Diels–Alder Reactions of Heterocyclic Azadienes: Scope and Applications

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I. Introduction

Since the initial report of the thermal formation of 1:1 dimerization products of selected dienes[2] and the subsequent observation and structure elucidation[4] of the 1:1 and 2:1 adducts derived from *p*-benzoquinone with selected dienes the thermal $[_{\pi}4_s + _{\pi}2_s]$ Diels–Alder cycloaddition reaction of dienes ($_{\pi}4_s$ component) with olefins ($_{\pi}2_s$ component) has been the subject of continued and extensive studies.[5] Initial studies empirically defined the regioselectivity and the stereoselectivity accompanying the [4 + 2] cycloaddition and provided the basis for understanding and predicting the products derived from the reaction process.[6] Subsequent studies further defined the factors which influence the rate, stereoselectivity, regioselectivity, and most recently the enantioselectivity of the $[_{\pi}4_s + _{\pi}2_s]$ Diels–Alder reaction[7] and have provided the basis for further classification of the Diels–Alder reaction into one of three processes: the normal ($HOMO_{diene}$-controlled) Diels–Alder reaction, the neutral Diels–Alder reaction, and the inverse electron demand ($LUMO_{diene}$-controlled) Diels–Alder reaction.[8] In these studies the rate of the Diels–Alder reaction has been related to the magnitude of the lowest HOMO–LUMO energy separation attainable by the reacting diene/dienophile components: $HOMO_{diene}$–$LUMO_{dienophile}$ or $LUMO_{diene}$–$HOMO_{dienophile}$. Factors effecting the individual 2π and 4π components of the reaction partners in a complementary manner to reduce the magnitude of the HOMO–LUMO energy separation result in suitable reaction rates (25–200 °C) for the [4 + 2] cycloaddition. Typically this is implementation of the normal ($HOMO_{diene}$-controlled) Diels–Alder reaction customarily employing an electron-rich diene (increased $HOMO_{diene}$)/electron-deficient dienophile (decreased $LUMO_{dienophile}$) and the inverse electron demand Diels-Alder reaction employing an electron-

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deficient diene (decreased $LUMO_{diene}$)/electron-rich dienophile (increased $HOMO_{dienophile}$).[9] This complementary choice of diene/dienophile partners for [4 + 2] cycloaddition and the recognition of the origin of the accompanying rate acceleration have played a major role in the development, predictive success, and application of the Diels–Alder reaction.[10]

Heteroaromatic systems which possess an electron-deficient azadiene are ideally suited for participation in inverse electron demand ($LUMO_{diene}$-controlled) Diels–Alder reactions. The recognition of this electron-deficient nature of heteroaromatic azadienes led to an early proposed and subsequently demonstrated reversal of the diene/dienophile electronic properties in the Diels–Alder reaction and led to the full investigations of the inverse electron demand ($LUMO_{diene}$-controlled) Diels–Alder reaction.[11]

In the interim, several general approaches have been investigated and shown to promote or accelerate the participation of electron-deficient heterocyclic azadienes in Diels–Alder reactions: (1) Additional substitution of the heterocyclic azadiene system with electron-withdrawing groups accents the electron-deficient nature of the heterodiene and permits the use of electron-rich, strained, or even simple olefins as dienophiles. (2) Substitution of the heterocyclic azadiene with strong electron-donating substituents in many instances is sufficient to overcome the electron-deficient nature of

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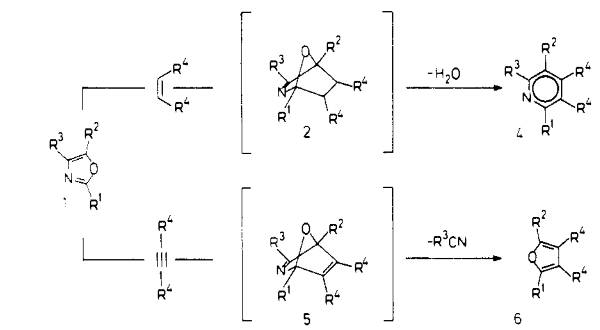
the azadiene and permits the use of conventional electron-deficient dienophiles in normal ($HOMO_{diene}$-controlled) Diels–Alder reactions. (3) The entropic assistance provided by the intramolecular Diels–Alder reaction is sufficient in most instances to override the reluctant azadiene participation in Diels–Alder reactions.[12] (4) The incorporation of the heterocyclic azadiene, or the dienophile, into a reactive system, e.g., heterocumulene, allows a number of specialized [4 + 2] cycloaddition processes which often proceed via the generation of dipolar intermediates in stepwise addition–cyclization reactions.[43]

II. Oxazoles

Since the initial report that alkyloxazoles participate in Diels–Alder reactions with maleic anhydride,[14] extensive efforts have defined the scope and synthetic utility of the [4 + 2] cycloaddition reactions of oxazole derivatives. This work has been the subject of several reviews.[5d,15]

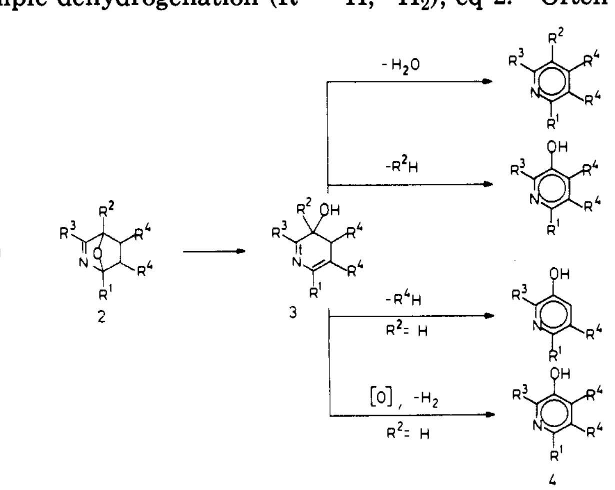
The observed course and facility of the Diels–Alder reaction of oxazoles is dependent upon the dienophile structure, eq 1, the oxazole/dienophile substitution, eq

(1)



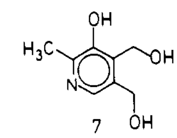
2, as well as the reaction conditions. Olefinic dienophiles provide pyridine products derived from the fragmentation of the initial [4 + 2] cycloadduct **2** to provide **3** which subsequently aromatize to provide the substituted pyridines. Simple dehydration of **3** provides pyridines (R^2 = R, H), and 3-hydroxypyridines are derived from **3** by elimination of R^2H (e.g., EtOH, R^2 = OEt), R^4H (e.g., HCN, R^4 = CN and R^2 = H), or simple dehydrogenation (R^2 = H, $-H_2$), eq 2. Often

(2)



times more than one pathway is followed and a mixture of pyridine products is obtained. Consequently, careful selection of the appropriate oxazole (e.g., R^2 = OEt, $OSiMe_3$, CN), complementary selection of an olefinic dienophile (e.g., R^4 = alkyl vs. CN) and conducting the reaction under defined reaction conditions (HOAc vs. C_6H_6) can determine or control the observed course of the reaction. The addition of electron-donating substituents to the oxazole nucleus increases its rate of 4π participation in normal ($HOMO_{diene}$-controlled) Diels–Alder reactions (OR > alkyl > 4-phenyl > $COCH_3$ > CO_2R ≫ 2- or 5-phenyl) with typical or representative electron-deficient and simple olefinic dienophiles. Although the number of studies of the regioselectivity of the Diels–Alder reaction of oxazoles with unsymmetrical olefinic dienophiles are limited, the generalization has been made that strong(est) electron-withdrawing olefinic substituents are found at position C-4 of the pyridyl products. A number of exceptions to this generalization have been observed.[15]

The annual commercial requirements for pyridoxol (**7**), vitamin B_6, are in excess of 200,000 lb per year.



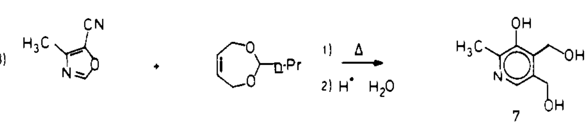
7

PYRIDOXOL

Thus, the potential for the development of a commercially viable process for the preparation of pyridoxol based on the Diels–Alder reactions of substituted oxazoles played a major role in the initial investigation and subsequent development of the scope of the oxazole [4 + 2] cycloaddition reactions. Much of this effort is summarized in Table I.[16–43]

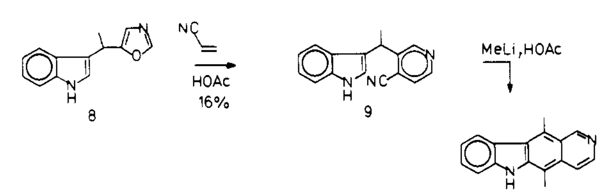
Despite the early recognition that heterocyclic azadiene systems are typically electron-deficient, little effort has been devoted to an exploration of the potential participation of electron-deficient oxazoles in inverse electron demand ($LUMO_{diene}$-controlled) Diels–Alder reactions with electron-rich or simple olefinic dienophiles. One such example, eq 3 (Table I, entry 26), exemplifies the potential of such investigations.[28]

(3)



A key step in the Kozikowski–Hasan approach to the antitumor agent ellipticine (**10**) was the regioselective [4 + 2] cycloaddition of acrylonitrile with the oxazole **8**, equation 4, providing the expected 4-cyanopyridine **9**.[44]

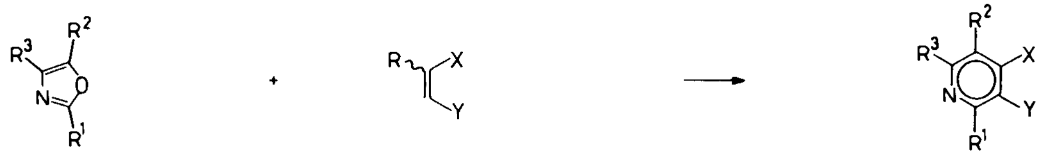
(4)



10 ELLIPTICINE

Weinreb and Levin have detailed a total synthesis of eupolauramine (**11**), an azaphenanthrene alkaloid, which is based on an intramolecular[45,46] alkene–oxazole Diels–Alder reaction and which illustrates the condition-dependent fragmentation, eq 2, of the initially formed oxazole Diels–Alder products. Thermal cycloaddition of **12**, even with the rigorous exclusion of ox-

TABLE I. Oxazole–Olefin Diels–Alder Reactions Employed in the Total Synthesis of Pyridoxol



entry	oxazole R^1	oxazole R^2	oxazole R^3	dienophile R	dienophile X	dienophile Y	Diels–Alder product R^3	Diels–Alder product R^2	Diels–Alder product X	Diels–Alder product Y	Diels–Alder product R^1	ref
1	H	$COCH_3$	CH_3	H	$-C(O)NHC(O)-$		CH_3	$COCH_3$	$-C(O)NHC(O)-$		H	16, 17
2	H	H	CH_3	CN	CH_2OCH_3	CH_2OCH_3	CH_3	OH	CH_2OCH_3	CH_2OCH_3	H	18
3				CN	H	CN	CH_3	OH	H	CN	H	19
4				H	CO_2R	CO_2R	CH_3	OH	CO_2R	CO_2R	H	23
5				H	CN	CN	CH_3	OH	CN	CN	H	20
6				H	$-C(O)NHC(O)-$		CH_3	OH	$-C(O)NHC(O)-$		H	21
7				H	CN	CH_2OH	CH_3	OH	CN	CH_2OH	H	22
8				H	CHO	CH_2OAc	CH_3	OH	CHO	CH_2OAc	H	23a
9				RSO_2	$-CH_2OCH_2-$		CH_3	OH	$-CH_2OCH_2-$		H	24
10	H	OEt(OR)	CH_3	H	$-CH_2OCH_2-$		CH_3	OH	$-CH_2OCH_2-$		H	23
11				H	CO_2Et	CO_2Et	CH_3	OH	CO_2Et	CO_2Et	H	23, 25, 26
12				H	$-C(O)OC(O)-$		CH_3	OH	$-C(O)OC(O)-$		H	23
13				H	CN	CN	CH_3	OH	CN	CN	H	27
14				H	$-C(O)NHC(O)-$		CH_3	OH	$-C(O)NHC(O)-$		H	16, 27
15				H	$-CH_2OCH(R)OCH_2-$		CH_3	OH	$-CH_2OCH(R)OCH_2-$		H	28
16				H	$-CH(OMe)OCH(OMe)-$		CH_3	OH	$-CH(OMe)OCH(OMe)-$		H	29
17				H	CH_2OR	CH_2OR	CH_3	OH	CH_2OR	CH_2OR	H	23, 30, 31, 32
18	H	OCO_2Et	CH_3	H	CN	CN	CH_3	OH	CN	CN	H	33
19				H	CO_2Et	CO_2Et	CH_3	OH	CO_2Et	CO_2Et	H	33
20	H	$OSiMe_3$	CH_3	H	$-C(O)NHC(O)-$		CH_3	OH	$-C(O)NHC(O)-$		H	34
21				H	CO_2Et	CO_2Et	CH_3	OH	CO_2Et	CO_2Et	H	34
22	H	OCH_2-CH_2OR	CH_3	H	$-CH_2OCH(R)OCH_2-$		CH_3	OH	$-CH_2OCH(R)OCH_2-$		H	35
23	H	OPr	CH_3	H	$-CH_2OCH(R)OCH_2-$		CH_3	OH	$-CH_2OCH(R)OCH_2-$		H	36
24	CO_2R	OEt	CH_3	H	$-CH_2OCH_2-$		CH_3	OH	$-CH_2OCH_2-$		H	37
25				H	$-CH_2OCH(R)OCH_2-$		CH_3	OH	$-CH_2OCH(R)OCH_2-$		H	37
26	H	CN	CH_3	H	$-CH_2OCH(R)OCH_2-$		CH_3	OH	$-CH_2OCH(R)OCH_2-$		H	28
27	H	OEt	CH_2-CO_2Et	H	CO_2Et	CO_2Et	CH_2CO_2Et	OH	CO_2Et	CO_2Et	H	38, 39
28				H	CN	CN	CH_2CO_2Et	OH	CN	CN	H	40
29							CH_3	OH	CN	CN	H	41
30				H	$-CH_2OCH(R)OCH_2-$		CH_2CO_2Et	OH	$-CH_2OCH(R)OCH_2-$		H	42
31				H	CH_2OH	CH_2OH	CH_3	OH	CH_2OH	CH_2OH	H	41
32	H	OEt	CH_2-CO_2H	H	CH_2OH	CN	CH_3	OH	CH_2OH	CN	H	32

TABLE II. Applications of the Diels-Alder Cycloadditions of 1,2-Diazines, 1,2,4-Triazines, and 1,2,4,5-Tetrazines

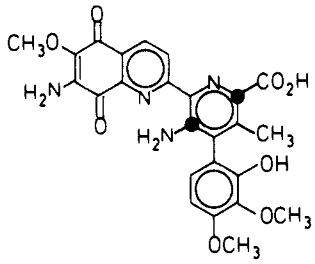
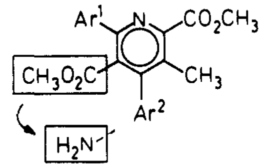
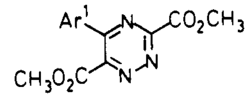
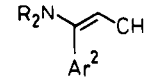
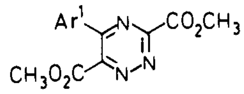
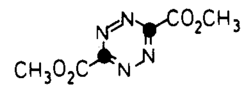
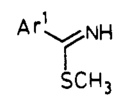
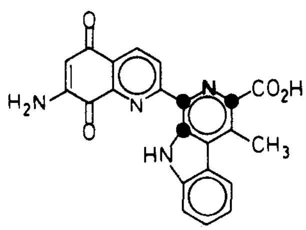
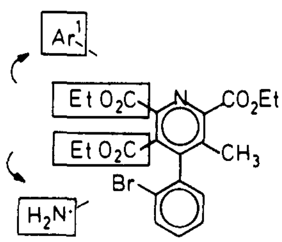
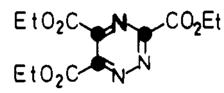
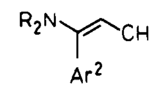
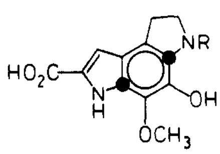
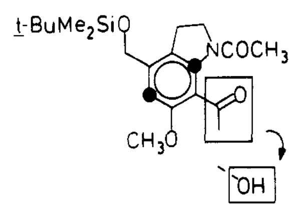
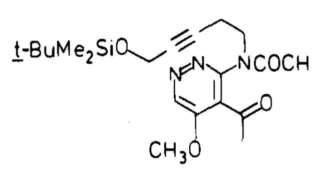
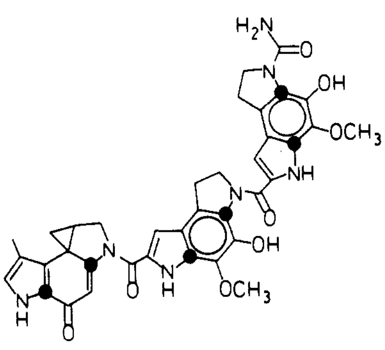
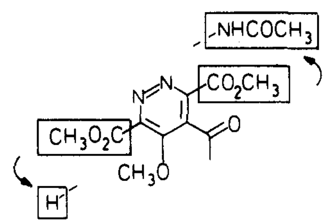
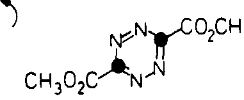
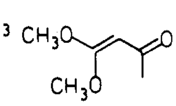
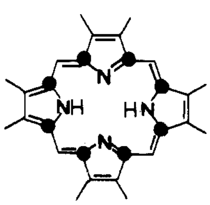
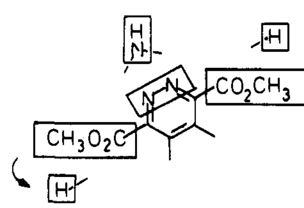
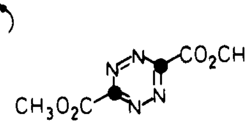
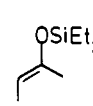
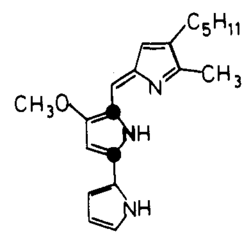
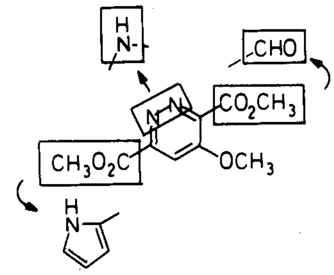
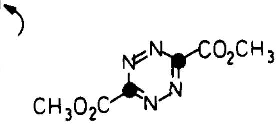
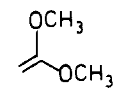
application	Diels–Alder product	azadiene	dienophile	ref
STREPTONIGRIN				86
				
				
LAVENDAMYCIN				87
				
PDE-I				69
PDE-II				90b
CC-1065				90b
				
 CC-1065				
OMP				89
				

TABLE II (Continued)

application	Diels–Alder product	azadiene	dienophile	ref
PRODIGIOSIN				90a
				

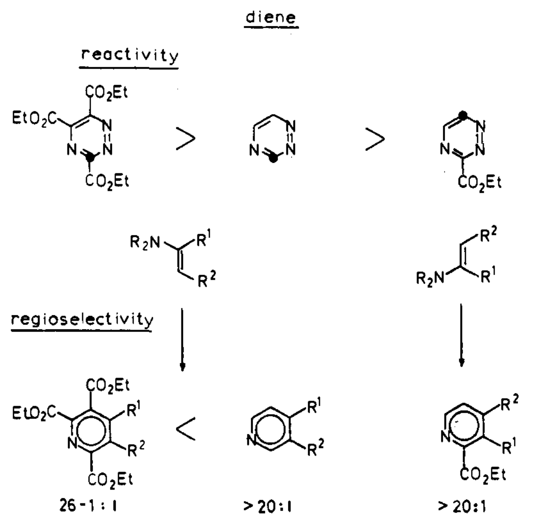
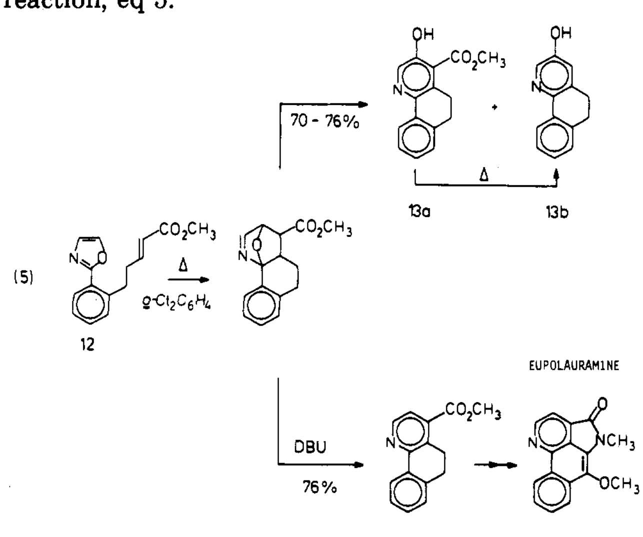


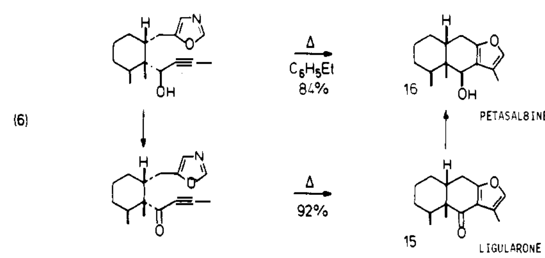
Figure 1.

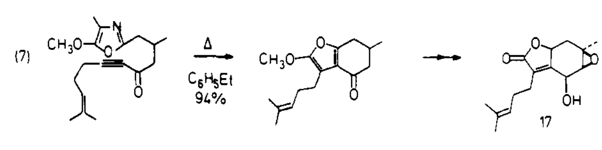
idizing agents, e.g., oxygen, from the reaction mixture provided a mixture of **13a** and **13b** resulting from the previously observed but rare dehydrogenation of the dihydropyridine intermediate (eq 2, $-H_2$). The desired and expected Kondrat'eva fragmentation involving the elimination of water could be observed effectively if the reaction was conducted with a nonnucleophilic base (DBU) present in the thermolysis reaction mixture (eq 2, $-H_2O$). In addition, the thermal cycloaddition of **12** represents a rare example of a 2-phenyloxazole effectively participating in a Diels–Alder reaction, and it is presumably the entropic assistance provided by the intramolecular reaction which accounts for the observed reaction, eq 5.

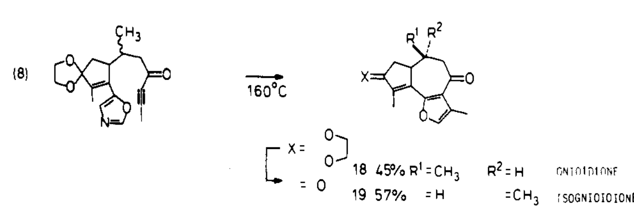


Acetylenic dienophiles including benzynes participate in a well-defined [4 + 2] cycloaddition process with oxazoles to provide substituted furans via a subsequent retro Diels–Alder reaction with loss of R^3CN from the initial Diels–Alder adduct **5**, eq 1.[15,47–48]

In a series of investigations, Jacobi and co-workers have systematically investigated the scope of the intramolecular alkyne–oxazole Diels–Alder reaction and have applied their findings in the total syntheses of (±)-ligularone (**15**) and (±)-petasalbine (**16**), eq 6, (±)-paniculide A (**17**), eq 7, (±)-gnididione (**18**), and (±)-isognididione (**19**), eq 8.[48]







III. Thiazoles

Thiazoles have been shown to be far more reluctant than oxazoles to participate in Diels–Alder reactions. Only two successful efforts have been described. Thiazoles, like oxazoles, react with olefinic dienophiles to provide pyridine products via a Kondrat'eva dehydration, eq 9,[49] and a selected intramolecular Diels–Alder reaction of an acetylenic thiazole provided the expected thiophene product, eq 10.[48g]

IV. Pyrroles

There are numerous examples of substituted pyrroles participating as all-carbon 4π dienes in Diels–Alder reactions;[50] however, their reported participation as an

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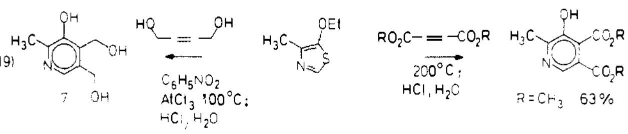

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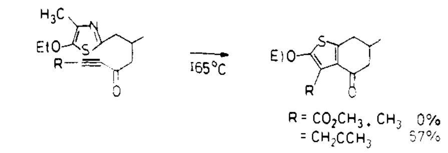

azadiene system in [4 + 2] cycloaddition reactions are limited to selected pyrroles.[51,52] Pentachloro-2*H*-pyrrole has been shown to participate in inverse electron demand Diels–Alder reactions with electron-rich dienophiles exclusively in the form of a 2-azadiene system,[51] pentachloro-3*H*-pyrrole, and one example of an intramolecular Diels–Alder reaction of a substituted, in situ generated 3*H*-pyrrole has been described.[52]

V. Pyrazoles

There are no known examples of pyrazoles participating as 4π components of a Diels–Alder reaction with cycloaddition occurring across N-2/C-5 of the pyrazole nucleus. The initial reports of the Diels–Alder participation of pyrazoles have been shown to have been incorrectly interpreted.[53]

VI. Imidazoles

Two imidazoles bearing selectively disposed functionality have been shown to participate in [4 + 2] cycloaddition reactions. Dimethyl imidazole-4,5-dicarboxylate behaves as a well-defined, electron-deficient, 1,4-diazadiene in an inverse electron demand Diels–Alder reaction, eq 11,[54] and one example of a

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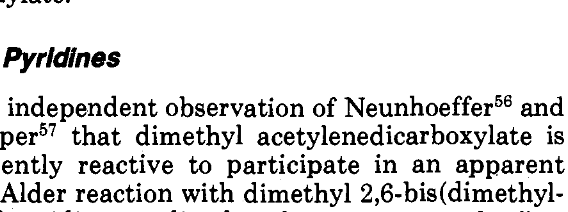

fused imidazole has been shown to participate in Diels–Alder reactions with dimethyl acetylenedicarboxylate.[55]

VII. Pyridines

The independent observation of Neunhoeffer[56] and Gompper[57] that dimethyl acetylenedicarboxylate is sufficiently reactive to participate in an apparent Diels–Alder reaction with dimethyl 2,6-bis(dimethylamino)pyridine-3,4-dicarboxylate represents the first evidence that pyridine systems appropriately substituted with strong electron-donating groups (pyridyl C-2/C-6) may function as 2-azadienes in [4 + 2] cycloaddition reactions with reactive, electron-deficient dienophiles, eq 12. The generality of this process as well as confirmation that the reaction proceeds by a [4 + 2] cycloaddition remain to be determined.

Studies of the Diels–Alder reactions of 2-pyridones (**20**) have been conducted and reviewed.[58]

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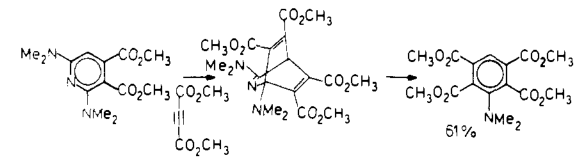
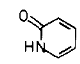
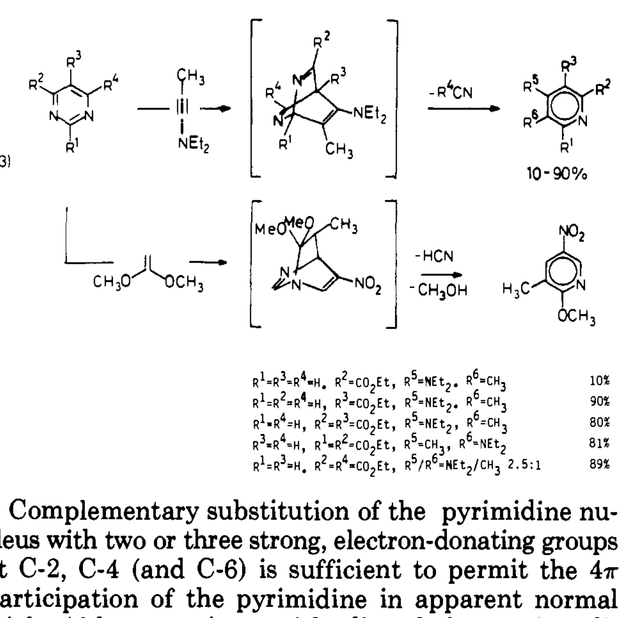



20

VIII. Pyrimidines (1,3-Diazines)

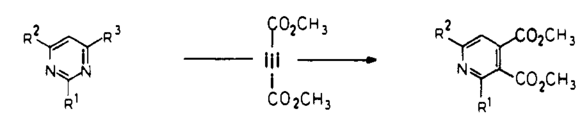
Three of the four general approaches to implementing useful heterocyclic azadiene Diels–Alder reactions have been applied to the pyrimidine series.

The addition of strong electron-withdrawing substituents to the pyrimidine nucleus increases the facility and rate with which the system participates in inverse electron demand [4 + 2] cycloaddition reactions with electron-rich dienophiles. The mode of cycloaddition (C-2/C-5[59] vs. C-4/N-1[60]) and the observed regioselectivity are dependent upon the dienophile employed as well as the position, type, and number of electron-withdrawing substituents present on the pyrimidine nucleus, eq 13.

(13)


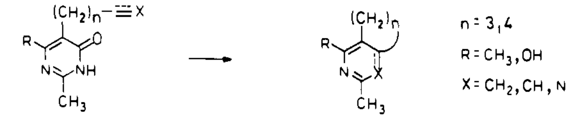
$R^1=R^3=R^4=H$, $R^2=CO_2Et$, $R^5=NEt_2$, $R^6=CH_3$	10%
$R^1=R^2=R^4=H$, $R^3=CO_2Et$, $R^5=NEt_2$, $R^6=CH_3$	90%
$R^1=R^4=H$, $R^2=R^3=CO_2Et$, $R^5=NEt_2$, $R^6=CH_3$	80%
$R^3=R^4=H$, $R^1=R^2=CO_2Et$, $R^5=CH_3$, $R^6=NEt_2$	81%
$R^1=R^3=H$, $R^2=R^4=CO_2Et$, $R^5/R^6=NEt_2/CH_3$ 2.5:1	89%

Complementary substitution of the pyrimidine nucleus with two or three strong, electron-donating groups at C-2, C-4 (and C-6) is sufficient to permit the 4π participation of the pyrimidine in apparent normal Diels–Alder reactions with dimethyl acetylenedicarboxylate, eq 14.[61,62]

(14)


$R^1=R^2=R^3=NMe_2$	53%
$R^1=R^2=NMe_2$, $R^3=H$	10%
$R^1=R^2=NMe_2$, $R^3=OCH_3$	70%
$R^1=OCH_3$, $R^2=R^3=NMe_2$	30%
$R^1=R^3=OCH_3$, $R^2=NMe_2$	55%
$R^1=R^2=R^3=OCH_3$	12%
$R^1=NMe_2$, $R^2=R^3=OCH_3$	40%
$R^1=NMe_2$, $R^2=OCH_3$, $R^3=H$	16%
$R^1=CH_3$, $R^2=R^3=OH$	62%

The intramolecular Diels–Alder reactions of simple, 4-hydroxy, or 4-alkyl-6-oxopyrimidines[62] bearing olefinic, acetylenic, or C≡N dienophiles have been investigated thoroughly and the observations subsequently applied to the total synthesis of (±)-actinidine (**21**),[64] eq 15–16.

(15)


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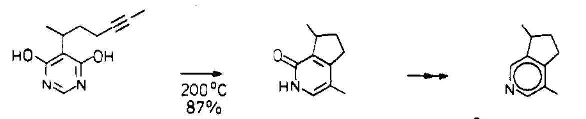
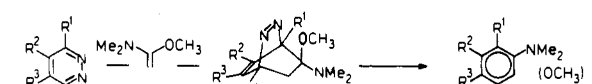


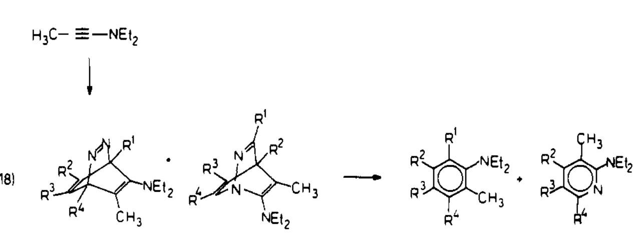
21 ACTINIDINE

IX. Pyridazines (1,2-Diazines)

Pyridazines substituted with additional electron-withdrawing substituents undergo clean inverse electron demand [4 + 2] cycloaddition reactions with electron-rich dienophiles.[65,66] In nearly all instances, cycloaddition occurs across C-3/C-6 of the 1,2-diazine nucleus and the regioselectivity of the reaction can be anticipated based on the 1,2-diazine substitution pattern, eq 17.[65] Exceptions to this generalization are restricted to the reactions of ynamines with electron-deficient 1,2-diazines where both C-3/C-6 and C-4/N-1 1,2-diazine cycloaddition have been observed, eq 18.[66] The number and position of electron-withdrawing substituents on the 1,2-diazine nucleus control the mode and regioselectivity of the ynamine 1,2-diazine cycloaddition, and in each case studied, only one reaction product was detected.[66]

(17)


		NMe_2:OCH_3
R^1=CO_2CH_3, R^2=R^3=R^4=H	60%	15 : 1
R^3=CO_2CH_3, R^1=R^2=R^4=H	57%	12 : 1
R^1=R^4=CO_2CH_3, R^2=R^3=H	90%	8 : 1
R^2=R^3=CO_2CH_3, R^1=R^4=H	80%	3 : 1
R^1=R^3=R^4=CO_2CH_3, R^2=H	93%	2 : 1
R^1=R^2=R^3=R^4=CO_2CH_3	88%	10 : 1

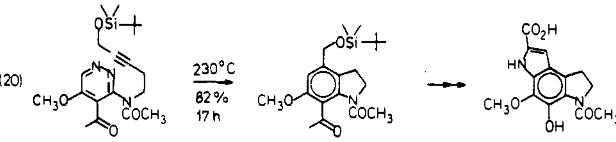
(18)


R^1=CO_2CH_3, R^2=R^3=R^4=H	23%	-
R^3=CO_2CH_3, R^1=R^2=R^4=H	-	30%
R^1=R^4=CO_2CH_3, R^2=R^3=H	-	75%
R^2=R^3=CO_2CH_3, R^1=R^4=H	74%	-
R^1=R^3=R^4=CO_2CH_3, R^2=H	-	85%
R^1=R^2=R^3=R^4=CO_2CH_3	73%	-

Intramolecular Diels–Alder reactions of unactivated and highly substituted alkenyl[67] and alkynyl[68] 1,2-diazines have been explored, eq 19. The reaction is sensitive to the diene/dienophile spacer as well as subtle features apparently important for substrate/product stability under the reaction conditions (200–230 °C). The results of these observations have found application

(19)


R^1=H	R^2=H	X=NCO_2CH_3	n=1	85%
	R^2=CH_3			77%
	R^2=CH_2OTBMS			92%
R^1=Cl	R^2=H	X=NCO_2CH_3	n=1	91%
			n=2	0%
			n=3	0%
		X=O	n=1-3	0%
	R^2=CH_3	X=NCO_2CH_3	n=1	85%
	R^2=CH_2OTBMS			72%

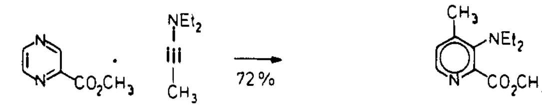
(20)


POE-II **22**

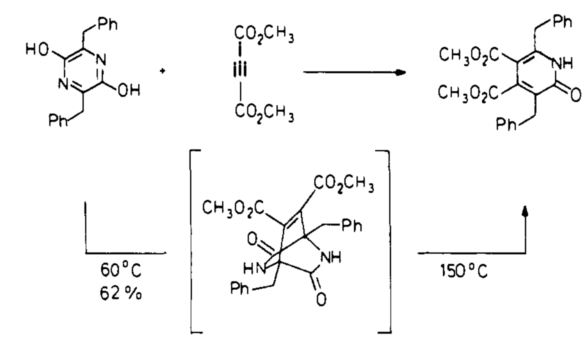
in the total synthesis of the cAMP phosphodiesterase inhibitor PDE-II (**22**),[69] eq 20 (Table II).

X. Pyrazines (1,4-Diazines)

The addition of electron-withdrawing substituents to the 1,4-diazine nucleus will increase its facility for participation in inverse electron demand [4 + 2] cycloaddition reactions with electron-rich dienophiles.[70] Both the rate and regioselectivity of the reaction are dependent upon the number and position of the electron-withdrawing substituents present on the 1,4-diazine, eq 21.

(21)


Alternatively, the addition of strong electron-donating substituents to the 1,4-diazine nucleus does permit the observation of [4 + 2] cycloaddition reactions with electron-deficient or strained, reactive dienophiles,[71] eq 22.

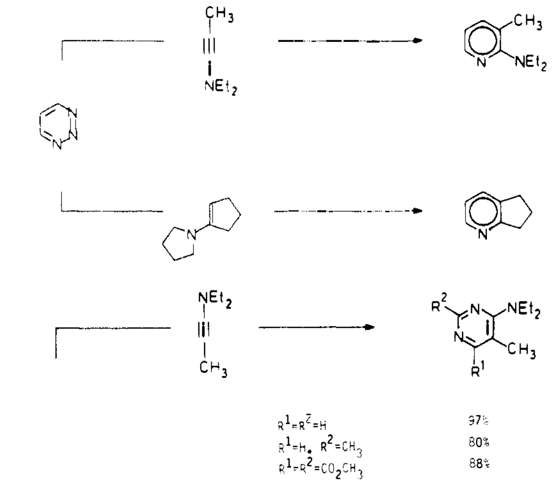
(22)


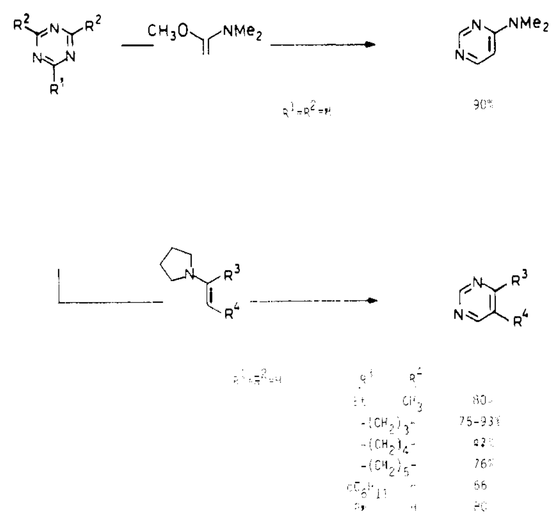
XI. 1,2,3-Triazines

The first successful preparation of 1,2,3-triazine has been realized[72] and a preliminary study has confirmed its potential for participation in inverse electron demand [4 + 2] cycloaddition reactions, eq 23.

XII. 1,3,5-Triazines

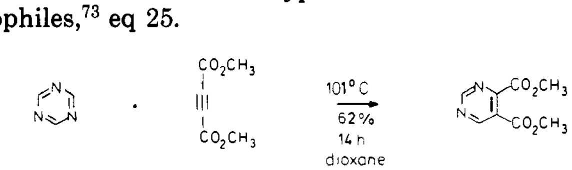
The 1,3,5-triazine nucleus is sufficiently electron-deficient and susceptible to nucleophilic attack that it is well-suited for participation in [4 + 2] cycloaddition processes with electron-rich dienophiles,[73,74] eq 24. The

(23) 

(24) 

addition of electron-withdrawing substituents to the 1,3,5-triazine nucleus will accelerate the rate of 1,3,5-triazine participation in the inverse electron demand cycloaddition reactions.[73] There are sufficient examples of the interception of dipolar intermediates in the observed or attempted inverse electron demand [4 + 2] cycloaddition reactions of selected 1,3,5-triazines to infer that the reaction proceeds with the generation of discrete dipolar intermediates.[73,75]

The intrinsic reactivity of the 1,3,5-triazine nucleus apparently does not preclude its participation in Diels–Alder reactions with typical electron-deficient dienophiles,[73] eq 25.

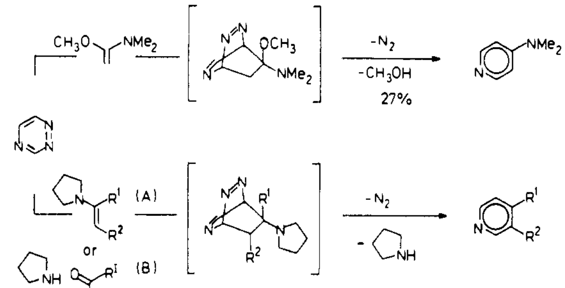
(25) 

XIII. 1,2,4-Triazines

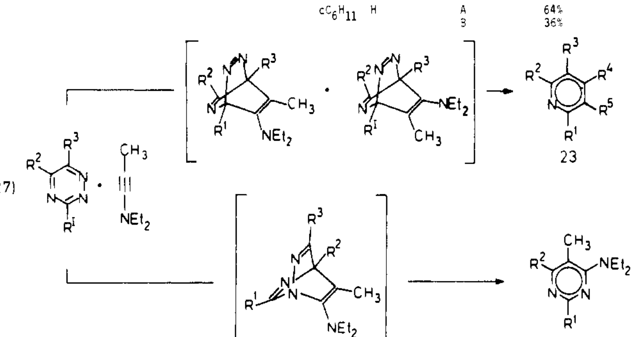
Aside from the [4 + 2] cycloaddition reactions of oxazoles (section II) and substituted 1,2,4,5-tetrazines (section XIV), the Diels–Alder cycloadditions of substituted 1,2,4-triazines constitute the most thoroughly investigated heteroaromatic azadiene system capable of 4π diene participation.[76] In contrast to the oxazole or s-tetrazine series, two potential and observed modes of cycloaddition are open to 1,2,4-triazines: cycloaddition across C-3/C-6 or C-5/N-2 of the 1,2,4-triazine nucleus; and the former is subject to 1,2,4-triazine substituent control of the observed regioselectivity.[77]

As expected, the complementary addition of electron-withdrawing substituents to the 1,2,4-triazine nucleus generally increases its rate of participation in inverse electron demand Diels–Alder reactions, influences the mode of [4 + 2] cycloaddition (C-3/C-6 vs. C-5/N-2 cycloaddition), and controls the observed regioselectivity. In addition, the reactivity of the electron-rich dienophile as well as the reaction conditions, polar vs. nonpolar solvent, have a pronounced effect on the observed course of the [4 + 2] cycloaddition reactions.[76]

In summary, all electron-rich dienophiles including *O,O*-ketene acetals, *O,S*-ketene acetals, *S,S*-ketene thioacetals, *O,N*-ketene acetals, *N,S*-ketene acetals, *N,N*-ketene aminals, enol ethers, enamines, and reactive or strained olefins cycloadd exclusively across C-3/C-6 of the 1,2,4-triazine nucleus, eq 26.[77–79,81] The only exception to this generalization is the cycloaddition reactions of ynamines with 1,2,4-triazines and the C-5/N-2 cycloaddition process is generally observed, eq 27.[80] Since C-5 of the unsubstituted 1,2,4-triazine

(26) 

R^1	R^2	Method	%Yield
Et	CH_3	A	68%
		B	93%
n-Pr	Et	A	71%
$-(CH_2)_3-$		A	74%
		B	52%
$-(CH_2)_4-$		A	40%
		B	66%
$-(CH_2)_5-$		A	78%
		B	86%
cC_6H_{11}	H	A	64%
		B	36%

(27) 

R^1	R^2	R^3	R^4	R^5	23	24
H	H	H	-	-	-	40%
CO_2CH_3	H	H	-	-	-	100%
CO_2CH_3	Ph	H	CH_3	NEt_2	85%	-
CO_2CH_3	H	Ph	-	-	-	100%
CO_2CH_3	Ph	Ph	-	-		42%
			NEt_2	CH_3	32%	
			CH_3	NEt_2	17%	
CO_2CH_3	CH_3	CH_3	-	-		62%
			NEt_2	CH_3	15%	
CO_2CH_3	CO_2CH_3	CO_2CH_3	-	-		10%
			CH_3	NEt_2	90%	
CH_3	H	H	-	-		72%
CH_3	H	Ph	-	-		70%
Ph	H	H	-	-		71%

nucleus is the site of attack by conventional nucleophiles, it is likely that the observed C-5/N-2 yn-

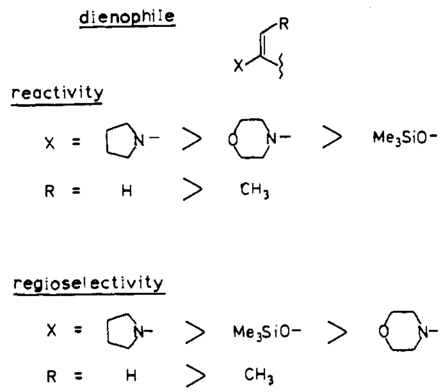
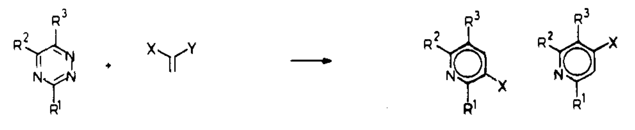


Figure 2.



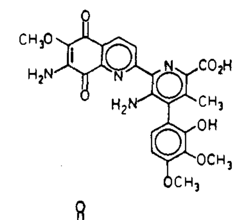
	X	Y	Conditions				
$R^1=R^2=R^3=CO_2CH_3$	OEt	OEt	C_6H_6, 20°C	0	:	100	19-48%
	NMe_2	OEt	dioxane, 20°C	0	:	100	21% X=NMe_2 70% X=OEt
	NMe_2	SCH_3		2	:	98	91%
	NMe_2	NMe_2		18	:	82	81%
$R^1=CO_2CH_3$, $R^2=R^3=Ph$	OEt	OEt	dioxane, 100°C	5	:	95	100%
	NMe_2	OEt		3	:	97	99%
	NMe_2	SCH_3		8	:	92	84%
	NMe_2	NMe_2		78	:	22	90%
$R^1=CO_2CH_3$, $R^2=Ph$, $R^3=H$	OEt	OEt	C_6H_6, 80°C	100	:	0	85%
	NMe_2	OEt	C_6H_6, 40°C	92	:	8	63% X=NMe_2 22% X=OEt
	NMe_2	SCH_3		96	:	4	90%
	NMe_2	NMe_2		90	:	10	91%
			CH_3CN, 40°C	36	:	64	85%
$R^1=CO_2CH_3$, $R^2=H$, $R^3=Ph$	NMe_2	NMe_2	C_6H_6, 80°C	55	:	45	78%
$R^1=CO_2CH_3$, $R^2=R^3=H$	OEt	OEt	CH_3CN, 40°C	100	:	0	57%
	NMe_2	OEt		100	:	0	74% X=NMe_2 22% X=OEt
	NMe_2	SCH_3		100	:	0	82%
	NMe_2	NMe_2		19	:	81	92%
			C_5H_5N, 40°C	35	:	65	54%
			acetone, 40°C	43	:	57	62%
			C_6H_6, 40°C	78	:	22	85%

Figure 3.

amine–1,2,4-triazine [4 + 2] cycloadditions proceed in two steps with the generation of discrete, dipolar intermediates. Others have attributed this behavior to secondary orbital interactions.[76]

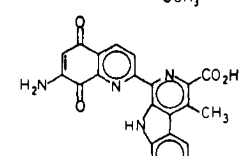
The regioselectivity of the C-3/C-6 cycloaddition process is subject to control by the electronic and steric properties of the 1,2,4-triazine substituents, the electronic and occasional steric parameters of the electron-rich dienophile, as well as the reaction conditions. There is a strong preference for the nucleophilic carbon of the electron-rich dienophile to attach to C-3 of the 1,2,4-triazine nucleus. The complementary positioning of additional electron-withdrawing substituents on the 1,2,4-triazine nucleus (e.g., C-6 or C-3/C-5/C-6) increases the rate of 1,2,4-triazine participation in the [4 + 2] cycloaddition and can enhance (e.g. C-6) the observed regioselectivity. In addition, the correct positioning of strong electron-withdrawing substituents on the 1,2,4-triazine nucleus (e.g., C-3 or C-3/C-5) is sufficient to reverse this normal regioselectivity and illustrates the [4 + 2] regiocontrol available through proper selection and positioning of the 1,2,4-triazine substituents.[78-79] Figure 1 summarizes representative observations derived from our investigations[79,86,87] which complement the extensive investigations of Sauer and Neunhoeffer.[78]

The electron-rich dienophile can control or alter the expected course of the [4 + 2] cycloaddition reaction. Figure 2 summarizes representative observations made in our own investigations[79,86,87] and, as anticipated, the more reactive electron-rich olefins participate in the [4 + 2] cycloaddition reactions under mild conditions and with increased regioselectivity. An unanticipated observation in our investigations was the loss of regioselectivity which accompanied the addition of alkyl substitution to the dienophile or the use of morpholino enamines. These observations were attributed to steric effects of the dienophile which precluded an endo transition state for the expected [4 + 2] cycloaddition.



streptonigrin

25

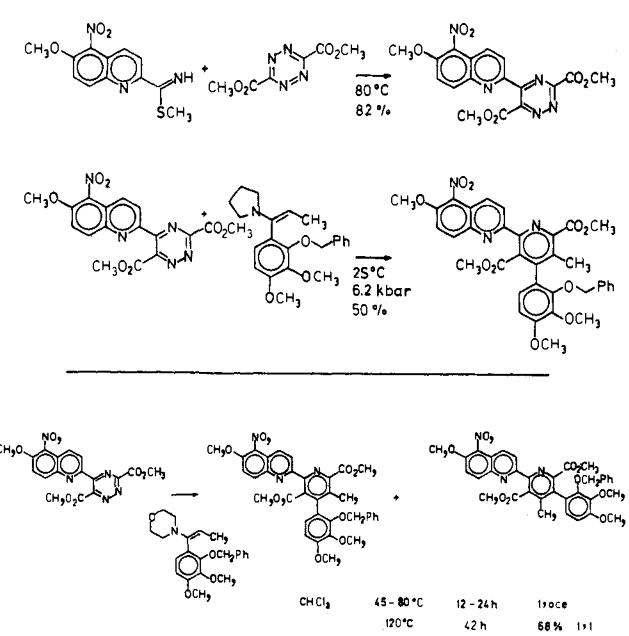


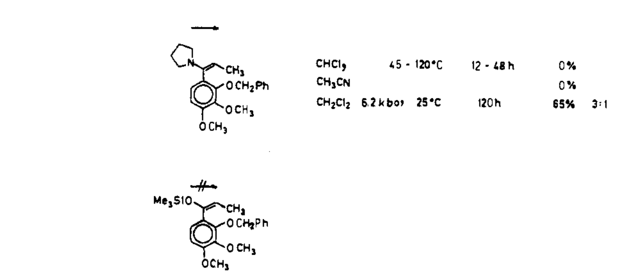
lavendamycin

26

Applications of these observations in the formal total synthesis of streptonigrin (**25**, eq 28)[86] and lavendamycin (**26**, eq 29)[87] are summarized in Table II.

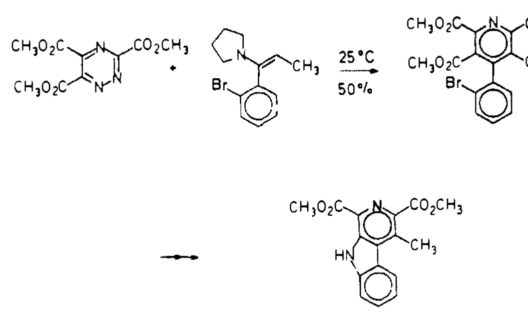
(28)

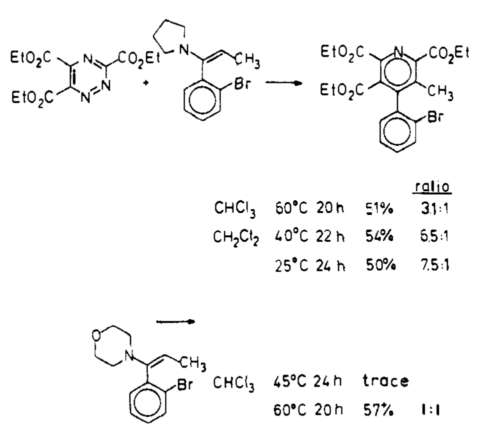




An extensive study by Sauer, Figure 3,[78b] further illustrates the expected and unanticipated, subtle features of dienophile reactivity which effect the 1,2,4-triazine C-3/C-6 cycloaddition regioselectivity.

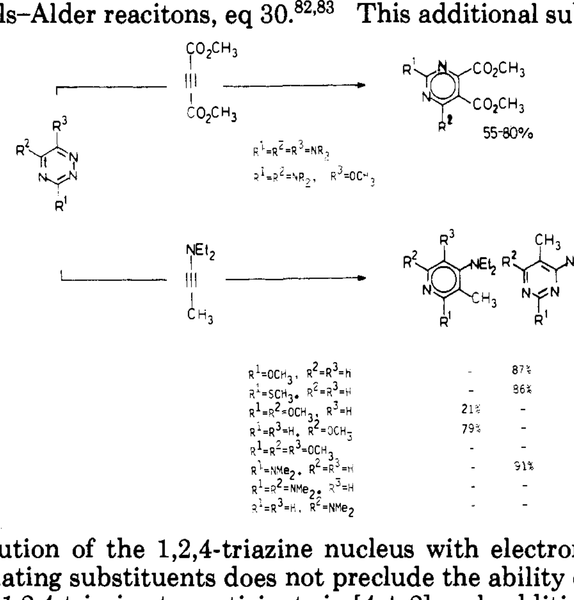
(29)





1,2,4-Triazines are sufficiently reactive to participate in [4 + 2] cycloaddition reactions with typical electron-deficient dienophiles. The additional substitution of the 1,2,4-triazine nucleus with strong electron-donating substituents ($-OCH_3$, $-NMe_2$) increases its rate of participation in normal ($HOMO_{diene}$-controlled) Diels–Alder reacitons, eq 30.[82,83] This additional sub-

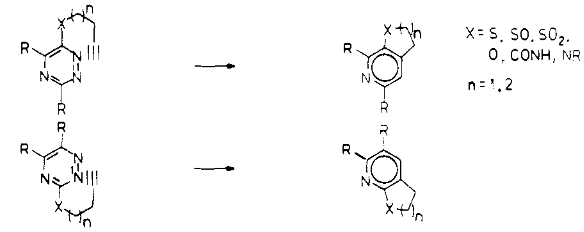
(30)



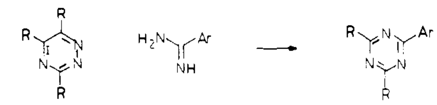
stitution of the 1,2,4-triazine nucleus with electron-donating substituents does not preclude the ability of the 1,2,4-triazine to participate in [4 + 2] cycloaddition processes with electron-rich dienophiles including ynamines.[82]

Recent studies have explored and confirmed the utility of the intramolecular Diels–Alder reactions of alkyne 1,2,4-triazines, eq 31,[84] and reports of the use of heterodienophiles, amidines[85a] and aldehyde *N,N*-dimethyl hydrazones,[85b] in [4 + 2] cycloaddition processes with 1,2,4-triazines have been detailed, eq 32.

(31)



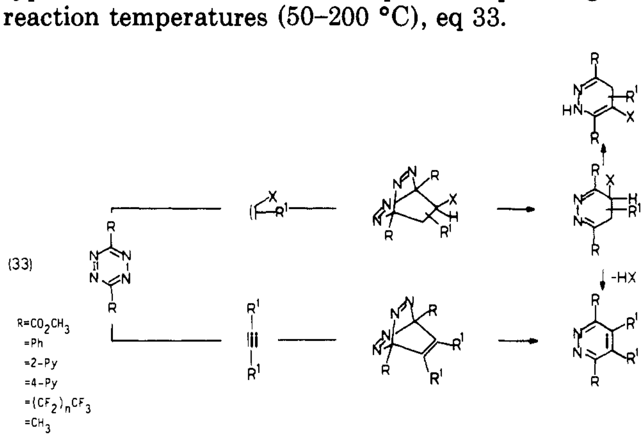
(32)



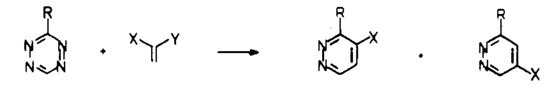
XIV. 1,2,4,5-Tetrazines

Since the initial report of symmetrical perfluoroalkyl 1,2,4,5-tetrazines participating in [4 + 2] cycloaddition reactions with representative olefins in a study which constituted the first demonstration of the viability of the inverse electron demand Diels–Alder reaction,[11] extensive investigations have defined the scope and potential of 1,2,4,5-tetrazine participation in [4 + 2] cycloaddition processes.[88–93] For most purposes a limited number of symmetrical 1,2,4,5-tetrazines have been investigated and to a large extent this reflects the current difficulty in the preparation[88a,b] or stability[91] of the 1,2,4,5-tetrazine system. A wide range of dienophiles and heterodienophiles are capable of participation in Diels–Alder reactions with the electron-deficient 1,2,4,5-tetrazines and include electron-rich, neutral, and electron-deficient olefins, acetylenes, allenes, dienes, enol ethers and acetates, enamines, ynamines, ketene acetals, enolates, benzynes, selected aromatics, imidates, amidines, thioimidates, aldehyde *N,N*-dimethyl hydrazones, imines, azirines, and cyanamides. Electron-rich dienophiles usually participate in 1,2,4,5-tetrazine [4 + 2] cycloaddition reactions at room temperature and the simple, neutral olefinic or typical electron-deficient dienophiles require higher reaction temperatures (50–200 °C), eq 33.

(33)



In the few cases studied,[92] unsymmetrical and electron-deficient 1,2,4,5-tetrazines participate in predictably regioselective Diels–Alder reactions with electron-rich dienophiles, eq 34, and recent reports have

(34) 

	X	Y	Conditions				
R = Ph	OEt	OEt	dioxane, 50°C	100 : 0	90%	
	NMe_2	OEt	neat, 20°C	100 : 0	96%	
			dioxane, 20°C	100 : 0	98%	72% NMe_2 26% OEt^2
			$CHCl_3$, 20°C	100 : 0	82%	60% NMe_2 40% OEt^2
			OME, 20°C	100 : 0	76%	40% NMe_2 60% OEt^2
	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°C	0 : 100	86%	
			CH_3CN, 20°C	0 : 100	91%	

described the first examples of intramolecular alkyne 1,2,4,5-tetrazine Diels–Alder reactions.[93]

Extensive reviews have summarized[88a–b] and compiled[88c] the results of studies to date.

Our own use of the Diels–Alder reactions of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate in the formal total synthesis of streptonigrin, equation 28,[86] the total synthesis of PDE-II, equation 20,[69] octamethylporphin,[89] and prodigiosin[90a] as well as current efforts on PDE-I and CC-1065[90b] are summarized in Table II.

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It is with appreciation that I acknowledge the individuals responsible for our own azadiene studies: James S. Panek, Michael D. Mullican, M. Patel, Robert S. Coleman, Masami Yasuda, and Daniel Yohannes. It is their efforts, enthusiasm, and dedication which are responsible for our studies and that have generated our interest in the topic. We gratefully acknowledge the financial support of the National Institutes of Health (CA 42056, 41986, 41101) and the Searle Scholars Program.

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