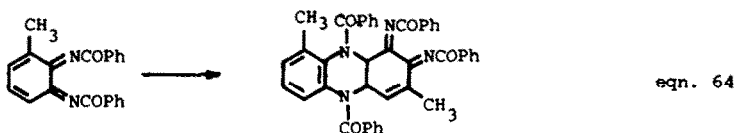
Pummerer has shown that dehydroindigo reacts with styrene, vinyl aryls, acrylonitrile, methyl acrylate and methyl propargylate,[115] eqn (66), under forcing conditions.

eqn. 66
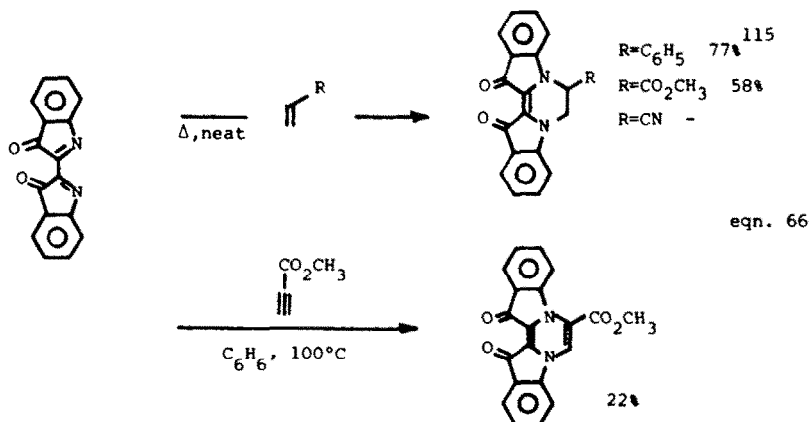
Benzofurans undergo cycloaddition with enamines,[116] Scheme 24, and ynamines,[117] eqn (67). Compounds 56, 57 and 58 failed to react with enamines.
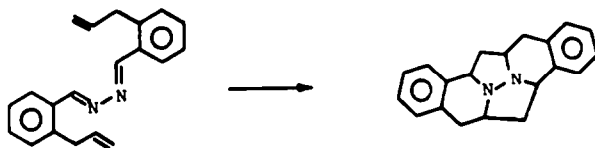
Scheme 24.

56
R=CH$_3$,Ph

57

58

eqn. 67[117]
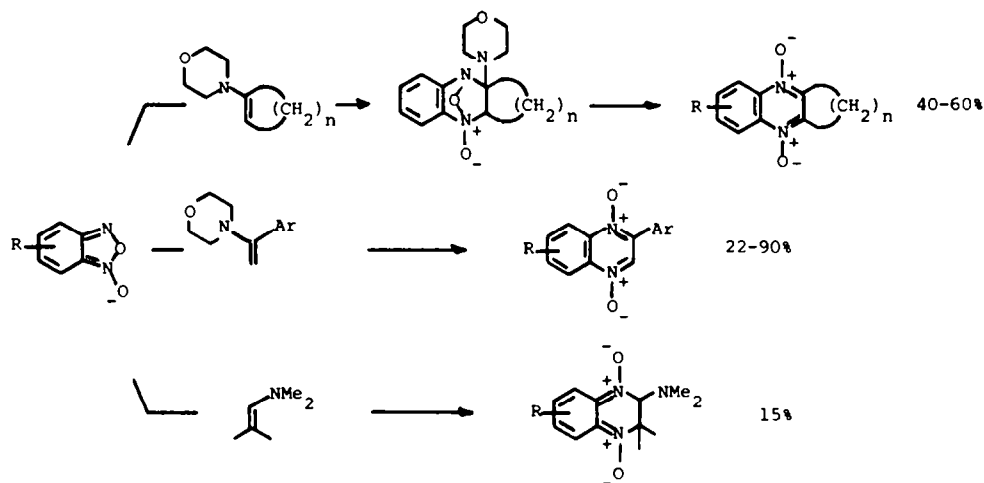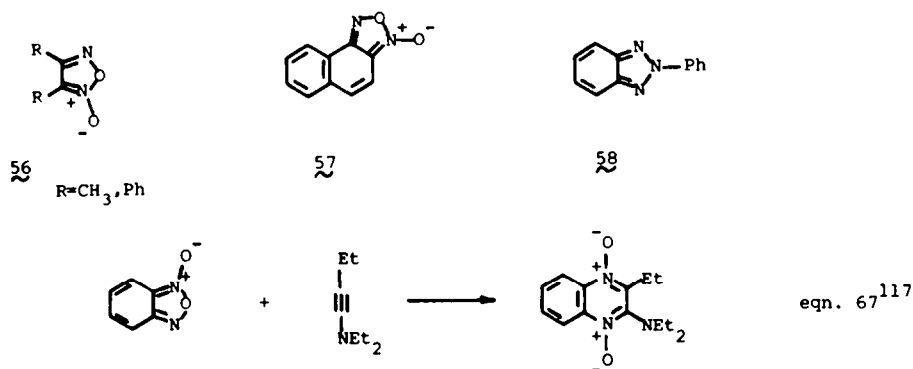
VII. 2,3-DIAZABUTADIENE SYSTEMS

The 2,3-diazabutadiene system rarely undergoes successful [4 + 2] cycloaddition with typical dienophiles and usually affords 2 : 1 adducts or [3 + 2] criss-cross products.[11] Such reactions of azines and imines with dienophiles have been reviewed.[11]


2,5-Diphenyl-3,4-diazacyclopentadienone (59, 3,6-diphenyl-4H-pyrazole-4-one) has been shown to be capable of acting as either a diene[118a-c,e] or dienophile,[118a-d,f,g] Scheme 25. Diazocyclopentadienone 59
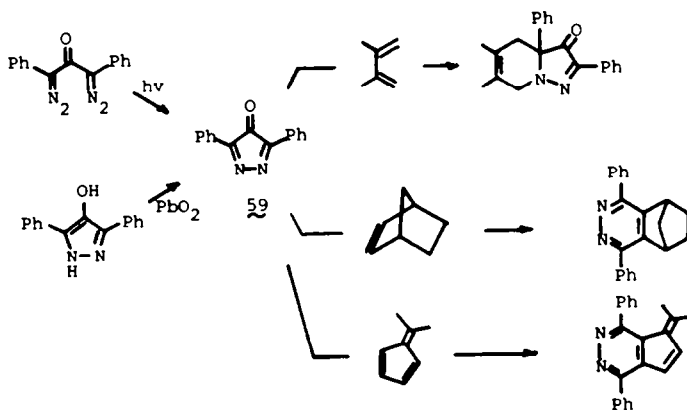
Scheme 25.

fails to react with conventional dienophiles:[118b] maleic anhydride, dimethyl acetylene dicarboxylate, diphenyl acetylene, dimethyl fumarate, isobutyl vinyl ether, cyclopentene, cyclohexene.

2,3-Diazacyclopentadiene **60** reacts with N-phenyltriazoline dione to give the Diels–Alder product **61**,[119] eqn (68). Additional examples of Diels–Alder reactions of cyclic 2,3-diazabutadienes include the


eqn. 68

60, R=CH₃,Ph   **61**
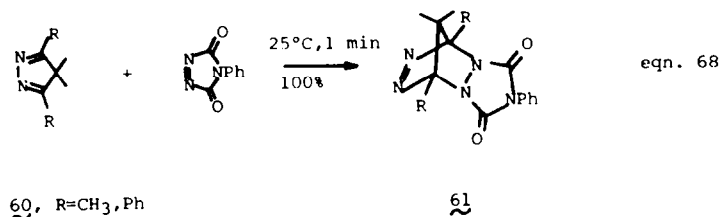
reactions of 4,5-dihydropyridazines, the products of the Diels–Alder reactions of 1,2,4,5-tetrazines with olefins and specific examples may be found in Section IX.10.

Recently, Steglich and co-workers[120] have reported the preparation and reactions of 2,5-diphenyl-6-oxo-1,3,4-oxadiazine **62**, eqns (69) and (70). Cycloaddition studies with ynamines and benzyne illustrate that nitrogen is preferentially lost from bicycloadduct **A** to give α-pyrones.
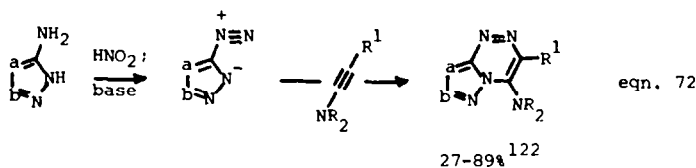
The reaction of **62** with reactive olefins has been described recently,[121] eqn (71).

eqn. 69

eqn. 70

eqn. 71
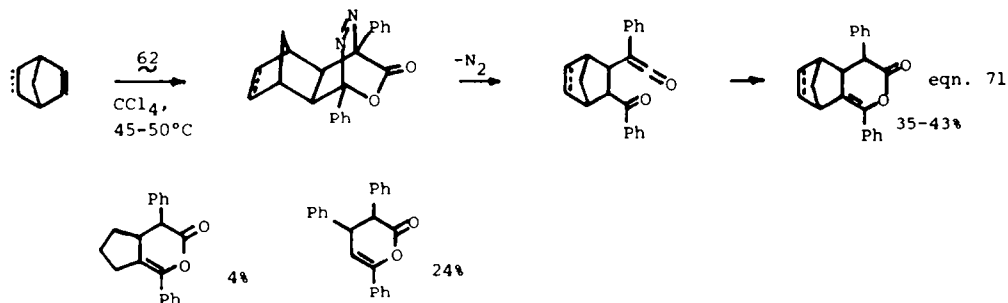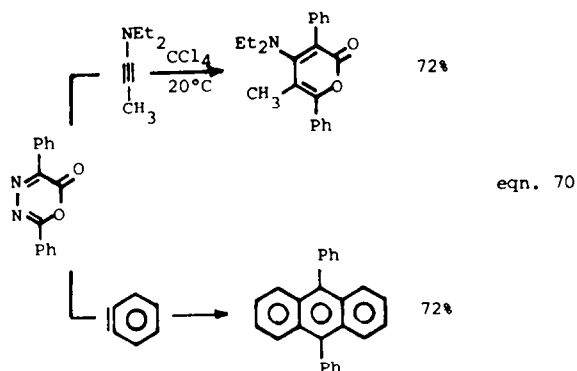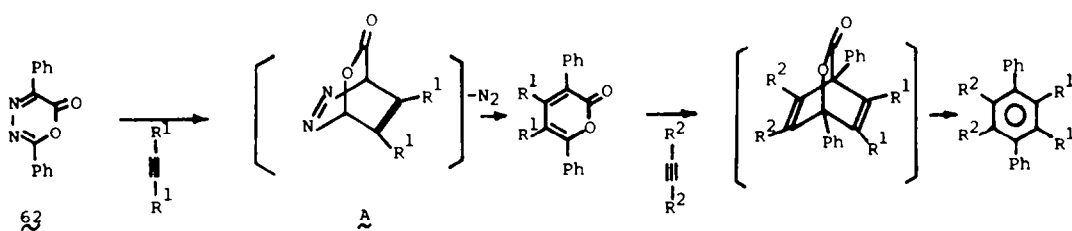
VIII. TRIAZABUTADIENE SYSTEMS

Only one example of a triazabutadiene system participating in a [4 + 2] cycloaddition reaction could be located,[122] eqn (72).

eqn. 72

27–89%[122]

IX. HETEROCYCLIC AZADIENES

IX. 1 Oxazoles

The ability of oxazoles to behave as dependable azadienes in Diels–Alder reactions with olefinic or acetylenic dienophiles continues to be utilized for the preparation of pyridine and furan derivatives,

Table 4. Diels–Alder reactions of oxazoles

Oxazole	Conditions	Product
	EtC$_6$H$_5$,reflux 72 h	94%[124a]
	EtC$_6$H$_5$,reflux 96 h	76%[124b]
	EtC$_6$H$_5$,reflux 36 h 26 h 26 h	R=H,R^1=R^2=O 76%[124b] R=CH$_3$,R^1=R^2=O 92%[124c] R=CH$_3$,R^1=OH,R^2=H 84%[124c]
	10 h,130°C 4 h,140°C 6 h,150°C	R=CH$_3$ 75%[125] R=Ph 74% R=Et 75%
	^{1}O$_2$	60–80%[126]
	200°C, 3.5 h	73%[127]
	200°C, 24 h	70%[128]
	25°C	_ [129]
	dioxane, 100°C	65–75%[130]

respectively, eqn (73). Recent reviews[123] cover much of the work to date and only a few of the more recent examples of these reactions are recorded in Table 4. Weinreb and Levin have described a total synthesis of eupolauramine utilizing an intramolecular oxazole/olefin Diels–Alder reaction.[125b]
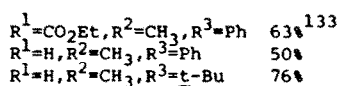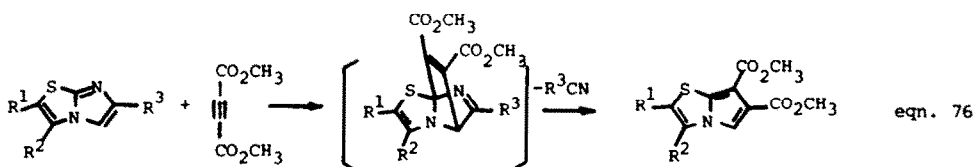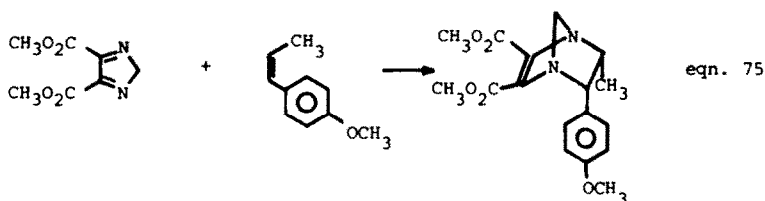

eqn. 73
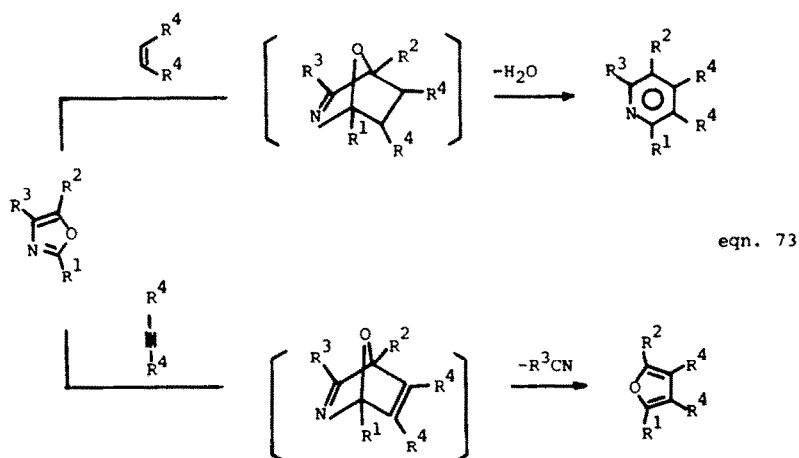
IX.2 Thiazoles

Thiazoles, like oxazoles, have been shown to undergo Diels–Alder reactions with olefins though they have been much less investigated. Eqn (74) summarizes a typical example.[131]


eqn. 74
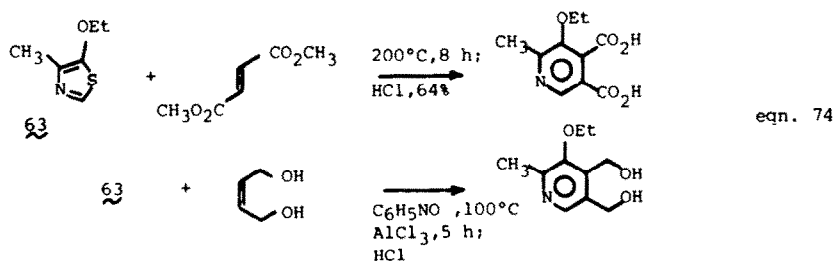
IX.3 Imidazoles

Reports of imidazoles participating in Diels–Alder reactions as either a reactive 1,4-diazabutadiene system, eqn (75),[132] or as a 2-azabutadiene system, eqn (76),[133] have been published.

eqn. 75

eqn. 76

R^1=CO$_2$Et,R^2=CH$_3$,R^3=Ph   63%[133]
R^1=H,R^2=CH$_3$,R^3=Ph   50%
R^1=H,R^2=CH$_3$,R^3=t-Bu   76%

IX.4 Pyridines

Neunhoeffer et al.[134] and recently Gompper[38] have described the Diels–Alder reaction of dimethyl 2,6-bis(dimethylamino)-3,4-pyridine dicarboxylate with dimethyl acetylene dicarboxylate, eqn (77). This


eqn. 77
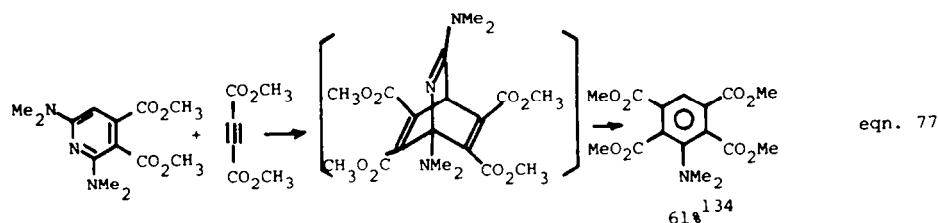
suggests that pyridines substituted with strong electron-donating substituents at positions 2 and 6 may function as suitable 2-azadienes. Additional examples may be found in Section IX.5, Table 6.

2-Pyridones constitute another class of pyridine derivatives capable of Diels–Alder reactions though in these cases the pyridyl nitrogen atom is not a member of the diene system.[135]

IX.5 Pyrimidines (1,3-diazines)

Electron-deficient pyrimidines participate in dependable inverse electron demand Diels–Alder reactions with ynamines, e.g. 1-(diethylamino)propyne, to afford pyridine products,[136] eqn (78). In each case,

eqn. 78
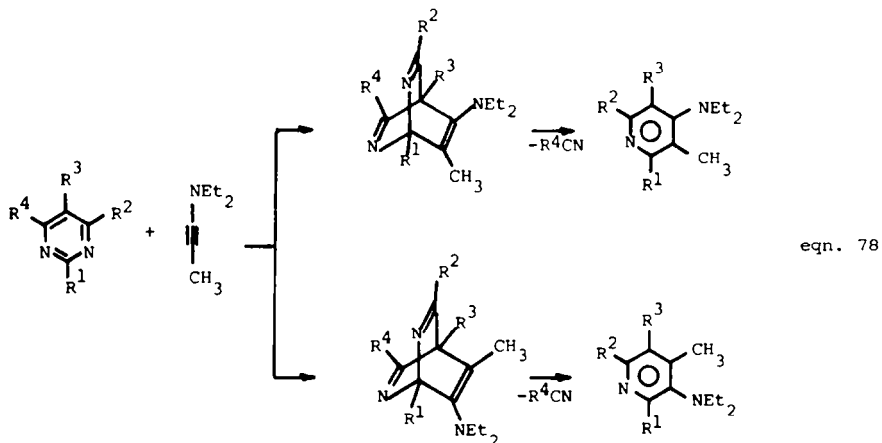
the electron-rich dienophile adds selectively across C-2/C-5 of the pyrimidine nucleus and the orientation of the addition is guided by the substitution pattern of the pyrimidine electron-withdrawing groups, Table 5. Guidelines for predicting the regiospecificity have been detailed and can be derived intuitively from the examples illustrated in Table 5. There is a strong preference for the nucleophilic carbon of the ynamine to be attached to C-2 of the pyrimidine nucleus unless sufficient electron-withdrawing groups are positioned to adequately decrease the electron density at C-5.

The application[137a] of these observations to the construction of the pentasubstituted pyridine found in streptonigrin, eqn (79), was prevented by the inability of aryl ynamine 65 (R^1=Ph) to cycloadd to


eqn. 79

64   65
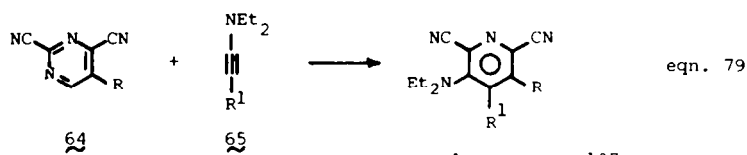
R=H,R^1=CH$_3$ 97%[137a]

R=H,R^1=C$_6$H$_5$ 20%

R=CH$_3$,R^1=CH$_3$ 36%

R=CH$_3$,R^1=C$_6$H$_5$ 0%

Table 5. Cycloaddition reaction of pyrimidine carboxylates with 1-(diethylamino)propyne[136]

Pyrimidine	Conditions	Product(s)	% Yield
(pyrimidine-4-CO₂Et)	dioxane, 101°C 7 days	(Et₂N, CH₃, CO₂Et pyridine)	10%
(5-CO₂Et pyrimidine)	CH₃CN, 20 min	(Et₂N, CH₃, CO₂Et pyridine)	90%
(4,5-diCO₂Et pyrimidine)	CH₃CN, 1 h	(Et₂N, CH₃, diCO₂Et pyridine)	80%
(4,6-diCO₂Et pyrimidine)	dioxane, 101°C, 20 h	(CH₃, Et₂N, diCO₂Et pyridine)	81%
(EtO₂C, 4,6-diCO₂Et pyrimidine)	CHCl₃, 25°C, 7 days	(Et₂N, CH₃, CO₂Et pyridine) 25% (CH₃, Et₂N, CO₂Et pyridine) 64%	

pyrimidine **64** (R=Me). Presumably, the reduced reactivity of ynamine **65** and the presence of the 5-alkyl substituent on the pyrimidine nucleus prevented the successful cycloaddition.
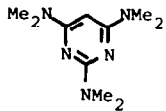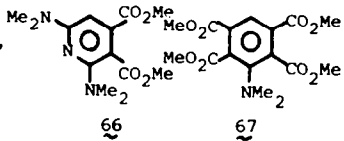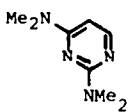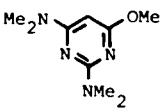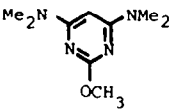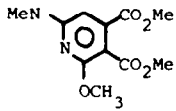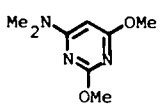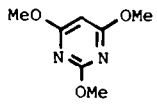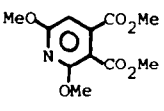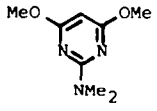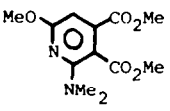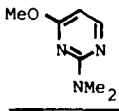
In contrast, the mode of cycloaddition and regiospecificity of the reaction of electron-rich dienophiles with 5-nitropyrimidine is such that the cycloaddition takes place across C–4/N–1 of the pyrimidine nucleus and the nucleophilic carbon of the dienophile attaches to C–4,[137b] Scheme 26.

R=H
X=morpholine 49–57%
X=piperidine 52%
R=CH₃
X=OCH₃ 17%
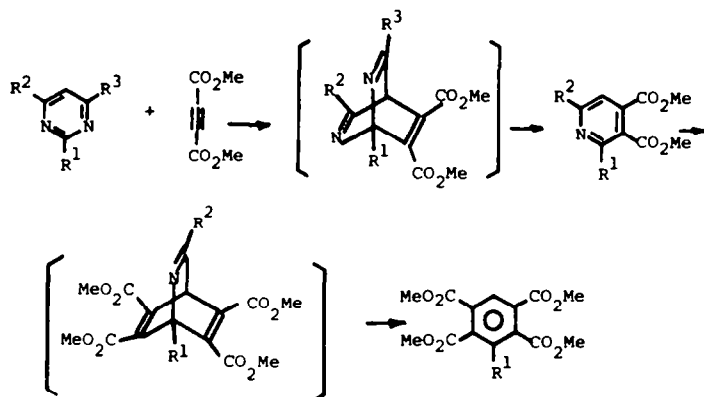
n=2,X=O 80%
n=1,X=– 60%
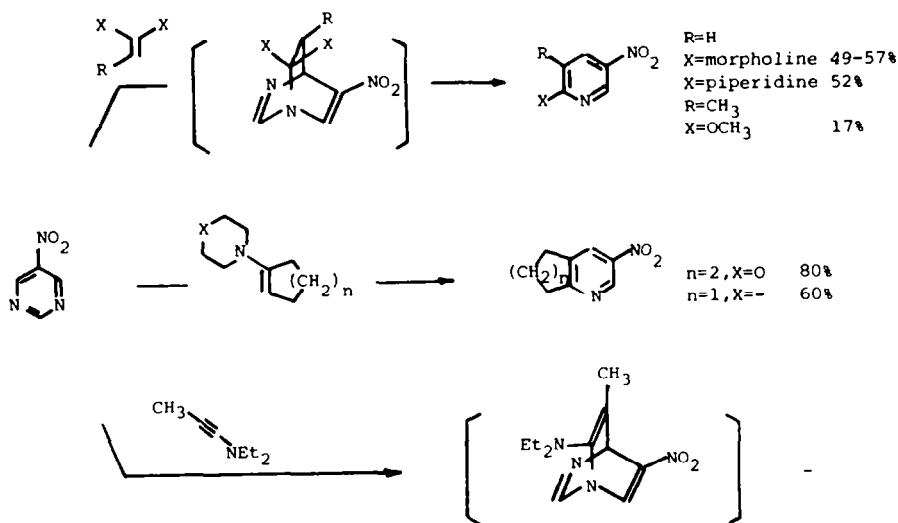
Scheme 26.

Electron-rich pyrimidines have been shown to react with dimethyl acetylene dicarboxylate to afford substituted pyridines. In each case, the mode of cycloaddition is such that the dienophile adds across C–2/C–5 of the pyrimidine nucleus, Table 6. A subsequent cycloaddition reaction of the product electron-rich pyridines with dimethyl acetylene dicarboxylate was occasionally observed, eqn 80.[138]

Table 6. Cycloaddition reaction of electron-rich pyrimidines with dimethyl acetylene dicarboxylate[138]

| Pyrimidine	Conditions	Product(s)	% Yield
(Me₂N, NMe₂, NMe₂ pyrimidine)	DMF, 150°C, 10 h	66, 67	66:67 53%:10%
(Me₂N, NMe₂ pyrimidine)	DMF, 150°C, 3 days	66/67	66:67 10%:32%
(Me₂N, OMe, NMe₂ pyrimidine)	DMF, 150°C, 3 h	66	70%
(Me₂N, NMe₂, OCH₃ pyrimidine)	DMF, 150°C, 6 h	68	68, 30%
(Me₂N, OMe, OMe pyrimidine)	DMF, 150°C, 10 h	68	55%
(MeO, OMe, OMe pyrimidine)	DMF, 150°C, 4 days	(product)	12%
(MeO, OMe, NMe₂ pyrimidine)	DMF, 150°C, 8 h	69	69:67 40%:15%
(MeO, NMe₂ pyrimidine)	-	69/67	69:67 16%:10%

eqn. 80

A number of heterocyclic systems containing a 3-hydroxy-2-azabutadiene unit have been shown to participate in [4 + 2] cycloaddition reactions. 4,6-Dihydroxypyrimidines[139] typify this class of azadiene and have been shown to react with electron-deficient dienophiles,[139a] eqn (81). Loss of cyanic acid from
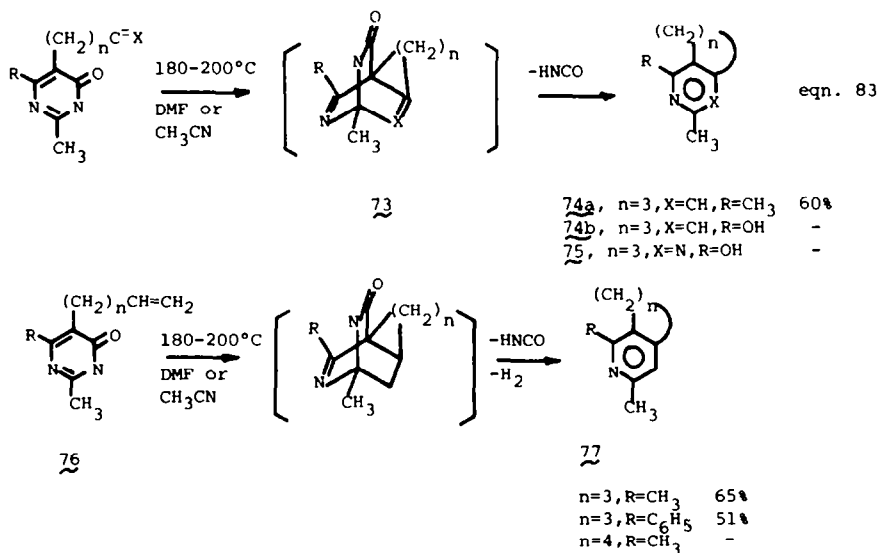

eqn. 81

70
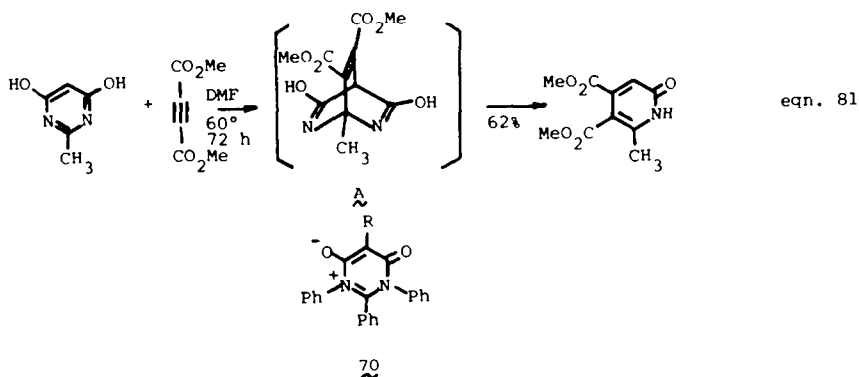
the bicycloadduct A affords the substituted pyridone directly. Mesomeric pyrimidine betaines, e.g. 70, behave similarly.[139c] Simple, strained, or electron-rich olefins failed to react with 4,6-dihydroxy-pyrimidines.[139f]

A nearly quantitative intramolecular Diels–Alder reaction has been observed with the 4-hydroxy-6-oxopyrimidines 71,[139b] eqn (82). The stability of the bicycloadducts 72 appears to result from amide formation, thus preventing or retarding the retro Diels–Alder reaction involving the thermal extrusion of cyanic acid.


eqn. 82

71 n=3
n=4

72 n=3,~100%
n=4, –
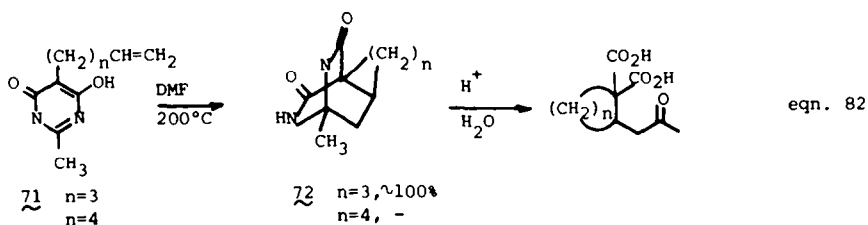
More recently the intramolecular cycloaddition of 4-hydroxy- and 4-methyl-6-oxopyrimidines containing a terminal alkyne or nitrile has been described.[139d,f] In these cases the bicycloadducts 73 readily lose cyanic acid (HNCO) to afford the substituted cyclopenteno-pyridines 74 or -pyrimidines 75 respectively, eqn (83).

eqn. 83

73

74a, n=3,X=CH,R=CH₃ 60%
74b, n=3,X=CH,R=OH –
75, n=3,X=N,R=OH –

76

77

n=3,R=CH₃ 65%
n=3,R=C₆H₅ 51%
n=4,R=CH₃ –

In addition, the 4-methyl- and 4-phenyl-6-oxopyrimidines **76** possessing a terminal alkene have been shown to undergo a similar intramolecular Diels–Alder reaction,[139e,f] eqn (83). Loss of cyanic acid (HNCO) and an apparent *in situ* oxidation (dehydrogenation) affords the cyclopenteno- and cyclohexenopyridines **77** directly. Only traces of the dihydropyridines could be detected.

Sammes *et al.* have recently applied this work to the total synthesis of (±)-acetinidine (**78**),[140] eqn (84).
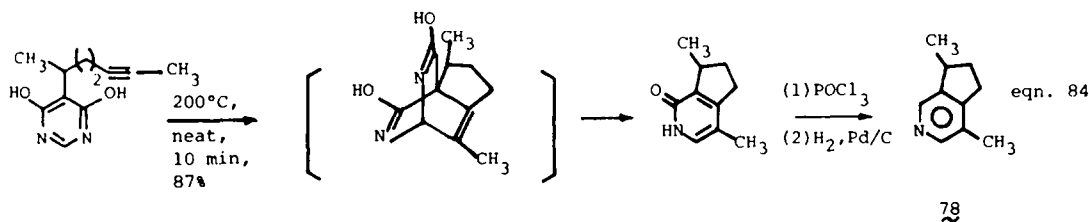
Takeshiba *et al.* have described an intramolecular Diels–Alder reaction of 2-aryloxy pyrimidines,[141] eqn (85).
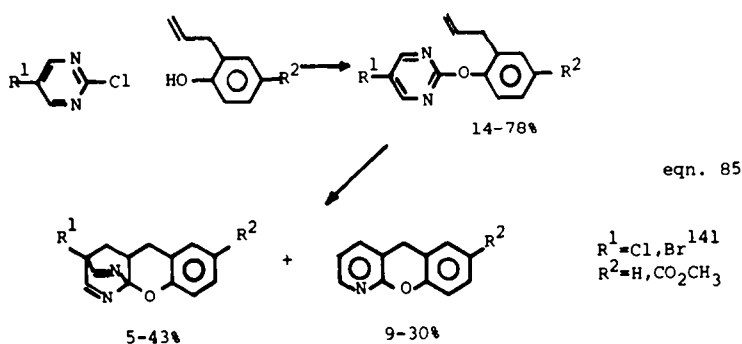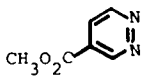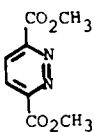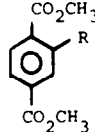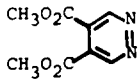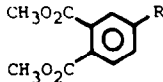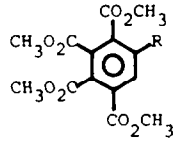
IX.6 Pyridazines (1,2-diazines)
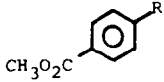
Electron-deficient pyridazine carboxylates have been shown to react with electron-rich dienophiles;[142] e.g. ynamines[142b] and 1-methoxy-1-(dimethylamino)ethylene,[142c] to afford products of [4 + 2] cycloaddition reactions. 1-Methoxy-1-(dimethylamino)ethylene adds selectively across C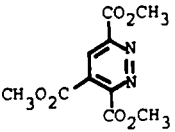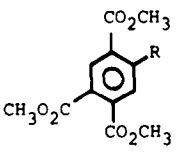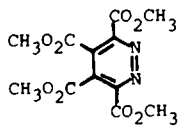–3/C–6 of the pyridazine nucleus and the regiospecificity of the addition is guided by the strong directing effect of the ester groups. Loss of nitrogen from the initial bicycloadduct followed by elimination of methanol or dimethylamine affords the dimethylamino- or methoxy benzenecarboxylates,[142c] eqn (86) and Table 7. Additional examples of this reaction have been reported.[142]
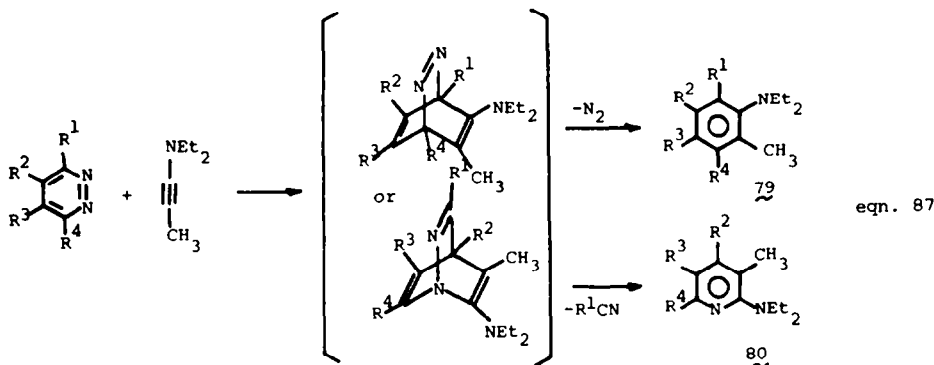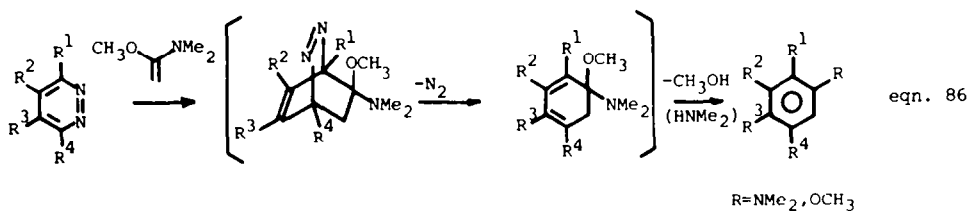
Table 7. Cycloaddition of 1,2-diazines with 1-methoxy-1-(dimethylamino)ethylene[142]

1,2-Diazine	Conditions	Products	% Yield
CO_2CH_3	dioxane, 101°C, 24–48 h	CO_2CH_3 R R=NMe$_2$:OCH$_3$ 15:1	60%
CH$_3$O$_2$C	dioxane, 101°C, 24 h	R CH$_3$O$_2$C R=NMe$_2$:OCH$_3$ 12:1	57%
CO_2CH_3 CO_2CH_3	dioxane, 101°C, 24 h	CO_2CH_3 R CO_2CH_3 R=NMe$_2$:OCH$_3$ 8:1	90%
CH$_3$O$_2$C CH$_3$O$_2$C	dioxane, 101°C, 24 h	CH$_3$O$_2$C R CH$_3$O$_2$C R=NMe$_2$:OCH$_3$ 3:1	80%
CO_2CH_3 CH$_3$O$_2$C CO_2CH_3	dioxane, 101°C, 1 h	CO_2CH_3 R CH$_3$O$_2$C CO_2CH_3 R=NMe$_2$:OCH$_3$ 2:1	93%
CO_2CH_3 CH$_3$O$_2$C CH$_3$O$_2$C CO_2CH_3	dioxane, 101°C, 30 min	CO_2CH_3 CH$_3$O$_2$C R CH$_3$O$_2$C CO_2CH_3 R=NMe$_2$:OCH$_3$ 10:1	88%

Two possible cycloaddition products may result from the Diels–Alder reaction of pyridazine carboxylates with ynamines, eqn (87), and lead to the preparation of 1-diethylamino-2-methyl-benzene carboxylates **79** or 2-diethylamino-3-methyl-pyridine carboxylates **80**.[142b]

The mode of cycloaddition and the observed regiospecificity depend strongly on the carboxylate substitution pattern and appear to be subject to accurate, predictable results, Table 8. It is remarkable that in each case only one of the two modes of cycloaddition is observed for each pyridazine carboxylate and in no case was a mixture of products **79/80** reported. As anticipated, the rate and yield of the reaction increase as the level of carboxylate substitution is increased. Additional examples of this reaction have been reported.[142b]

An interesting intramolecular cycloaddition of 3-chloro-6-(2-allylphenoxy)-pyridazine (**81**, R^1=R=H) has been described.[143a] Heating **81** with or without solvent afforded xanthene **82** in high yield, eqn (88).
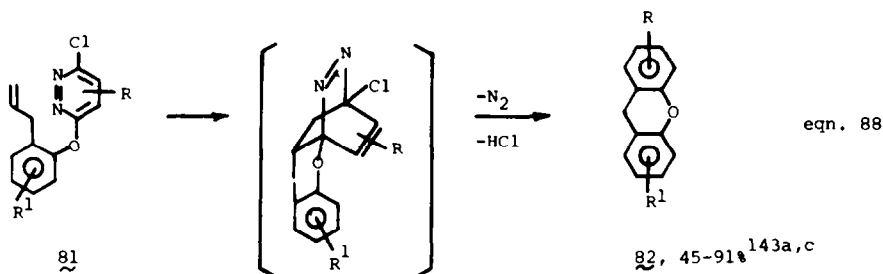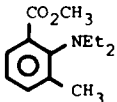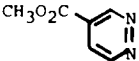
eqn. 88

81   82, 45–91%[143a,c]
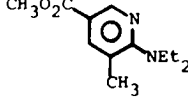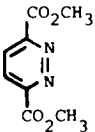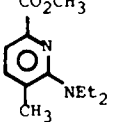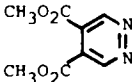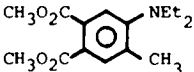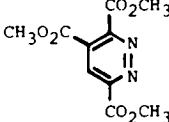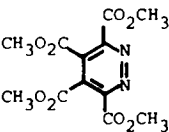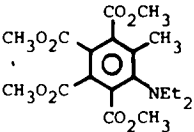
Table 8. Cycloaddition of 1,2-diazines with 1-(diethylamino)propyne[142]

1,2-Diazine	Conditions	Product	% Yield
	xylene, reflux, 40 h		23%
	dioxane, 101°C, 24-48 h		30%
	dioxane, 101°C, 50 h		75%
	CH₃CN, reflux		74%
	dioxane, 101°C 24 h		85%
	xylene, 25°C, 3 h		73%

The reaction has been shown to be general and affords the substituted xanthenes usually in excellent yield.[143c] A subsequent study has shown that the intramolecular cycloaddition of 3-substituted-6-(2-allylphenoxy)- or [2-(2-methylallyl)phenoxyl-pyridazines give rise to dihydroxanthenes,[143b] eqn (89).
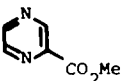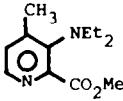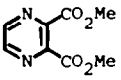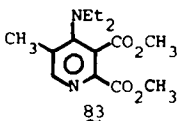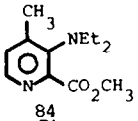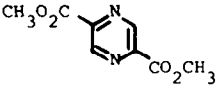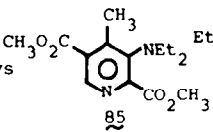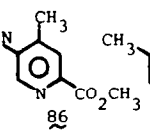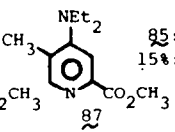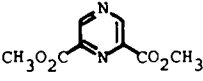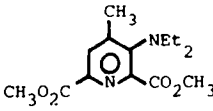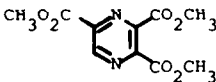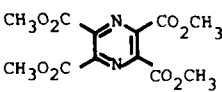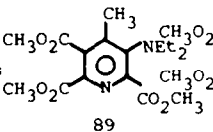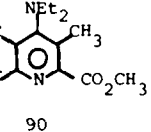
Examples of Diels–Alder reactions of 4,5-dihydropyridazines may be found in Section IX.10.

eqn. 89

11-100%[143b]
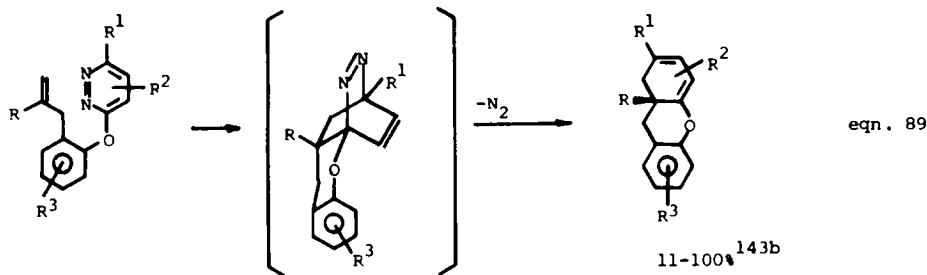
IX.7. Pyrazines (1,4-diazines)

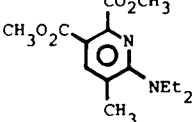Electron-deficient 1,4-diazines react with 1-(diethylamino)propyne to give substituted pyridines,[144] eqn (90), Table 9. The rate of reaction and the observed regioselectivity are strongly dependent on the number and position of electron-withdrawing groups on the pyrazine nucleus. Alkyl substituted pyraz-

Table 9. Cycloaddition reactions of 1,4-diazine carboxylates (pyrazine carboxylates) with 1-(diethylamino)propyne

1,4-Diazine	Conditions	Product(s)	% Yield
(pyrazine-CO₂Me)	CHCl₃, 25°C, 7 days	(4-CH₃, 3-NEt₂, 2-CO₂Me pyridine)	72%
(pyrazine-2,3-diCO₂Me)	CH₃CN, reflux, 12 h	**83** and **84**	83:84 75%:8%
(CH₃O₂C pyrazine CO₂CH₃)	CHCl₃, 25°C, 14 days	**85**, **86**, **87**	85:86:87 15%:68%:15%
(CH₃O₂C pyrazine CO₂CH₃)	CHCl₃, reflux, 1 h	**88**	
(CH₃O₂C pyrazine CO₂CH₃)	CHCl₃, reflux, –	**88**	78%
(CH₃O₂C pyrazine diCO₂CH₃)	CHCl₃, 25°C, 14 days	**89** and **90**	89:90 29%:58%

eqn. 90

ines may participate in a similar [4 + 2] cycloaddition reaction with ynamines but the rate of reaction is slow and yield of pyridyl products is low.[144]

2,5-Dihydroxy-1,4-diazines, e.g. **91**, have been shown to react with electron-deficient and strained olefins, eqn (91).[145] Pyrazinone **92** was shown to react rapidly with electron-deficient dienophiles and unactivated olefins,[145] eqn (92). Adduct **93** showed no tendency to lose methyl isocyanate even at 200°C.

eqn. 91

eqn. 92
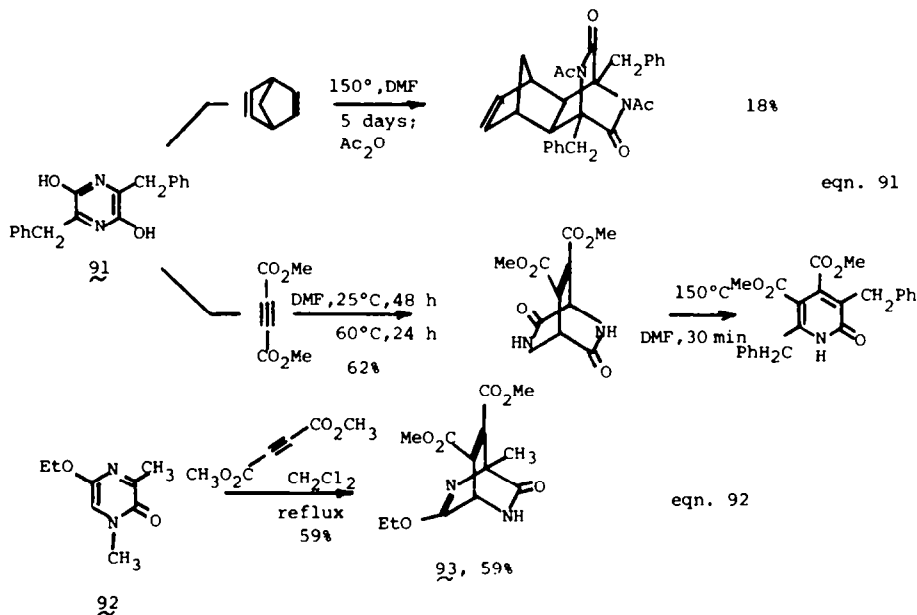
IX.8 1,3,5-Triazines

1,3,5-Triazines, *sym*-triazines, have been shown to undergo [4 + 2] cycloaddition reactions with electron-rich dienophiles; e.g. ynamines,[146] 1-ethoxy-1-(dimethylamino)ethylene[146] and pyrrolidine enamines,[147] eqns (93)–(95). The regiospecificity of the addition of 1-(diethylamino)propyne to sub-

eqn. 93

eqn. 94

eqn. 95
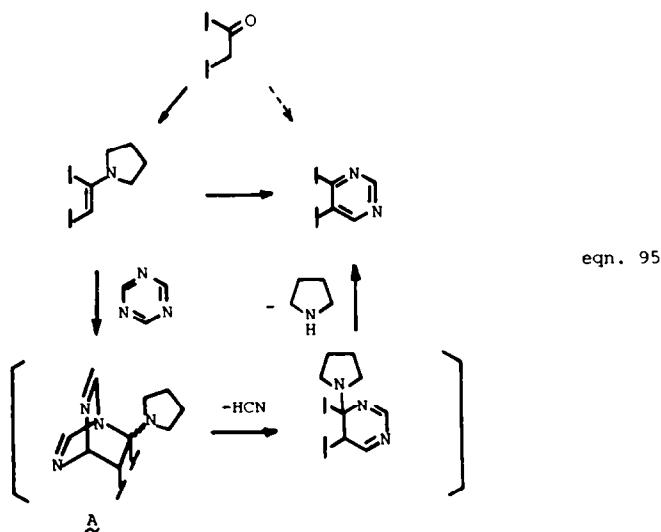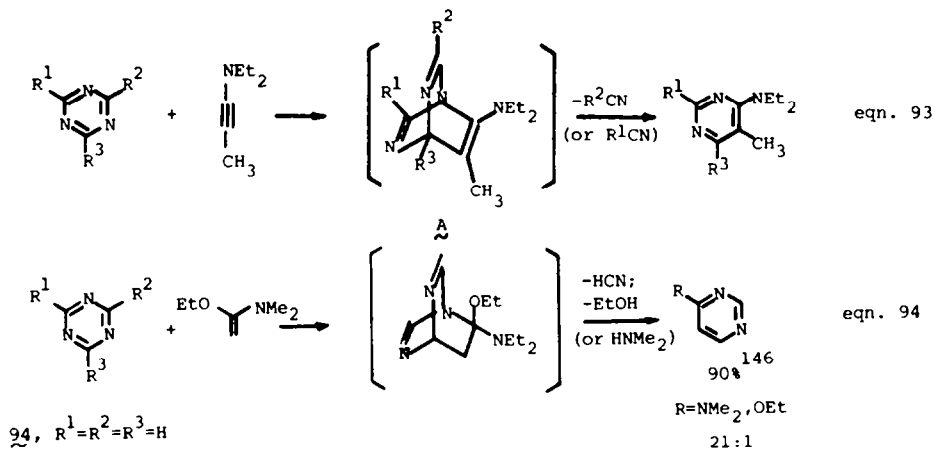
Table 10. Cycloaddition reactions of 1,3,5-triazines[146]

1,3,5-Triazine	Dienophile	Conditions	Product(s)	% Yield
1,3,5-triazine	NEt₂ / CH₃ substituted ethylene (enamine)	dioxane, 25°C, 4 h	pyrimidine with NEt₂ and CH₃	97%
2-CH₃-1,3,5-triazine		dioxane, 25°C, 4 h	two pyrimidine products (NEt₂, CH₃; CH₃, NEt₂, CH₃) — 78 : 22	96%
2,4-di-CH₃-1,3,5-triazine		dioxane, 25°C, 2 h	pyrimidine (H₃C, NEt₂, CH₃)	80%
2,4,6-tri-CO₂Et-1,3,5-triazine		dioxane, 25°C, 2 h	pyrimidine (EtO₂C, NEt₂, CH₃, CO₂Et)	88%
1,3,5-triazine	EtO—C=C—NMe₂	neat, 25°C, 10 h	two pyrimidine products (NMe₂; OEt) — 21 : 1	90%
R¹, R²-2-CH₃-1,3,5-triazine		dioxane, 25°C, 5–6 h	triazine with =C(NMe₂)CH₃ side chain	33–65%
2,4,6-tri-Cl-1,3,5-triazine		dioxane, 25°C, 24 h	triazine with CH(NMe₂)(OEt) side chain	84%
1,3,5-triazine	CO₂CH₃—C≡C—CO₂CH₃	dioxane, 101°C, 14 h	pyrimidine (CO₂CH₃, CO₂CH₃)	62%

stituted 1,3,5-triazines has been investigated briefly, Table 10, and in the absence of strong directing groups the nucleophilic carbon of the polarized dienophile prefers attachment to an unsubstituted carbon of the 1,3,5-triazine nucleus. The subsequent loss of R^2CN (or R^1CN) from the initial bicyclo adduct **A** affords the substituted pyrimidines in high yield.

1-Ethoxy-1-(dimethylamino)ethylene participates in a [4 + 2] cycloaddition reaction with the unsubstituted 1,3,5-triazine (**94**), eqn (**94**), whereas its reaction with methyl substituted 1,3,5-triazines take an entirely different course, Table 10. In one instance, 1,3,5-triazine (**94**) has been shown to react with an electron-deficient dienophile, dimethyl acetylene dicarboxylate, to give dimethyl 4,5-pyrimidine dicarboxylate in high yield, Table 10. The generality of this reaction remains to be investigated.

Pyrrolidine enamines have been shown to undergo a regiospecific[147] cycloaddition reaction with 1,3,5-triazine, eqn (**95**) and Table 11. The loss of HCN from the bicycloadduct **A** followed by elimination of pyrrolidine provided 4,5-substituted pyrimidines under mild conditions.

Table 11. Cycloaddition reaction of 1,3,5-triazine **94** with pyrrolidine enamines[147]

Pyrrolidine Enamine	Conditions	Product	% Yield
	dioxane, 90°C, 24 h		80%
	dioxane, 90°C, 5 h CHCl₃, 45°C, 5 h toluene, 90°C, 5 h		75%,[147] 93%,[146] 38% 21%
	dioxane, 90°C, 48 h		47%
	dioxane, 90°C, 10 h dioxane, 90°C, 24 h		47% 76%
	dioxane, 90°C, 43 h		66%
	dioxane, 90°C, 5 h dioxane, 90°C, 24 h		23% 80%
	dioxane, 90°C, 18 h		51%
	dioxane, 90°C, 49 h		50%

IX.9 1,2,4-Triazines

1,2,4-Triazines behave as reactive, electron-deficient dienes in inverse electron demand Diels–Alder reactions with electron-rich or strained olefins.[148] As expected, the addition of electron withdrawing groups to the 1,2,4-triazine nucleus generally increases the reactivity, influences the mode of cycloaddition and determines the observed regioselectivity. In addition, the course of the Diels–Alder reaction of 1,2,4-triazines with electron-rich olefins is sensitive to the reactivity of the dienophile.

The reaction of 1,2,4-triazines with 1-ethoxy-1-(dimethylamino)ethylene has been shown to afford pyridine products, eqn (96) and Table 12.[149] Cycloaddition occurs exclusively across C-3/C-6 of the
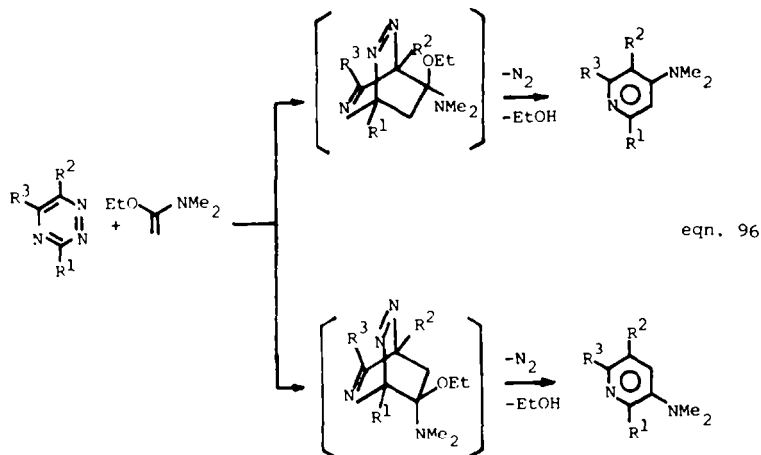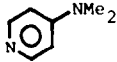
eqn. 96
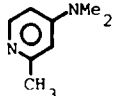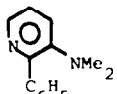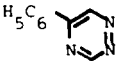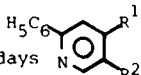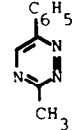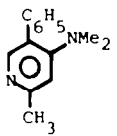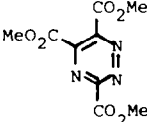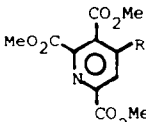
Table 12. Cycloaddition reaction of 1,2,4-triazines with 1-ethoxy-1-(dimethylamino)ethylene[149]

1,2,4-Triazine	Conditions	Product(s)	% Yield
	dioxane, 100°C, 12 h		27% [149a]
	dioxane, 100°C, 3-6 days		60% [149a]
	dioxane, 100°C, 3-6 days		81% [149a]
	dioxane, 100°C, 1-6 days	$R^1=NMe_2$, $R^2=H$ 58% [149a] $R^1=H$, $R^2=NMe_2$ 8%
	dioxane, 100°C, 3-6 days		83% [149a]
	dioxane, 100°C, 3 days	$R^1=R=CH_3$ 90% [149b] $R^1=CH_3$, $R=H$ 55% $R^1=H$, $R=CH_3$ 82% $R^1=R=H$ 18% $R^1=CH_3$, $R=C_6H_5$ 67%
	dioxane, 20°C	$R=NMe_2$, 77% [149c,d] $R=OEt$, 23%

1,2,4-triazine nucleus and there is a strong preference for the nucleophilic carbon of the dienophile to be attached to C-3 of the 1,2,4-triazine, Table 12. The reaction of 5-methyl-1,2,4-triazines with 1-ethoxy-1-(dimethylamino)ethylene takes an entirely different course, Table 12.[149b]

A detailed study of the reaction of ketene acetals and aminals with 1,2,4-triazines has been published[149d] and reveals the effects of dienophile reactivity, substitution pattern/steric effects, and electron withdrawing groups on the observed mode and regioselectivity of cycloaddition, Table 13.

In sharp contrast, the cycloaddition reaction of 1,2,4-triazines with 1-(diethylamino)propyne has been shown to afford 4-diethylamino-5-methyl pyrimidines 95 and occasionally pyridine products, eqn (96) and Tables 14 and 15. Thus, in this case there is a strong preference for cycloaddition to take place across C-5/N-2 of the 1,2,4-triazine nucleus and the nucleophilic carbon of the ynamine attaches to C-5 of the 1,2,4-triazine nucleus, resulting in pyrimidine products. Substitution at C-5 may result in a switch in the mode of cycloaddition and the ynamine may add across C-3/C-6 of the 1,2,4-triazine nucleus. In these cases, there is a strong preference for the nucleophilic carbon of the ynamine to attach to C-3 of the 1,2,4-triazine nucleus. However, the presence of electron-withdrawing substituents at C-3 and C-6 will control the observed regioselectivity of such cycloadditions, Tables 14 and 15.

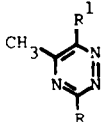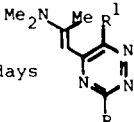The 1,2,4-triazine nucleus is sufficiently electron-deficient that substitution with electron-donating groups, e.g. $-OMe/-NMe_2$, does not prevent cycloaddition reactions with 1-(diethylamino)propyne,[150f,g] Table 16.

In cases where the 1,2,4-triazine nucleus is fully substituted with electron-donating groups, e.g. 96,

95
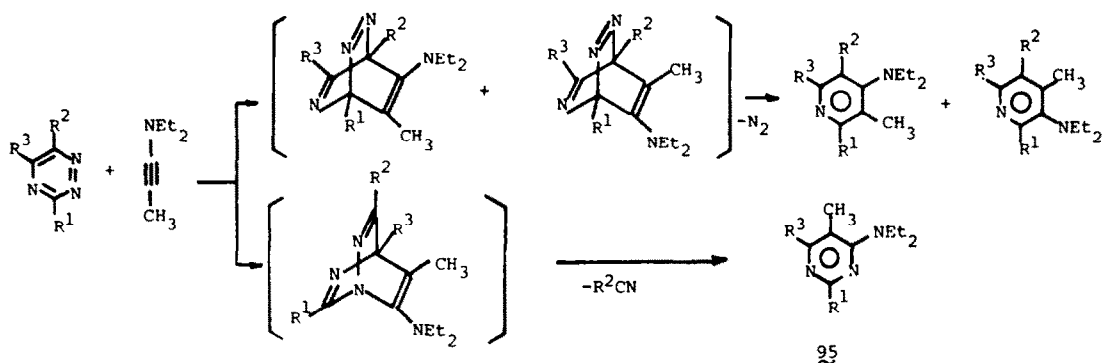
Table 13. Study of the factors governing the regiospecificity of the cycloaddition reaction of 1,2,4-triazines with ketene acetals[149d]

1,2,4-Triazine	ketene acetal	Conditions	Products		% Yield

A	1			% Yield
				19-48%
OEt	OEt	C_6H_6, 20°C	0 : 100	
NMe₂	OEt	dioxane, 20°C	0 : 100	21% (+70% X=OEt)
NMe₂	SCH₃	dioxane, 20°C	<2 : >98	91%
NMe₂	NMe₂	dioxane, 20°C	18 : 82	81%

X	Y			% Yield
				100%
OEt	OEt	dioxane, 100°C	<5 : >95	
NMe₂	OEt	dioxane, 100°C	3 : 97	99%
NMe₂	SCH₃	dioxane, 100°C	8 : 92	84%
NMe₂	NMe₂	dioxane, 100°C	78 : 22	90%

X	Y			% Yield
				85%
OEt	OEt	C_6H_6, 80°C	100 : 0	
NMe₂	OEt	C_6H_6, 40°C	92 : 8	63%(+22% X=OEt)
NMe₂	SCH₃	C_6H_6, 40°C	96 : 4	90%
NMe₂	NMe₂	C_6H_6, 40°C	90 : 10	91%
		CH₃CN, 40°C	36 : 64	85%

X	Y			% Yield
NMe₂	NMe₂	C_6H_6, 80°C	55 : 45	78%

X	Y			% Yield
				57%
OEt	OEt	CH₃CN, 40°C	100 : 0	
NMe₂	OEt	CH₃CN, 40°C	100 : 0	74%(+22% X=OEt)
NMe₂	SCH₃	CH₃CN, 40°C	100 : 0	82%
NMe₂	NMe₂	CH₃CN, 40°C	19 : 81	92%
		C₅H₅N, 40°C	35 : 65	54%
		CH₃COCH₃, 40°C	43 : 57	62%
		CH₃CO₂Et, 40°C	57 : 43	39%
		C_6H_6, 40°C	78 : 22	85%

Table 14. Cycloaddition reaction of 1,2,4-triazines with 1-(diethylamino)propyne[150a,b]

1,2,4-Triazine	Conditions	Product	% Yield
	$CHCl_3$, 25°C, 2 h		40%
	$CHCl_3$, 25°C, 16 h	96	72%
	$CHCl_3$, 25°C, 2 h	96,	70%
	$CHCl_3$, 25°C, 2 h		71%
	C_6H_6, 20°C, –		100%

the system is sufficiently electron-rich to participate in Diels–Alder reactions with dimethyl acetylene dicarboxylate, eqn (97).[150f,g] Normally, the reaction of 1,2,4-triazines with dimethyl acetylene dicarboxylate takes an entirely different course.[151]

In an early survey of the Diels–Alder reactions of substituted 1,2,4-triazines, Sauer et al.[152] were able to demonstrate that a symmetrical enamine, enol ethers and acetates, strained olefins and acetylenes add across C-3/C-6 of the 1,2,4-triazine nucleus to afford pyridine products, Scheme 27.

Scheme 27.

eqn. 97

96, $R^1 = NR_2$
$R^1 = OCH_3$

55-80%
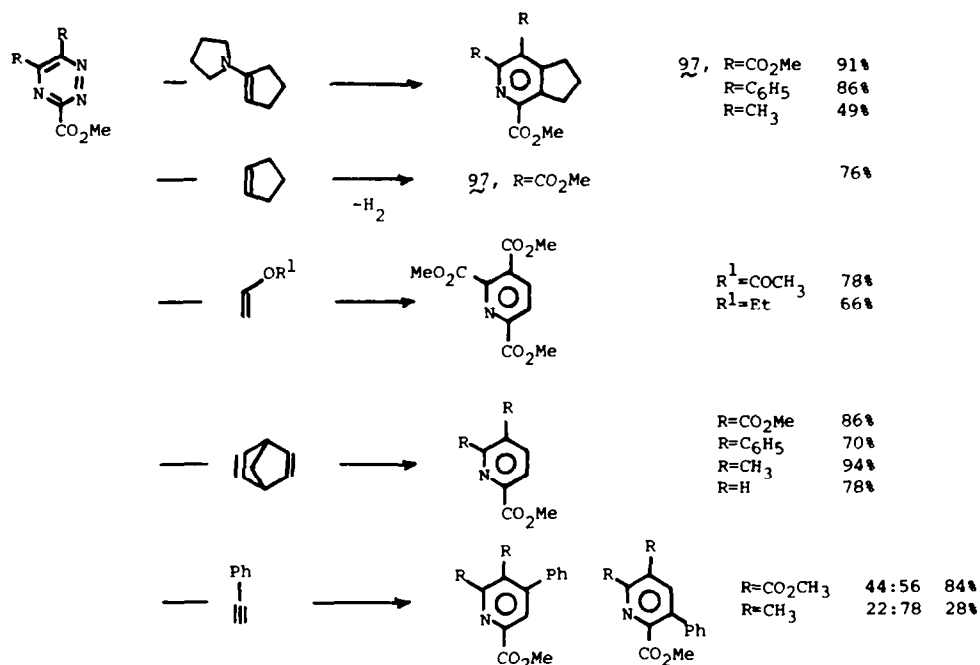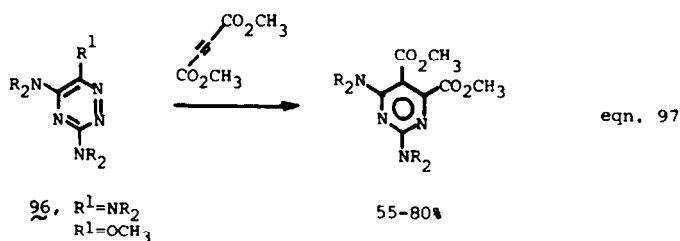
Table 15. Substituent effects on the mode and regiospecificity of the Diels–Alder reaction of 1,2,4-triazines with ynamines.[150e]

1,2,4-Triazine	Ynamine	Conditions	Product(s)	Ratio	% Yield
	R=Et	C_6H_6,20°C		100:0:0	100%
	R=Et; R=Me;	C_6H_6,20°C C_6H_6,80°C		0:0:100 0:0:100	85% 89%
	R=Et;	C_6H_6,20°C		100:0:0	100%
	R=Et; R=Me;	C_6H_6,80°C CH_3CN,20°C C_6H_6,80°C		45:35:20 17:75:8 42:28:30	89% 90% 80%
	R=Et; R=Me;	C_6H_6,80°C CH_3CN,20°C C_6H_6,80°C		82:0:18 87:0:13 76:0:24	67% 55% 73%
	R=Et:C_6H_6,20°C CH_3CN,20°C p-xylene,20°C R=Me:C_6H_6,20°C			15:0:85 22:0:78 10:0:90 22:0:78	– – 95% 84%

$E = CO_2CH_3$

Table 16. Diels–Alder reactions of electron-rich 1,2,4-triazines with 1-(diethylamino)propyne[150f,x]

1,2,4-Triazine	Conditions	Products
(structure, XCH₃)	Et₂O, 25°C, 1 h Et₂O, 25°C, 20 min	(pyrimidine, CH₃, NEt₂, XCH₃) X=O, 87% X=S, 86%
(structure, CH₃O)	dioxane, 101°C, 6 days	(pyridine, CH₃O, NEt₂, CH₃) 79%
(structure, CH₃O, OCH₃)	dioxane, 101°C 15 days	(pyridine, CH₃O, NEt₂, CH₃, OCH₃) 21%
(structure, OCH₃, CH₃O, OCH₃)	dioxane, 101°C	no reaction
(structure, CH₃O, OCH₃ bis-triazine)	dioxane	(Ar, NEt₂, CH₃, OCH₃) 17% (Ar, CH₃, NEt₂, OCH₃) 81%
(structure, NMe₂)	dioxane, 101°C 5 days	(CH₃, NEt₂, NMe₂) 91%
(structure, R¹, R)	dioxane, 101°C 9 days	no reaction R^1=NMe₂, R=H R^1=R=NMe₂

In a recent study, enamines have been shown to behave as dependable dienophiles in a regiospecific cycloaddition reaction with 1,2,4-triazine to afford 3,4-disubstituted pyridines, eqn (98).[153a] In each case cycloaddition occurs across C-3/C-6 of the 1,2,4-triazine nucleus and the nucleophilic carbon of the dienophile attaches to C-3, eqn (98) and Table 17. This reaction has been reduced experimentally to a one-flask annulation of a pyridine ring onto a preexisting ketone, eqn (99), Table 18.[153b]

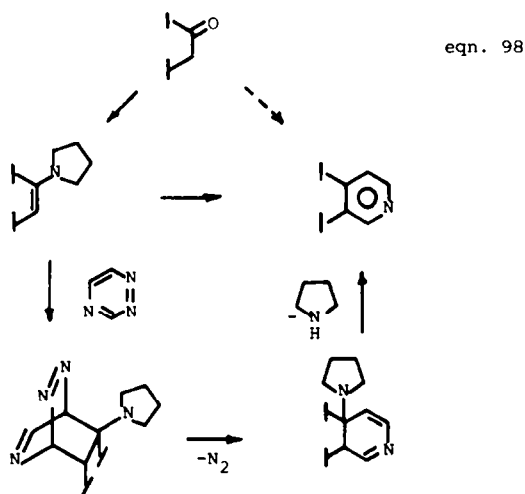eqn. 98
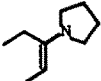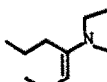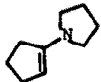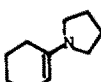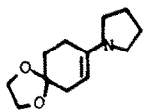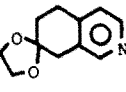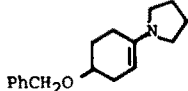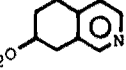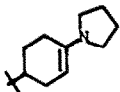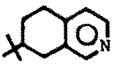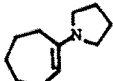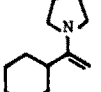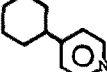
Table 17. Diels–Alder reaction of 1,2,4-triazine with pyrrolidine enamines

Enamine	Conditions	Product	
	CHCl$_3$, 45°C, 23 h		68%
	CHCl$_3$, 45°C, 20 h		71%
	CHCl$_3$, 45°C, 35 h		74%
	CHCl$_3$, 45°C, 23 h		40%
	CHCl$_3$, 45°C, 28 h		22%
	CHCl$_3$, 45°C, 27 h		23%
	CHCl$_3$, 45°C, 27 h		35%
	CHCl$_3$, 45°C, 16 h		78%
	CHCl$_3$, 45°C, 20 h		64%

eqn. 99
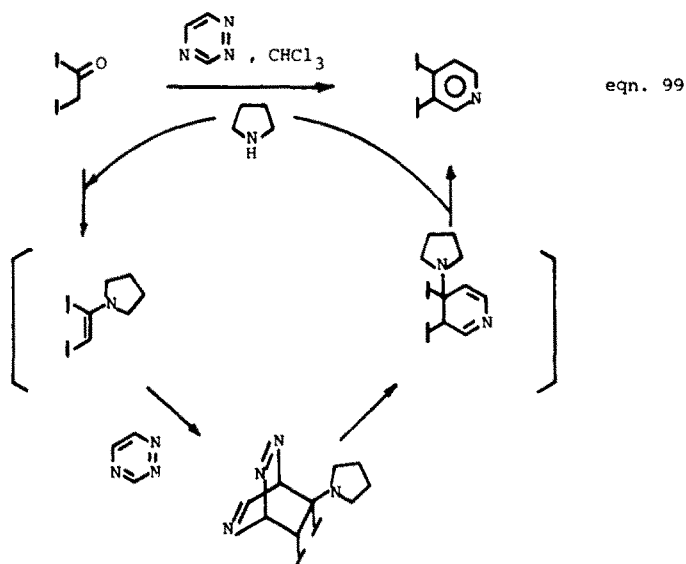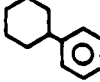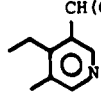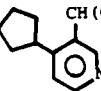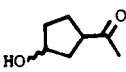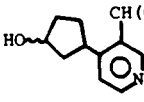
Table 18. Catalytic Diels–Alder reaction of 1,2,4-triazines[153b]

Ketone	1,2,4-Triazine	Conditions temp, time, equiv. of pyrrolidine	Product	% Yield
		CHCl$_3$, 45°C 22 h, 0.2		52%
		CHCl$_3$, 45°C 58 h, 0.2		86%
		CHCl$_3$, 45°C, 96 h, 2.0		93%
		CHCl$_3$, 45°C, 32 h, 1.0		66%
		CHCl$_3$, 50°C, 84 h, 4.0		36%
		CHCl$_3$, 45°C, 72 h, 1.0		43%
		CHCl$_3$, 45°C, 28 h, 4.0		34%
		CHCl$_3$, 45°C, 48 h, 2.0		50%

Although no systematic study of the effect of electron-withdrawing substituents on the mode of cycloaddition and the observed regioselectivity of the reaction of 1,2,4-triazines with enamines has been conducted, preliminary results indicate that they can control the observed regioselectivity, [153c,d] eqn (100).

R=H, 47%[153d]
R=CH$_3$, 37%

eqn. 100

R=H, 45%[153c]
R=CH$_3$, 73%
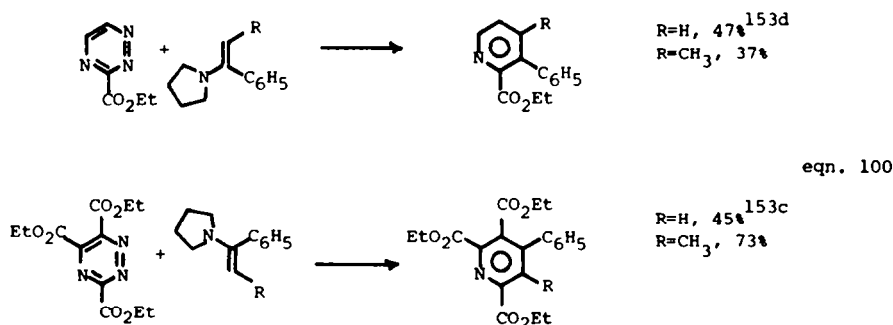
Two separate reports of the use of the Diels–Alder reaction of 1,2,4-triazines for the preparation of the pyridyl CD ring system present in streptonigrin have been described, eqns (101)[153c] and (102).[154] A formal total synthesis of streptonigrin (98) based on this work has been described,[153e] Scheme 28.

eqn. 101

CHCl$_3$, 3 h,
45°C, 59%

3 : 2

eqn. 102

dioxane, 80°C, 22 h
72%

98

Scheme 28.
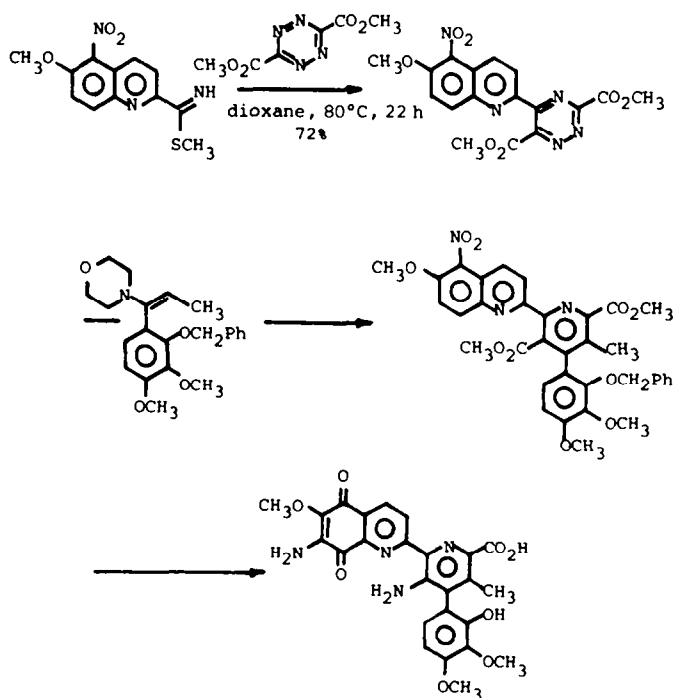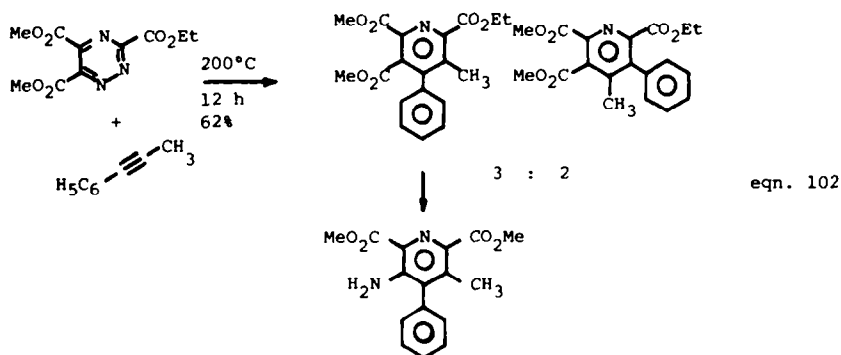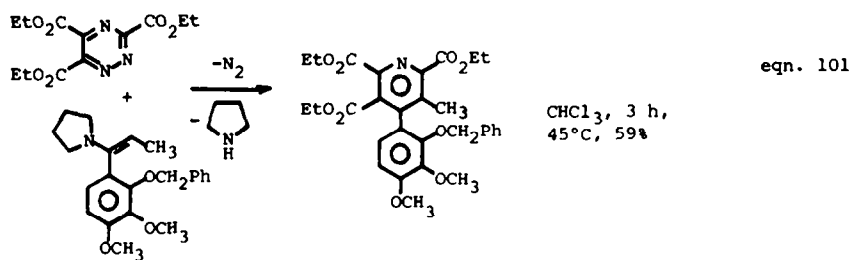
Since the initial observation that strained olefins often undergo Diels–Alder reactions with 1,2,4-triazines[152a] a number of additional examples have been investigated in detail. The cycloaddition of 1,2,4-triazines with norbornadiene, eqn (103);[152a] norbornene, eqn (104);[152] cyclopropenes, eqn (105);[155] benzocyclopropenes,[156] eqn (106); and cyclobutenes,[157] eqn (107), have been reported. In many instances the course of the reaction is determined by choice of reaction conditions.

eqn. 103

$R^1=CO_2CH_3, R=CH_3$ 76%
$R^1=C_6H_5, R=Et$ 74%
$R^1=CH_3, R=Et$ 17%

eqn. 104

$R^1=CO_2Me, R=CH_3$ 80%
$R^1=C_6H_5, R=Et$ 88%
$R^1=CH_3, R=Et$ 61%

eqn. 105

eqn. 106

eqn. 107
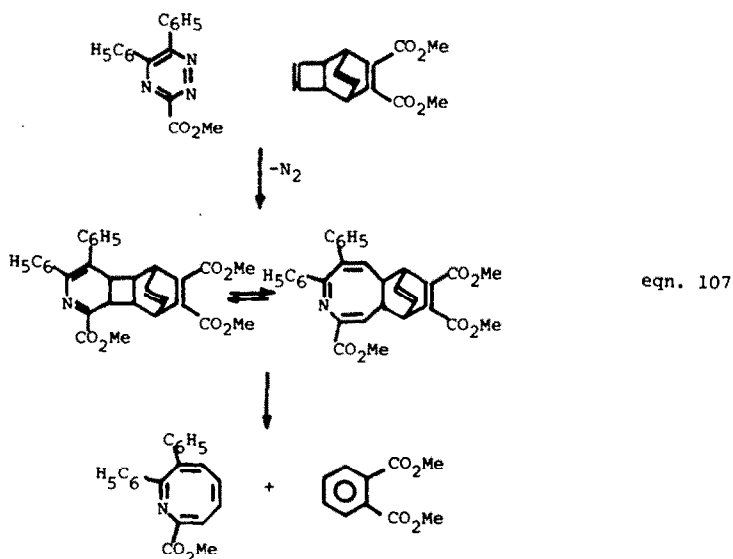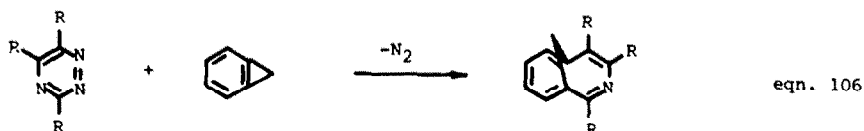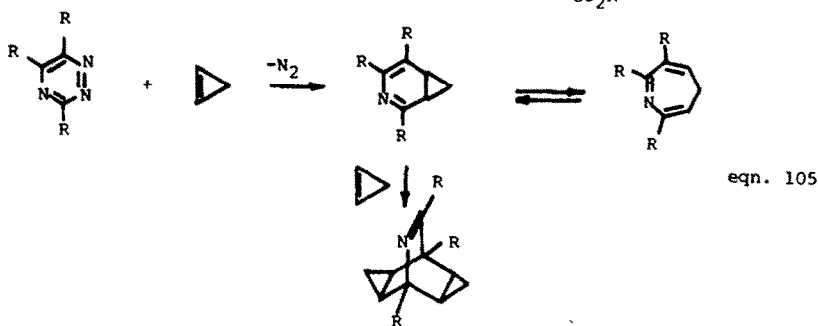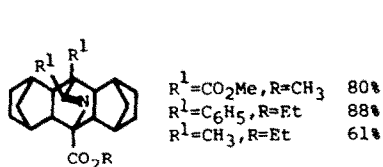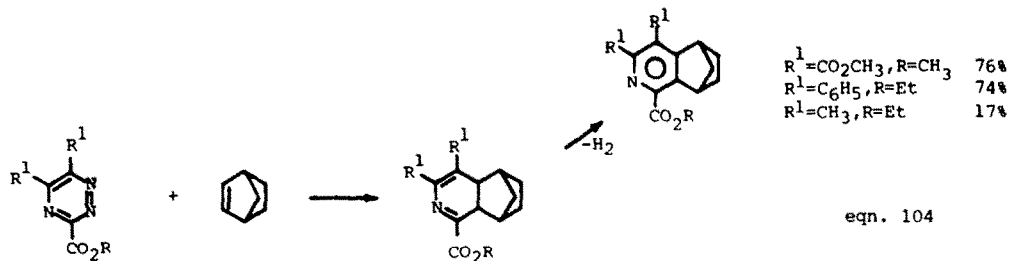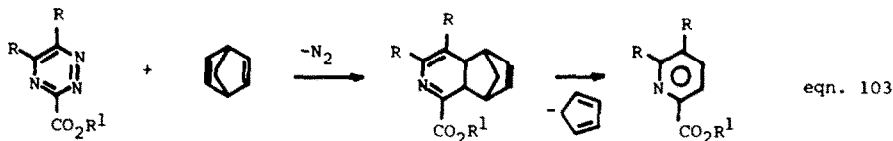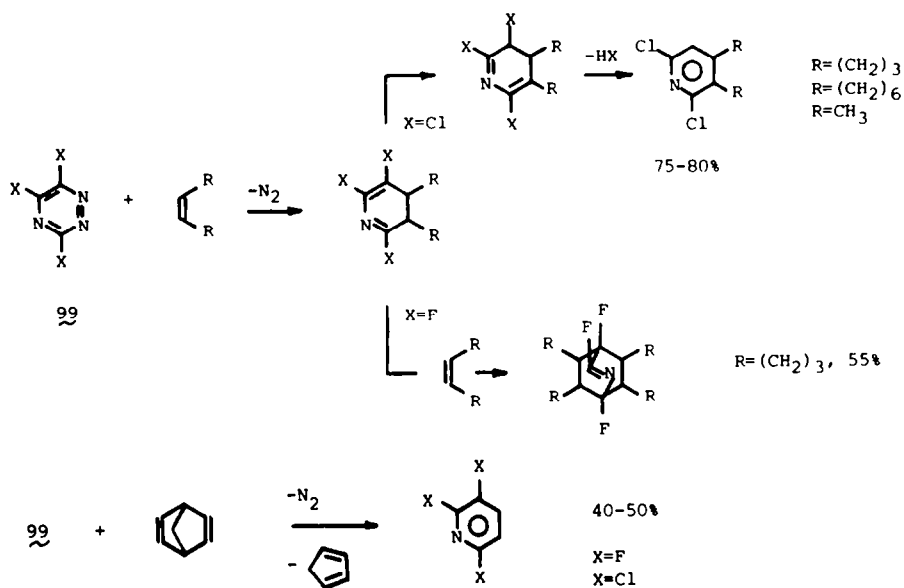
Scheme 29.

Trichloro- and trifluoro-1,2,4-triazine are sufficiently reactive to participate in [4 + 2] cycloaddition reactions with *cis*-olefins,[158] Scheme 29.

In a recent study of the reaction of 1,2,4,5-tetrazines with aryl amidines a subsequent, competing cycloaddition reaction of the product 1,2,4-triazines with aryl amidines was observed,[159a] eqn (108).

eqn. 108
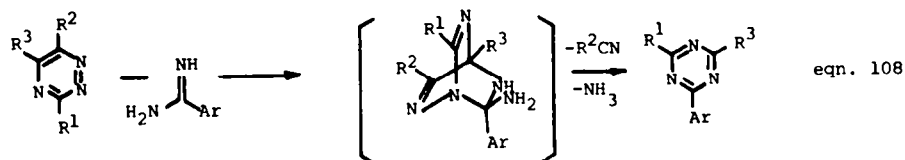
IX.10 1,2,3-*Triazines*

The first successful preparation of 1,2,3-triazine has been realized and a preliminary study indicates that it is capable of participation in inverse electron demand Diels–Alder reactions with electron-rich dienophiles, eqn (109).[159b]

eqn. 109
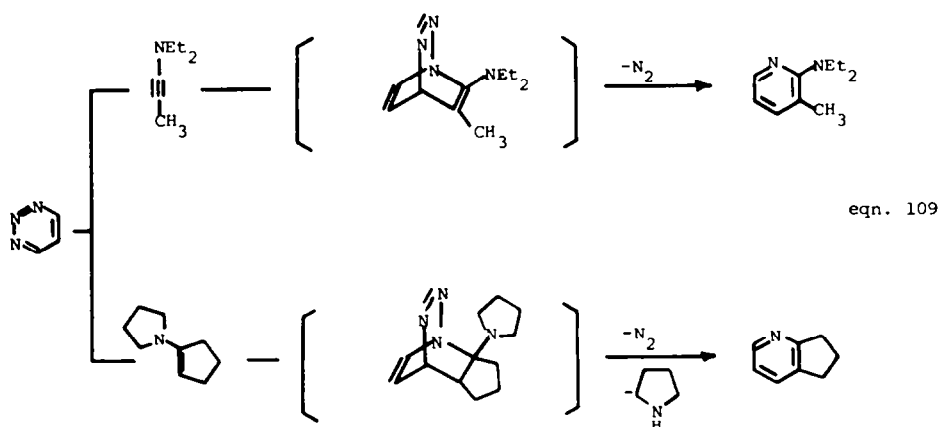
IX.11 1,2,4,5-Tetrazines

The Diels–Alder reactions of 1,2,4,5-tetrazines,[160] first described by Carboni et al.,[161] represent the most extensively studied examples of inverse electron demand Diels–Alder reactions,[17c,d] eqn (110), Table 19.

For most purposes, a limited number of 1,2,4,5-tetrazines have been used as dienes and they have been shown to react with a wide range of dienophiles including olefins to give 1.4-dihydropyridazines,
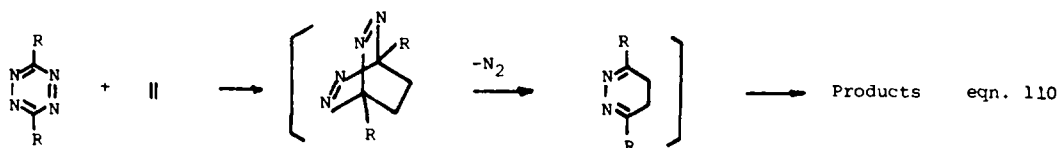
Table 19. Diels–Alder reactions of 1,2,4,5-tetrazines

1,2,4,5-Tetrazine	Dienophile	Conditions	Product(s)	% Yield
		ether-pentane, 25°C		60% [161]
		neat, 25°C		62% [161]
				– 160
		toluene, 100°C, 5 days		64% [161]
		toluene, 110°C, 3 days		86% [161]
		rate of reactivity X=p-OCH₃,R=H>X=R=H>> X=p-OCH₃,R=CH₃>o-OCH₃, R=CH₃> X=H,R=CH₃>>>X=p-OCH₃, R=CO₂Et;X=H,R=Ph[161]		– 161
		neat, 0°C, 1 h		100% [162]
		neat, 25°C, 1 h		88% [162]

Table 19. (Contd).
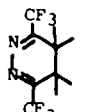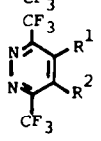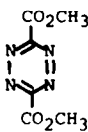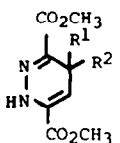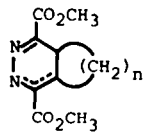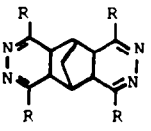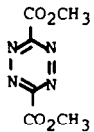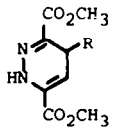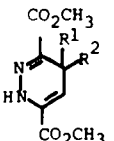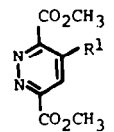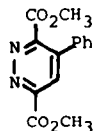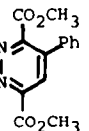
1,2,4,5-Tetrazine	Dienophile	Conditions	Product(s)	% Yield
		neat. 25°C, 2 weeks	CF_3 ... pyridazine ... CF_3	91%[162]
	R^1 ≡ R^2	neat, 25°C, 48 h neat, 25°C, 10 days Et_2O, 0°C, 2 days	CF_3 ... R^1 ... R^2 ... CF_3	$R^1=R^2=H$ 79%[162] $R^1=H, R^2=CH_3$ 91% $R^1=R^2=SnMe_3$ 78%
CO_2CH_3 ... CO_2CH_3	R^1 R^2	CH_2Cl_2, 25°C, <30 min	CO_2CH_3 R^1 R^2 ... CO_2CH_3	$R^1=R^2=H$ 98%[163] $R^1=R=CH_3$ 81% $R^1=CH_3, R^2=Ph$ 91%
	$(CH_2)_n$	CH_2Cl_2, 25°C, <30 min	CO_2CH_3 ... $(CH_2)_n$ ... CO_2CH_3	n=2 83%[163] n=4 71% n=5 50% n=6 57%
R ... tetrazine ... R	(bicyclic dienophile)	neat, 25°C CH_2Cl_2, 25°C CH_2Cl_2, 25°C neat, 25°C	100 : 0, R=CFHCF_3 0 : 100, R=CO_2CH_3 0 : 100, R=Ph 0 : 100, R=CF_3	—[161] 87%[164a] 95%[164] 59%[162]
CO_2CH_3 ... CO_2CH_3	R	dioxane, 101°C dioxane, 25°C, 10 min dioxane, 25°C, 5 min dioxane, 25°C, 20 h CCl_4, reflux	CO_2CH_3 R ... CO_2CH_3	$R=CO_2CH_3$ 87%[165] $R=C_6H_5$ 80% $R=p-OCH_3C_6H_4$ 98% $R=p-NO_2C_6H_4$ 62% $R=(CH_2)_3CH_3$ 99%
	R^1 R^2	dioxane, 25°C, 20 h dioxane, 25°C, 140 h	CO_2CH_3 R^1 R^2 ... CO_2CH_3	$R^1=CH_3, R^2=C_6H_5$ 88%[165] $R^1=R^2=C_6H_5$ 88%
	R^1 OR	dioxane, 25°C, <15 min dioxane, 25°C, 15 min dioxane, 25°C, 2 h dioxane, 25°C, <15 min dioxane, 25°C, 1 h	CO_2CH_3 R^1 ... CO_2CH_3	R=Et, $R^1=H$ 100%[165] R=Ac, $R^1=H$ 95% R=Et, $R^1=CH_3$ 100% R=Et, $R^1=OEt$ 100% $R=CH_3$, $R^1=C_6H_5$ —
	morpholine-Ph	dioxane, 25°C, 1 h	CO_2CH_3 ... Ph ... CO_2CH_3 100	91%[165]
	Ph ≡	dioxane, 101°C	100	44-52%[165]

Table 19. (Contd).

1,2,4.5-Tetrazine	Dienophile	Conditions	Product(s)	% Yield

		dioxane, 25°C, <30 min	**101**	64%[165]
		dioxane, 25°C	**101**	59%[165]
		toluene, 110°C, 14 days	R=Ph, X=O	78%[166a]
		dioxane, 60°C, 30 min	R=CO$_2$CH$_3$, X=O	80%[166a]
		dioxane, 101°C, 40 h	R=CH$_3$, X=O	90%[166b]
		toluene, 110°C, 48 h	R=Ph, X*CH$_2$	71%[166a]
		dioxane, 25°C, 12 h	R=CO$_2$CH$_3$, X=CH$_2$	80%[166a]
		toluene, 110°C, 15 min	R=Ph	65%[166a]
		dioxane, 25°C, 2 h	R=CO$_2$CH$_3$	73%[166a]
		dioxane, 25°C. 2 h	R=CH$_3$	89%[166b]
		dioxane, 45°C, 3 h / 100°C, 30 min	R=CO$_2$CH$_3$	63%[166a]
		dioxane, 85°C, 2.5 h	R=CO$_2$CH$_3$	77%[166a]
		dioxane, 101°C	R=CO$_2$CH$_3$	18%[166a]
		CH$_2$Cl$_2$, 25°C, 16 h	R=CH$_3$, R^1=CH$_3$	35%[166b*]
		CH$_2$Cl$_2$, 25°C, 48 h	R=CH$_3$, R^1=(CH$_2$)$_3$CH$_3$	48%[166b*]
		dioxane, 101°C, 3 h	R=CH$_3$	36%[166b*]
		toluene, 110°C, 50 h	R=Et, R^1=H	94-97%[165]
		toluene, 110°C, 70 h	R=Ac, R^1=H	92-96%
		toluene, 110°C, 2 h	R=Et, R^1=OEt	100%
		toluene, 110°C, 60 h	R=CH$_3$, R^1=Ph	99%
		toluene, 110°C, 20 h		91%[165]

*1,4-dihydrotetrazine produced in reaction media.

Table 19. (Contd).

1,2,4,5-Tetrazine	Dienophile	Conditions	Product(s)	% Yield
		toluene, 25°C, <30 min		91%[165]
			toluene, 110°C, 100 h, 80%	
		$C_6H_5NO_2$, 30°C, 24 h p-benzoquinone		_[165]
		CH_2Cl_2, 25°C		R=CO_2CH_3, 73%[164,165] R=Ph, 67%
				R=CO_2CH_3 43%[164a]
				R=CO_2CH_3 43%[164a] R=Ph 94%
	$-O_2C$	CCl_4, 60°C, 3 h		R=Ph 8%[164b]
		EtOAc, 25°C, 24 h		95%[167]
		toluene, 110°C, 46 h		56%[167]
				_[168]
	SOPh	toluene, 110°C		97%[169]
	NCO_2CH_3	25°C		_[170]

Table 19. (*Contd*).

1,2,4,5-Tetrazine	Dienophile	Conditions	Product(s)	% Yield

First entry (Ph-tetrazine-Ph; dienophile K⁺O⁻ with R¹/R²):
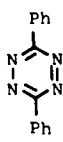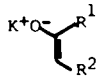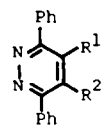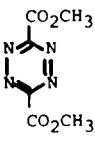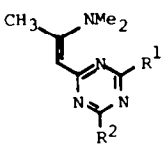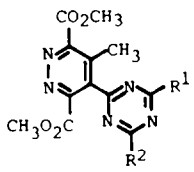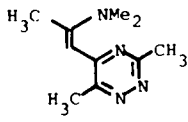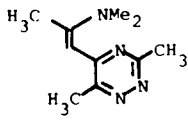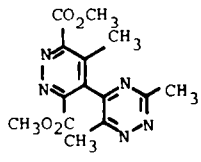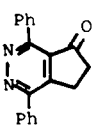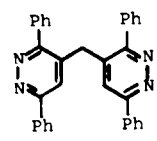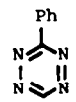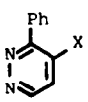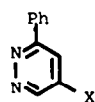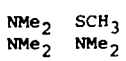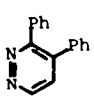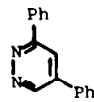
Conditions:
THF, 25°C, 8 min
3 min
2 min
4 min
1.5 min
13 min
5 min
1.5 min
25 min
120 min
1 min
3 min
8 min
12 h

R^1	R^2	% Yield[171]
H	H	88
CH_3	H	31
Et	H	41
H	$CH(OMe)_2$	56
Ph	H	74
H	Ph	58
H	CH_3	72
$PhCH_2$	H	51
CH_3	CH_3	52
CH_3	Et	30
$-(CH_2)_3-$		67
$-(CH_2)_4-$		58
$-(CH_2)_5-$		61
$-(CH_2)_6-$		11

Second entry: dioxane, 25°C, 3 h

$R^1=R^2=H$ 66%[172]
$R^1=CH_3, R^2=H$ 74%
$R^1=R^2=CH_3$ 51%

Third entry: dioxane, 101°C, 1 h 40%[172]

Fourth entry: C_6H_6, Me_2NH, 25°C, 48 h 89%[172]

Fifth entry: $CHCl_3$, Me_2NH, 25°C, 24 h 60%[172]

Sixth entry (Ph-tetrazine; dienophile Y–X): dioxane, 50-60°C

X	Y				% Yield[172d]	
OEt	OEt	dioxane, 50-60°C	100 : 0		90%	
NMe_2	OEt	neat, 20°C	100 : 0		96%	X=NMe_2:OEt (>98:2)
		dioxane, 20°C	100 : 0		98%	(73:27)
		$CHCl_3$, 20°C	100 : 0		82%	(60:40)
		DME, 20°C	100 : 0		76%	(40:60)
NMe_2	SCH_3	dioxane, 20°C	100 : 0		85%	
NMe_2	NMe_2	CH_2Cl_2, 20°C	0 : 100		91%	
		C_6H_6, 20-80°C	0 : 100		86%	
		CH_3CN, 20°C	0 : 100		91%	

Last entry (Ph–C≡C–H): toluene, 25°C, 7 days 19:1, 76%[172e]

Table 19. (Contd).
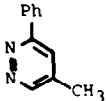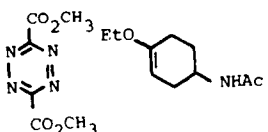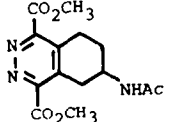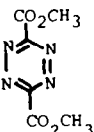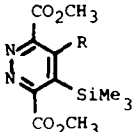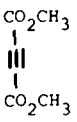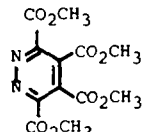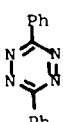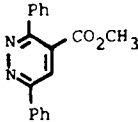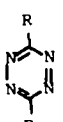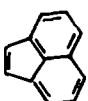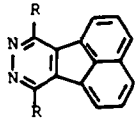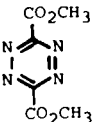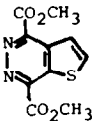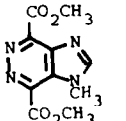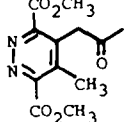
1,2,4,5-Tetrazine	Dienophile	Conditions	Product(s)	% Yield

toluene, 25°C, 14 days — 20%[172e]

dioxane, 25°C, 72 h — 73%[173]

C6H6, 75°C, 12 h
C6H5NO2, 110°C, 8 h

BrCH2CH2Br, 75-100°C
6-24 h

R=H   70%[174]
R=SiMe3   85%

R=CH3   69%
R=CH2CH3   36%
R=(CH2)2CH3   40%
R=(CH2)3CH3   34%
R=(CH2)4CH3   31%
R=(CH2)5CH3   25%

xylene, reflux, 15 h — 53%[142b]

xylene, reflux, 70 h — 83%[142b]

xylene, 180°C, 1 h
xylene, 180°C, 1 h

R=Ph   80%[175]
R=2-Py   60%

CH2Cl2, reflux — 24%[176a]

CH2Cl2, reflux — 36%[176a,c]

CH2Cl2, reflux — 83%[176a]
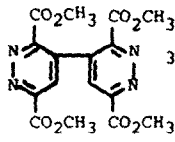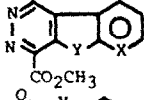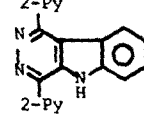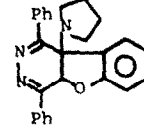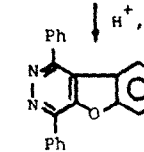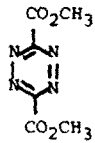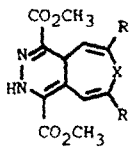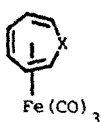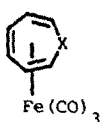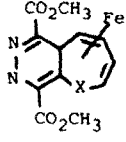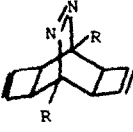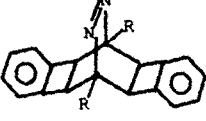
1,2,4,5-Tetrazine	Dienophile	Conditions	Product(s)	% Yield
	N-CH₃	CH₂Cl₂, reflux		39% [176a]
		CH₂Cl₂, reflux		Y=S X=CH₂ 47% [176b] Y=NCH₃ X=N 57%
				Y=O, X=CH₂ 59% [176b] Y=NCH₃, X=CH₂ 45%
2-Py N≡N N-N 2-Py	N H	toluene, 110°C, 3 h	2-Py	35% [177]
Ph N≡N N-N Ph		CH₂Cl₂, 25°C, 12 h		70% [178]
		↓ H⁺, 86%		
CO₂CH₃ N≡N N-N CO₂CH₃		CH₂Cl₂		X=O, R=CH₃ 15% [179] X=NCO₂Et, R=H 24%
	Fe(CO)₃	CH₂Cl₂, 25°C, 7 h CH₂Cl₂, 25°C, 15 min CH₂Cl₂, 25°C, 12 h		X=NCO₂Et 100% [180] X=CH₂ 72% X=C=O 89%
R N≡N N-N R	Fe(CO)₃	acetone, Ce⁺⁴, 0°C, 30 min acetone, Ce⁺⁴, 0°C, 20 min		R=Ph 76% [181] R=CH₃ 21%
	Fe(CO)₃	acetone, Fe⁺³, 0°C, 20 min		R=Ph 85% [181] R=CH₃ 63%

Table 19. (Contd).

1,2,4,5-Tetrazine	Dienophile	Conditions	Product(s)	% Yield

$E=CO_2CH_3$ 70%[182a]
(1:1)

$X=S$
$=-$
$=CH_2$
$=(CH_2)_2$
$=(CH_2)_3$
$=CH_2SCH_2$
55-95%[182b]

C_6H_6, 25°C, 7 days
C_6H_6, 25°C, 2 h
R=Ph, X=CH_2 —[183]
R=Ph, X=NHAc 75%

CH_2Cl_2, -78° to 25°C
R=2-Py 25%[184]

$CHCl_3$,25°C,<12 h
$CHCl_3$,50°C,48 h
R=2-Py 80%[185]
R=Ph 77%

dioxane, 25°C or
$CHCl_3$, 0°C
DMSO, 25°C
R=2-Py 186a-d
X=C=CMe_2 186a,b
X=C=CPh_2 186f
X=C=CH_2 186g,h
X=O, 65% 186h
=NH 186h
=NCH_3 186h
=NCO_2Et 186h
=NCO_2tBu 186i

$CHCl_3$, 25°C
R=2-Py 70-90%[186a]
X=O W=CF_3
X=C=CMe_2 W=CO_2CH_3
X=C=CPh_2 W=CO_2CH_3
X=C=C(SMe)_2 W=CO_2CH_3 69%[186b]

$CHCl_3$, -40° to 25°C
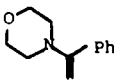R=2-Py[187,186j,k]

Table 19. (*Contd*).

1,2,4,5-Tetrazine	Dienophile	Conditions	Product(s)	% Yield
		-		R=2-Py ca. 100%[1861]
		toluene, 25°C		55%[188]
		CH_2Cl_2, -20°C		55%[188]
2-Py				- 189
R		Et$_2$O, 25°C, 1 h Et$_2$O, 25°C, 20 min		R=Ph 93%[190] R=CO$_2$CH$_3$ 87%
		CH_2Cl_2, 25°C, 12 h		E=CO$_2$CH$_3$[191]
R		Et$_2$O, 25°C, 15 h		R=CO$_2$CH$_3$ 72%[192]
		C_6H_6, 80°C, 24 h CHCl$_3$, 25°C, 14 h		R=Ph 60%[193] R=2-Py 83%
		C_6H_6, 25°C, 5 days		R=Ph 40%[193]
		C_6H_6, 25°C, 8 days C_6H_6, 25°C, 6 days C_6H_6, 25°C, 8 days C_6H_6, 80°C, 48 h		R=Ph R'=CH$_3$,R"=H; 36%[194] R'=-(CH$_2$)$_5$-,R"=H; 33% R'=CH$_3$,R"=CH$_3$ 35% R'=CH$_3$,R"=Ph 92%

Table 19. (Contd).

1,2,4,5-Tetrazine	Dienophile	Conditions	Product(s)	% Yield

CH₃CN, 25°C → product, R^3=H 60-93%[195i,j]

Et₂O, 25°C → product, R=CO₂CH₃[195]
R^1=R^2=R^3=H 79%
R^1=R^2=H,R^3=CH₃ 60%
R^1=R^2=CH₃,R^3=H 59%

Et₂O, 25°C → product, R=CO₂CH₃, R^1=R^2=R^3=H 100%

CH₂Cl₂, reflux → product, R^1=R^2=R^3=H[195j]
R=CO₂CH₃ 38%
R=Ph 11%
R=p-CF₃C₆H₄ 40%

Ce⁺⁴, acetone, 0-25°C → product, R^1=R^2=R^3=H[195m]
R=Ph 36%

product, R=CO₂CH₃ 48%[196]
R=Ph 45%
R=CH₃ 38%

4,5-dihydropyridazines or pyridazines (via *in situ* aeriol oxidation or with excess 1,2,4,5-tetrazine serving as the oxidant), acetylenes, allenes, dienes, enol ethers and acetates, enol lactones, enamines, ynamines, ketene acetals, enolates, benzynes, or aromatics; Table 19. In the few cases where unsymmetrical 1,2,4,5-tetrazines were studied, predictable regiospecificity was usually observed in the [4 + 2] cyclo-addition reaction.[160]

The Diels–Alder reactions of 1,2,4,5-tetrazines with several heterodienophiles have been investigated in recent years, Table 20, and represent additional examples of inverse electron demand [4 + 2] cycloaddition reactions. Imidates,[197] amidines,[198] and thioimidates[199] undergo [4 + 2] cycloaddition reactions with *sym* tetrazines and the synthetic utility of these reactions appear to require a careful match of the diene-dienophile reactivity.[199] Apparently, alkyl amidines[197b] and imidates[198b] prefer to react through the isomerized N,N-ketene aminal and N,O-ketene acetal form, respectively. While aldehyde dimethyl hydrazones undergo clean cycloaddition with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate, ketone dimethyl hydrazones react only through their ene-hydrazine tautomers.[200] Electron-rich N-substituted cyanamides[201] react with electron-deficient 1,2,4,5-tetrazines while simple nitriles were found to be

Table 20. Cycloaddition reactions of 1,2,4,5-tetrazines with heterodienophiles

1,2,4,5-Tetrazine	Dienophile	Conditions	Product(s)

dioxane, 60°C, 10 h

R=R¹=C₆H₅   0% [197a]
R=CO₂CH₃,R¹=CH₃ 13%
R=CO₂CH₃,R¹=Ph   27%

toluene, 110°C

R¹	R²				
2-pyridyl	2-pyridyl	33%		5%	[198a]
C₆H₅	C₆H₅	34%		–	
C₆H₅	2-pyridyl	7.5%	30%	6%	28%
C₆H₅	CH₃	–	70%	–	7%
2-pyridyl	CH₃	–	35%	–	–

toluene, 110°C

R=C₆H₅,R²=CH(Me)₂ 89% [198b]
R=C₆H₅,R²=C(Me)₃ 22%
R=2-Py,R²=CH(Me)₂ 78%
R=2-Py,R²=C(Me)₃ 76%

R=CH₃,Ph 9-21% [197b]

R=H,n=1-3 8-47% [197b]
R=CH₃,n=1

–
dioxane, 80°C, 8-12 h
dioxane, 80°C, 6 h

X=NH₂ 0% [199]
X=NEt₂ 0%
X=OEt 33-43%
X=SCH₃ 47%

dioxane, 80°C, 4 h
dioxane, 80°C, 4 h
dioxane, 80°C, 20 h

X=SCH₃
R¹=R²=H 70% [199]
R¹=H,R²=OCH₃ 78%
R¹=NO₂,R²=OCH₃ 72%

dioxane, 80°C, 20 h

X=OEt
R¹=R²=H 33% [199]

CHCl₃, 25°C

R=CH₃ 81% [200a]
R=CH₂CH₃ 79%
R=CH(CH₃)₂ 76%
R=CH₂CH₂CH₃ 56%
R=C₆H₅ 70%

Table 20. (Contd).

1,2,4,5-Tetrazine	Dienophile	Conditions	Product(s)

$R^1=H,R^2=CH_3$ 200a
$R^1/R^2=(CH_2)_3$
$R^1/R^2=(CH_2)_4$

CH_2Cl_2, 0–25°C
MeOH, 25°C

R=CH_3	–	75% 200b
R=C_6H_5	78%	17%

C_6H_5Cl, reflux 78% 201

C_6H_5, 80°C, 48 h 10–30% 202

CH_2Cl_2, 25°C 73% 201

major

203

2-Py

Ph CH_2Cl_2, –78 to 25°C 25% 184

unreactive.[199] A number of reports of the reaction of 1-azirines[203] with *sym* tetrazines have appeared and the nature of the final products depend on the reaction conditions and substitution pattern.

X. CONCLUSION

The observations that conjugated systems containing nitrogen generally show diminished reactivity toward typical electrophilic dienophiles focused attention on the fact that the presence of a nitrogen atom in conjugated systems may decrease their nucleophilic character and even confer electrophilic character to the system. These observations and the recognized shortcomings of attempting Diels–Alder reactions between 2π and 4π components of a similar electrophilic nature have led to the development of several general approaches to the implementation of useful azadiene Diels–Alder reactions.

Recognition of the electrophilic character of azadienes lead to the investigation and development of the inverse electron demand Diels–Alder reaction. Additional substitution of an azadiene system with electron-withdrawing groups accents the electron-deficient nature of the diene and accommodates the use of electron-rich, strained, or even simple olefins as dienophiles. A continued development of useful azadiene Diels–Alder reactions can be expected as the ability to reliably choose azadiene (diene)/dienophile partners for inverse electron demand Diels–Alder reactions matures.

Substitution of the azadiene system with strong electron-donating substituents increases the nucleophilic character of the azadiene and accommodates the use of typical electron-deficient dienophiles in Diels–Alder reactions.

The entropic assistance provided by intramolecular cycloaddition reactions is sufficient in many instances to override the reluctance of azadiene systems to undergo Diels–Alder reactions.

Incorporation of the azadiene, or dienophile, into a reactive or sensitive system, e.g. heterocumulene, allows numerous, though specialized, azadiene Diels–Alder reactions. Many such examples represent polar cycloadditions.

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