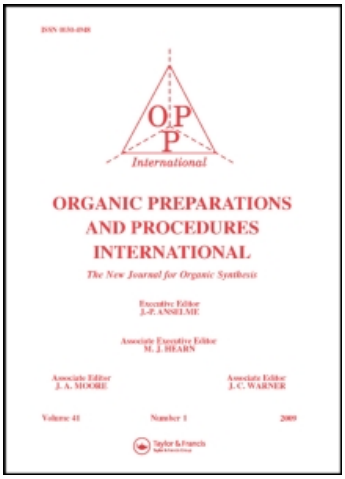

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N-DIENYL AMIDES AND LACTAMS: PREPARATION AND DIELS-ALDER REACTIVITY

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N-DIENYL AMIDES AND LACTAMS. PREPARATION AND DIELS-ALDER REACTIVITY

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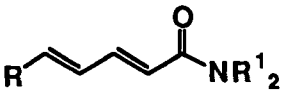
INTRODUCTION

The use of functionalized 1,3-butadienes in the Diels-Alder reaction is increasingly important for the synthesis of complex natural products.[1] Oxygenated dienes such as Danishefsky's diene[2] are widely used in synthesis.[3] The corresponding 1- and 2-thioalkyl (and thioaryl)-butadienes are less important but have been prepared[4] and used in the Diels-Alder reaction.[5] Derivatives of 2,4-pentadienoic acid are, of course, well-known partners in the Diels-Alder reaction.[6] The dienyl amide



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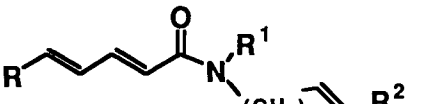

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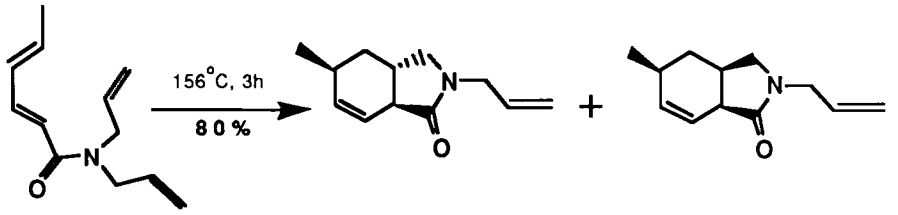
derivatives derived from dienoic acids (*1* and *2*) are interesting and useful eno-

philes. 2,4-Dienamides such as ***1*** exhibit both physiological and insecticidal activity.[7] Several synthetic methods for their preparation have appeared and they have been used as key intermediates in several syntheses.[8]

An extremely useful analog of dienamide ***1*** is the *N*-alkyl derivative (***2***) which has been used in several intramolecular versions of the Diels-Alder reaction.[9] Frater's report of the internal cyclization of ***3*** to a 40:60 mixture of ***4*** and ***5*** is a useful illustration of this type of reaction.[10] Martin has used this methodology in the syntheses of hydroindole and hydroquinoline alkaloids.[11]. Similar work by Oppolzer generated the dienamide moiety by thermal ring opening of benzocyclobutene carboxamides.[12]



3 ***4*** ***5***

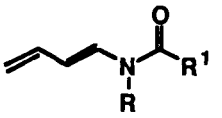
An alternative and useful isomer of ***1*** and ***2*** has the dienyl moiety attached to nitrogen rather than the carbonyl of the amide (as in ***6***) or a lactam (such as ***9***). Such *N*-functionalized dienes are compatible with both inter- and intramolecular Diels-Alder reactions. Several methods for the preparation of these compounds have appeared, as well as many examples describing their utility in the Diels-Alder reaction.

Fallis described several of these reactions in his review of intramolecular Diels-Alder reactions.[9]. Oppolzer's[13] as well as Brieger and Bennett's review[14] of the intramolecular Diels-Alder reaction included examples of these systems. Petrzilka and Grayson's review[15] of heterosubstituted 1,3-dienes also gave many excellent examples of *N*-dienyl amides and Lenz described these systems in a review of the photochemistry of enamides.[16] By necessity, this review will repeat some of the information contained in these previous reviews. The emphasis will be on dienyl

amides and lactams, which previous reviews included as a small portion of a broader review but were never the exclusive focus. The emphasis here will be on the preparation, spectroscopic properties and reactions of six major structural types of dienyl amides and lactams.

(a) *N*-Acyl-1-Amino-1,3-butadienes such as ***6***
(b) *N*-Acyl-2-Amino-1,3-butadienes such as ***7***
(c) *N*-Acyl-1-azadienes such as ***8***
(d) *N-Dienyl* lactams such as ***9***
(e) 2-(1H)-Pyridones such as ***10***
(f) *N*-Acyl-1,2-Dihydropyridines such as ***11***

There are several derivatives of ***10*** which are fused to an aromatic ring and undergo Diels-Alder cyclization. These will be omitted from this review and attention will be given exclusively to derivatives of ***10*** and ***11*** which are structurally related and show reactivity similar to ***6-9.***



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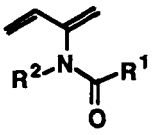

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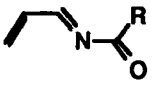

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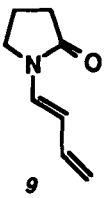

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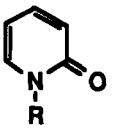

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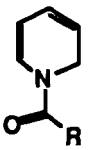

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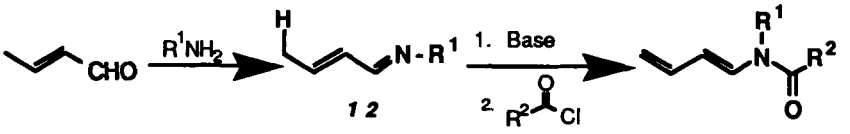
1. PREPARATION

1a. Preparation of *N*-Acyl-1-Amino-1,3-Butadienes

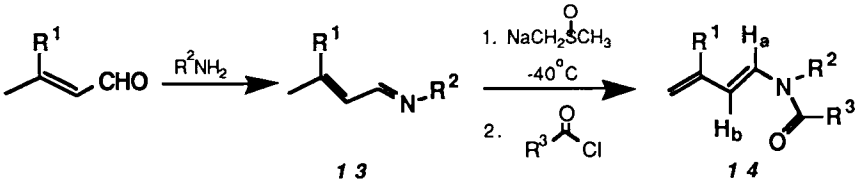
One of the first syntheses of *N*-acyl dienylamides was that of Oppolzer.[17] Primary amines were reacted with crotonaldehyde (25°C, benzene, molecular sieve



12

3Å) to give the azomethine ***12.*** Proton abstraction with strong bases (such as dimsyl sodium or sodium *bis*-trimethylsilylamide) gave a delocalized anion which was followed by reaction with an acyl chloride to give the *trans-N*-acyl-1-amino-butadiene stereoselectively. These were stable to chromatography, distillation and extended storage in a freezer, although they decomposed at temperatures greater than 200°C to urethane derivatives. This is in contrast to the closely related *N,N*-dienyl-1-amino-1,3-butadienes, which are rather unstable compounds.[18] Oppolzer's synthesis was later improved[19] by direct acylation of ***13*** in an inert solvent, in the presence of tertiary amines, to give ***14*** in high yield (see Table 1).[19,17]

Table 1. Preparation of *N*-Acyl-1-amino-1,3-butadienes.



13 ***14***

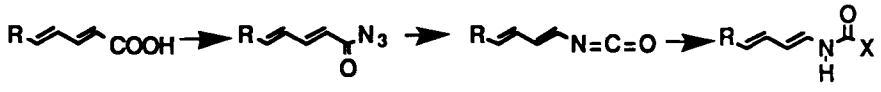
Entry	R^1	R^2	R^3	Method	% *14*[a]
1	H	Bn	Ph	B	80
2	H	Bn	OCH_2Ph	B	81
3	H	cyclohexyl	OMe	B	65
4	H	cyclohexyl	Me	B	88
5	H	cyclohexyl	Ph	A	70
6	H	iPr	Me	B	65
7	Me	nC_3H_7	OMe	B	49
8	H	Ph	Ph	B	56
9	H	4-pentenyl	OMe	A	36
10	H	4-pentenyl	Me	A	57
11	H	cyclohexyl	iPr	A	78
12	H	cyclohexyl	OMe	A	41
13	H	Pr	3-butenyl	A	60
14	H	Ph	OMe	A	51
15	H	4-pentenyl	OMe	A	65
16	H	4-pentenyl	OPh	A	61
17	H	4-pentenyl	Me	A	57

[a] Yield of ***13*** → ***14***

Method A: (i) ***13*** + $NaCH_2SOCH_3$, -40°C (ii) R^3COCl
Method B: ***13*** + 3° amine + R^3COCl, 25°

The spectroscopic properties of ***14*** allowed ready identification. The amide and carbamate moieties absorbed between 1662-1730 and 1632-1654 cm^{-1} in the infrared. For entry 1 (see R^1 = H, R^2 = Bn, R^3 = Ph in Table 1) ν_{max} was 1666 and 1638 cm^{-1}. For entry 12 (R^1 = H, R^2 = cyclohexyl, R^3 = OMe) the carbamate moiety showed ν_{max} at 1730 and 1654 cm^{-1}.[19] The ultraviolet showed a strong band at 250-278 nm and λ_{max} for entry 1 was at 256 nm in methanol (log ε= 4.25).[19] The ^1H NMR signal for H_a of ***14*** was also reported to be 7.00 ppm for entry 1, with $J_{a,b}$ = 14 Hz. For entry 5 (R^1 = H, R^2 = cyclohexyl, R^3 = Ph), H_a appeared at 6.43 ppm ($J_{a,b}$ = 14 Hz) and H_a for entry 12 was at 6.79 ppm with Ja,b = 13 Hz.

Overman also developed significant methodology for the synthesis of dienyl amides. The synthesis of *trans-N*-acylamino-1,3-dienes from the corresponding dienoic acid was reported.[20]. In this approach a 1,3-dienoic acid (***15***) was converted to the acyl azide ***16*** by reaction of an intermediate 'mixed' anhydride with sodium azide. Subsequent heating (in refluxing toluene) in the presence of a free radical inhibitor such as 4-*t*-butylcatechol gave the acylamino-1,3-diene ***18*** via a modified Curtius rearrangement sequence.[21]

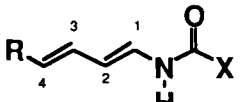


15 ***16*** ***17*** ***18***

The initial Curtius product was the dienyl isocyanate ***17***, which could be trapped as it formed in refluxing toluene. Alternatively, the isocyanate was cooled to room temperature prior to addition of the trapping agent. Trapping ***17*** *in situ* was preferred for preparation of diene carbamates (trapped with alcohols) but inferior for preparation of diene ureas (trapped with amines) which were more reactive and decomposed in refluxing toluene. The precursor dienoic acids were prepared by Knoevenagel and Wittig type reactions.[22] Examples of the preparation of ***18*** are shown in Table 2.[20]

This procedure generated the *trans*-dienyl carbamate as the major regioisomer. This was confirmed by the ^{1}H and ^{13}C NMR which was characteristic of functionalized dienes. Chemical shifts for the carbons of representative dienyl carbamates from Table 2 are shown in Table 3.[20b] As stated by Overman, "the presence of the C_3 carbon at about 135 ppm confirms the expected *trans*-stereochemistry since C_3 would be shifted noticeably upfield if the substituent at C_1 were *cis*- oriented".[20b]

Table 2. Preparation of *N*-Acyl-1-Amino-1,3-butadienes from Dienoic Acids.



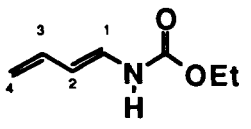
18

R	X	Procedure	% *18*
H	OBn	A	53
		B	35
H	O*t*-Bu	A	59
		B	44
Me	OEt	A	80
H	OEt	A	71
Me	OPh	A	72
H	OPh	B	66
Me	$N(CH_2)_4$	B	77
		A	10
H		B	44
Me	SPh	B	78
H	SPh	B	47

METHOD A: Isocyanate trapped at 100°C
METHOD B: Isocyanate formed at 110°C, cooled to 25°C and trapping agent added

As X (in Table 3) varies, $CCl_3 \rightarrow OEt \rightarrow N(CH_2)_4$, the chemical shifts of C_2 and C_4 move upfield (118.6 →112.1 → 109.7 ppm respectively).

The proton NMR for ***19*** gave signals for the dienyl moiety at 5.3-6.9 (m, vinylic) and 4.5-5.1 ppm (m, $=CH_2$).[20b] Carbamate ***20*** showed similar signals at 5.0-7.0 (m, vinylic) and 1.67 ppm (d, J = 6 Hz, $=CCH_3$). In the infrared, strong absorption



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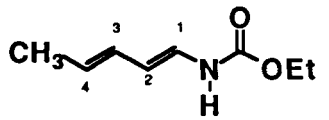
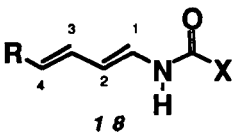


20

bands appeared at 3360, 1695, 1665 and 1530 cm^{-1} for ***19*** and at 3300, 1705, 1670, 1640 and 1520 cm^{-1} for ***20***.

Overman also reported an alternative synthesis of dienes ***14*** by solution thermolysis of the trichloroacetimidic esters of propargylic alcohols.[23] The 2,2,2-tri-chloro-*N*-dienyl acetamides (***21***) were prepared by base catalyzed addition of propargylic alcohols to trichloroacetonitriles.[23,24] This method gave excellent yields with secondary propargylic alcohols but low yields with the analogous tertiary

Table 3. ^{13}C NMR Shifts for Dienyl Carbamates, *18*.



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		Chemical Shifts (ppm)[a]				
R	X	C_1	C_2	C_3	C_4	C=O
H	OBn	127.2	112.5	134.6	113.5	153.7
H	Ot-Bu	127.8	111.3	134.9	112.7	152.9
H	OEt	127.6	112.1	134.8	113.2	154.1
H	OPh	126.7	113.5	134.3	114.1	151.9
H	SPh	125.7	114.3	134.2	115.0	164.6
H	$N(CH_2)_4$	128.8	110.0	135.5	111.6	153.4
H	CCl_3	124.4	118.6	133.4	117.3	159.1
Me	OEt	124.8*	111.9	128.9	125.4*	154.0
Me	OPh	123.9	113.3	128.5	126.4	152.1
Me	SPh	123.1	114.2	128.5	127.2	164.3
Me	$N(CH_2)_4$	126.0	109.7		123.6	153.3

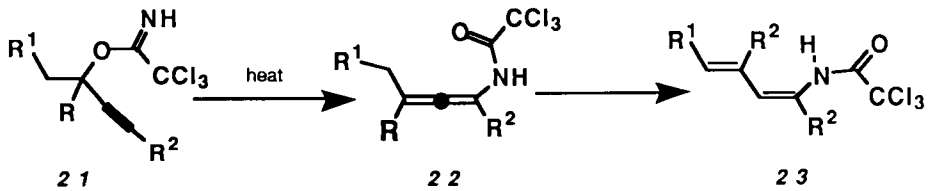
[a] ($CDCl_3$) in ppm from internal tetramethylsilane * assignments may be reversed

alcohols. Heating a dilute solution of ***21*** was accompanied by a thermal [3,3]-sigmatropic rearrangement to ***22*** which gave the *cis*-1-(trichloroacetamide)-1,3-

diene (***23***) when an allylic proton was available. If this rearrangement was not possible, formation of the 2-substituted dienyl amide was favored (see section 1b.).

Dienes such as ***21*** were less stable when R was H, and reasonable yields of the rearranged products were obtained only by heating dilute solutions of the propargylic acetamide. When thermal rearrangement was accomplished at 0.15 M rather than 0.03 M,[23b] the yield of acylamino butadiene ***23*** (R = R^1 = R^2 = H decreased from 38% to 13%. The major diene product had the 1-*cis*, 3-*trans*- stereochemistry. Conversion to the more stable 1-*trans*, 3-*trans*-derivative (85:15 equilibrium mixture) was observed by refluxing ***23*** in xylene with 0.4 M

Table 4. Conversion of Trichloroacetimidic Esters to *N*-Acyl-1-amino-1,3-Butadienes.



21 *22* *23*

R	R^1	R^2	% *22*	% *23*
H	H	H	85	38
H	Me	H	86	51
H	Et	H	84	66
H	*t*-Bu	*t*-Bu	81	92
H	Ph	Ph	60	55
H	Ph	*t*-Bu	88	68
H	Me	Pr	80	86
H	Me	Ph	60	80
$CH_2CH_2CH_2CH_2CH_2$-		H	38	83

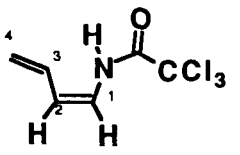
triethylamine. When R^2 in ***23*** was allyl, however, the 1-*cis*, 3-*trans*-product was not isomerized. Several representative examples for the preparation of derivatives of ***23*** are shown in Table 4.[23b]

As in Oppolzer's work, the ^1H and ^{13}C NMR spectra for the dienyl moiety were

diagnostic for identification of the *cis*- or *trans*-isomer. The chemical shifts for C_1, C_2 and C_3 in the ^{13}C NMR showed an upfield shift for the *cis*-isomer relative to the *trans*-.[23b] A comparison of the proton and carbon NMR spectra for ***24*** and ***25*** in Table 5 illustrates these differences.[23b]

Clearly, C_1 for the *cis*-derivative is shifted upfield by 3.9 ppm, C_2 by 3.2 ppm and C_3 by 5.3 ppm relative to the *trans*-derivative. In the ^1H NMR, the C_1 hydrogen for ***24*** is 0.27 ppm upfield of that hydrogen in ***25***. The C_2 hydrogen in ***24*** is also shifted upfield by 0.4 ppm. The C_3 hydrogen is shifted downfield in ***24*** relative to ***25,***

Table 5. NMR Chemical Shifts of *24* and *25*.



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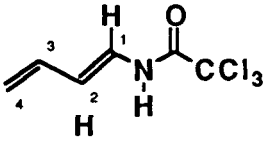

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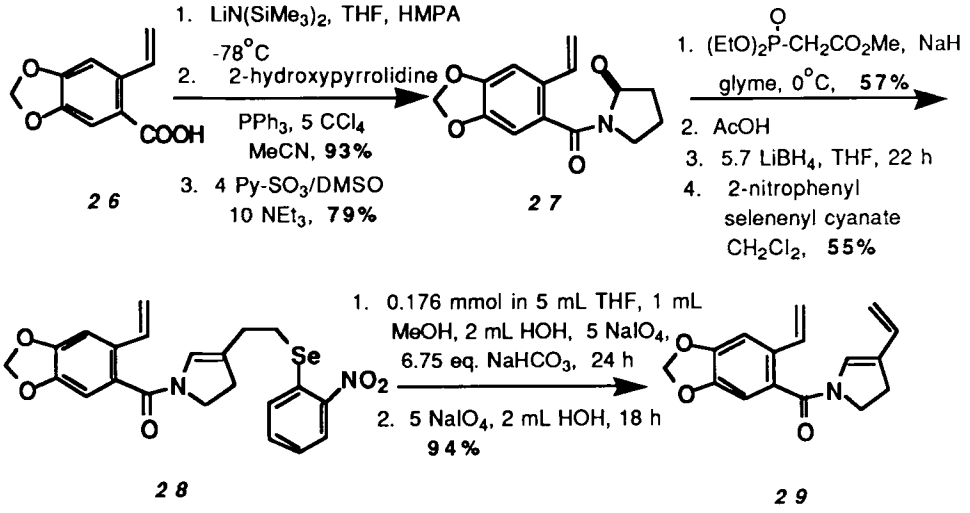
Nuclei	Carbon	*24* (ppm)	*25* (ppm)
^1H	C_1H	6.60 (t, J = 9.5 Hz)	6.87 (dd, J = 10.8,13.7 Hz)
	C_2H	5.70 (dd, J = 10,10 Hz)	6.10 (dd, J = 13.7,10.8 Hz)
	C_3H	6.43 (ddd, J = 16.5,10,10 Hz)	6.34 (d of t, J = 10.8,16.9,10.4 Hz)
	cis-C_4H	5.38 (d, J = 16.5 Hz)	5.22 (d, J = 16.9 Hz)
	trans-C_4H	5.28 (d, J = 10 Hz)	5.12 (d, J = 10.4 Hz)
	NH	8.5 (br s)	8.2 (br s)
^{13}C	C_1	120.5	124.4
	C_2	115.4	118.6
	C_3	128.1	133.4
	C_4	119.6	117.6
	C=O	158.8	159.1
	CCl_3	92.2	92.0

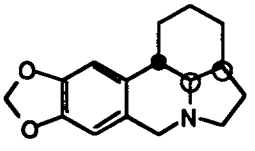
however, by 0.09 ppm and both the *cis*-C_4 and *trans*-C_4 hydrogens in ***24*** are shifted downfield by 0.16 ppm. The coupling constants also vary with the geometry of the diene. In ***24***, $J_{1,2}$ and $J_{2,3}$ are 10 Hz, $J_{3\text{-}cis4}$ = 16.5 and $J_{3\text{-}trans4}$ is 10 Hz. In ***25***, $J_{1,2}$ = 13.7 Hz, $J_{2,3}$ = 10.8, $J_{3\text{-}cis4}$ = 16.9 and $J_{3\text{-}trans4}$ = 10.4 Hz. The major

point of difference is $J_{1,2}$, which is larger for the *trans*-isomer. In addition to the NMR data, the infrared shows the NH absorption at 3367 and 3430 cm^{-1} for ***24*** and ***25***, respectively. The carbonyl signals are at 1736 and 1731 cm^{-1}, respectively.

Dienyl amide methodology was used by Stork for the synthesis of lycorine alkaloids. Stork's synthetic route to α-lycorane (***30***) proceeded via alkenyl amide ***28***. The synthetic precursor was acid ***26***, prepared from the corresponding lactone, ***31***.[25]



Lactone ***31*** was converted to acid ***26*** in 95% yield and amidation (93%) was followed by oxidation to ***27*** in 79% yield.[25] Horner-Emmons olefination (57%) followed by reduction and selenation gave ***28*** in 55%. The oxidation-elimination sequence for the selenide required exacting conditions, as shown, to give ***29*** in 94%.[25]



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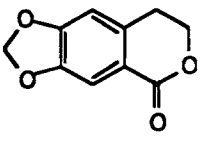

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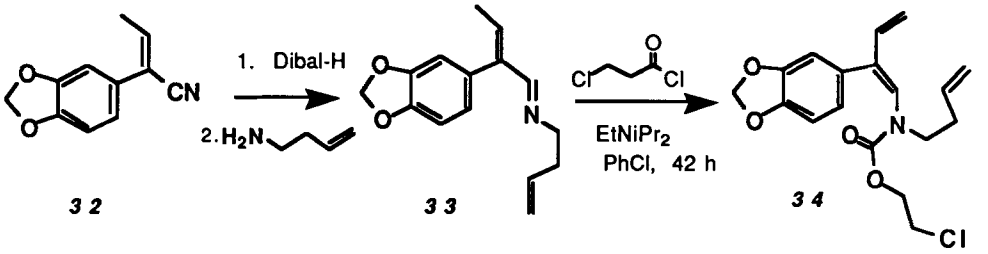
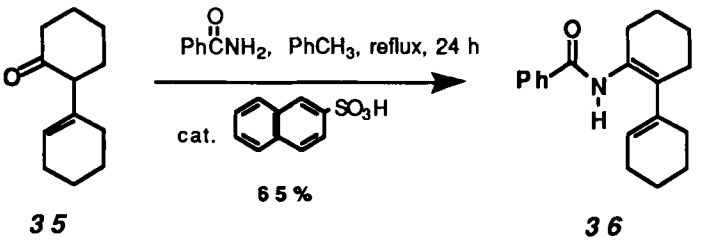
Magnus used Oppolzer's methodology for a synthesis of 1,12-didehydrolycorane, generating the aldehyde by reduction of a nitrile.[26] Nitrile ***32*** was prepared (46%) from piperonyl acetonitrile and acetaldehyde. Reduction of the nitrile with diisobutylaluminum hydride and condensation with but-3-enyl amine gave ***33***. The trienyl carbamate (***34***) was generated *in situ* by addition of chloro 2-chloroethylformate and Hünig's base (diisopropylethylamine) in chlorobenzene for 42 hours. Heating to 140°C for seven hours gave the internal Diels-Alder cyclization (see section 3a).

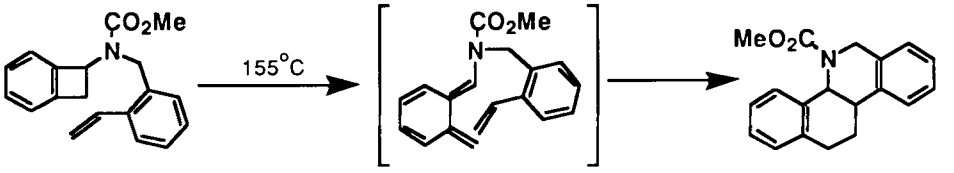


An alternative route to dienyl amides is similar to Oppolzer's imine methodology but involved reaction of alkenyl ketones with aryl amides. Couture showed that reaction of benzamide with β,γ-enones, in the presence of acid, gave the *N*-acyl-amino buta-diene.[27] Condensation of (cyclohex-1-enyl)-cyclohexan-2-one (***35***) and benzamide, for example, gave ***36*** in 65% yield.



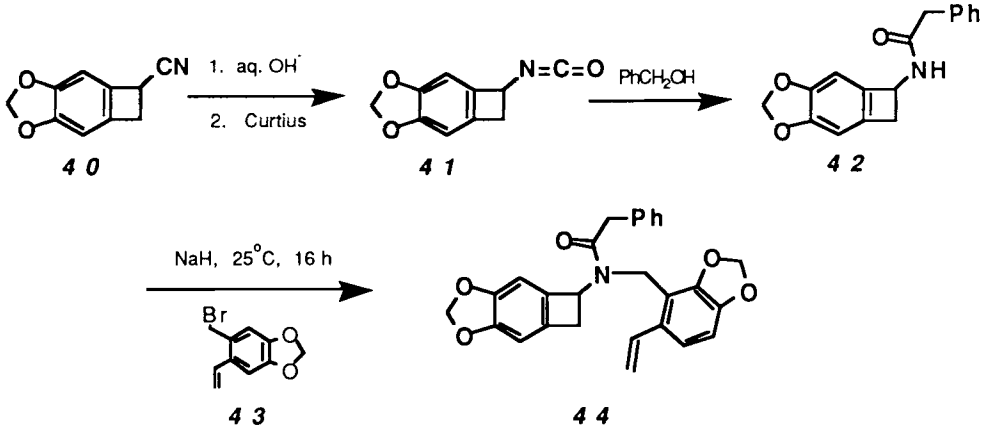
A completely different approach to 1-aminobutadiene derivatives involved generation of a transitory acyl 1-aminobutadiene derivative. Oppolzer showed that therm-

olysis (155°C) of *N*-(1-benzocyclobutenyl)-acyl urethanes such as ***37*** generated ***38***, *in situ*. This diene could not be isolated but spontaneously gave the Diels-Alder cyclization product (***39***, see Section 3a).[28,29] The requisite urethane was prepared from the cyanide, as in the conversion of ***40*** to ***42***.[28] The sequence began with hydrolysis to the amide and Curtius degradation to isocyanate ***41***. Reaction with benzyl alcohol gave urethane ***42*** in 47% overall yield. Condensation of ***42*** and



37 ***38*** ***39***

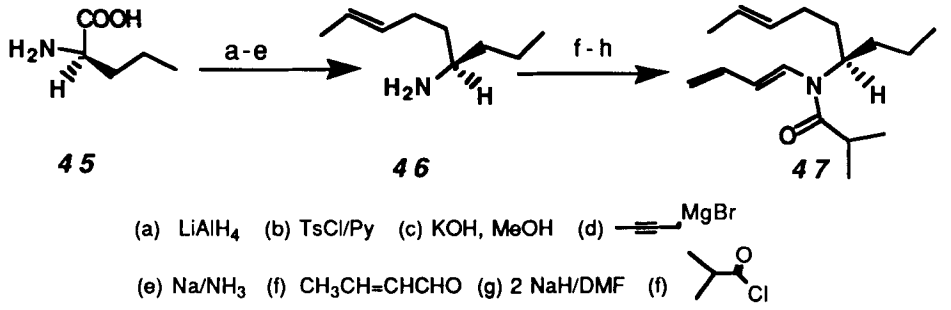
43 with sodium hydride in DMF gave the requisite alkenyl urethane derivative (***44***) in 77% yield, which was converted to *dl*-chelidonine (see section 3a).[28]



40 ***41*** ***42***

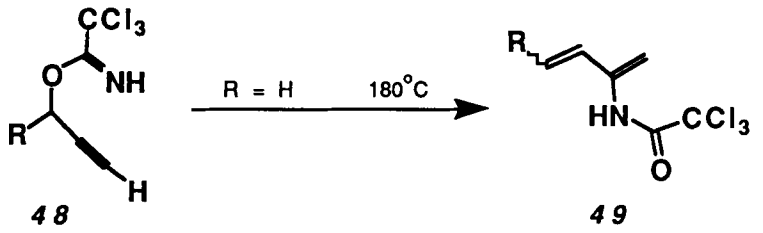
43 ***44***

This methodology has been expanded to include an asymmetric derivative. Oppolzer prepared a chiral acyl-1-amino-1,3-butadiene in connection with an asymmetric synthesis of (-)-pumiliotoxin C from ***47***.[30] The appropriate triene (***47***) was prepared from *R*-norvaline (***45***) in an eight step synthesis via ***46***.

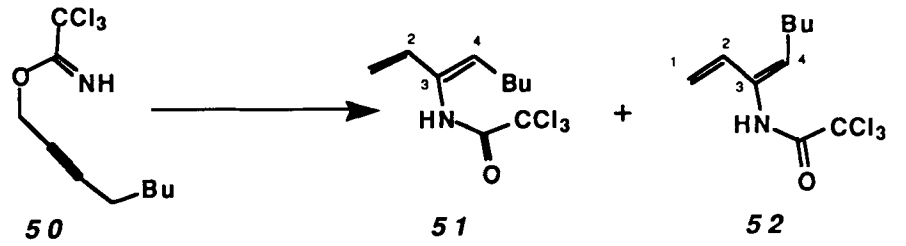


1b. Preparation of *N*-Acyl-2-Amino-1,3-Butadienes.

There are fewer examples of the 2-aminobutadienes (***7***), probably due to the greater difficulty in their synthesis. Overman's [3,3]-sigmatropic rearrangement of trichloroacetimidates[23] appears to be the most general route to the 2-amido butadienes. This is the same method used to prepare the 1-amidobutadienes but 2-amido-butadienes can be prepared only in cases where formation of a 1-(trichloroacetamido-1,3-diene) is not possible. Therefore, formation of the 2-substituted diene demands



that R in ***48*** be H and not alkyl. Thermolysis of ***48*** (0.008 M in refluxing *o*-dichlorobenzene) afforded ***49*** in only 14% yield.[23] The low yield is a reflection of the vulnerability of ***49*** to further reaction at 180°C. The more highly substituted derivative ***50*** proved to be more stable and similar thermolysis gave a 3:1 mixture of ***51*** and ***52*** in 74% yield. The *cis*- and *trans*-dienes were separable by HPLC. Diene ***52*** was prepared in good yield by thermal equilibration with ***51*** at 110°C, in the presence of triethylamine.



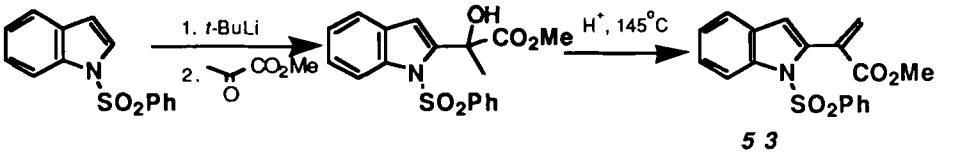
50 *51* *52*

Identification of the *cis*- and *trans*-isomers was straightforward by ^{1}H and ^{13}C NMR. As shown in Table 6,[23] C_2 and C_4 of diene ***52*** (129.0, 129.3 ppm) were upfield of C_2 and C_4 in ***51*** (133.5, 134.3 ppm), "consistent with the *cis*-relationship for the vinyl and butyl groups in this isomer".[23,31] "The ^{1}H NMR also shows long range coupling (J = 1.7 Hz) for the C_1 and C_4 vinyl hydrogens of ***52***".[23]

Table 6. Spectral Data for 2-Acylamido Butadienes.

Spectrum	Signal	***51*** (ppm)	***52*** (ppm)
^{1}H NMR	*cis*-C_1H	5.14 (d, J = 16.7 Hz)	5.24 (d, J = 10.6 Hz)
	trans-C_1H	5.03 (d, J = 10.4 Hz)	5.18 (dd, J = 16.8,1.7 Hz)
	C_2H	6.27 (dd, J = 16.7,10.5 Hz)	6.57 (dd, J = 16.8,10.6 Hz)
	C_4H	5.60 (t, J = 7.4 Hz)	6.09 (br t, J = 7.8 Hz)
^{13}C NMR	C_1	112.5	113.7
	C_2	133.5 or 134.3	129.0 or 129.3
	C_3	131.0	129.7
	C_4	133.5 or 134.3	129.0 or 129.3
	C=O	160.0	160.2
IR	NH	3360 cm^{-1}	3358 cm^{-1}
	C=O	1730 cm^{-1}	1730 cm^{-1}

Only one other 2-amido diene could be found in this class. The related 2-substituted dienyl amide, *N*-sulfonyl indole-2-acrylate ester (***53***), was prepared by

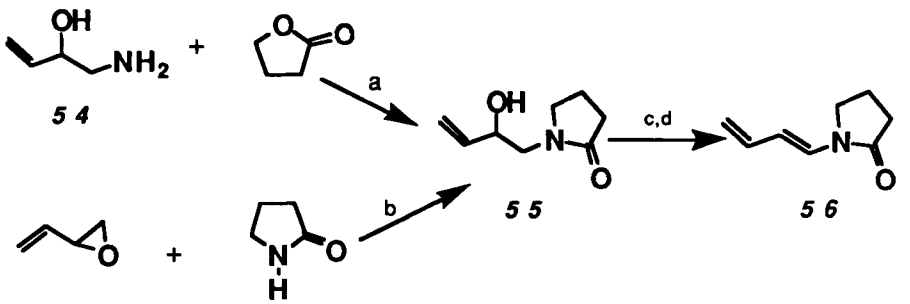


53

Sundberg.[32] Its synthesis involved generation of 2-lithio indole and condensation with ethyl pyruvate. The resulting alcohol was melted with 4 mol% of tosic acid to give ***53*** in 84% yield.

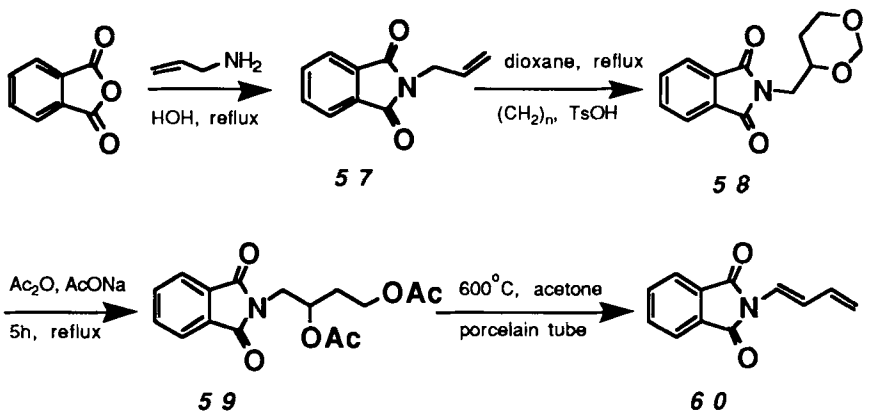
1c. *N*-Dienyl Lactams and *N*-Dienyl Imides

Although dienyl amides have been greatly exploited in synthesis, the corresponding dienyl lactams have been largely ignored. None of the methods shown previously are readily amenable to similar reaction with lactams. The first report of this class of diene was by Murata and Terada, who showed that 1-amino-3-buten-2-ol (***54***) reacted at 180° (sealed tube) with γ-butyrolactone to give the *N*-substituted lactam ***55*** in 59% yield.[33] An improved yield of 65% was realized by condensation of γ–butyrolactone with 1,2-epoxy-3-butene at 150° in a sealed tube with a few



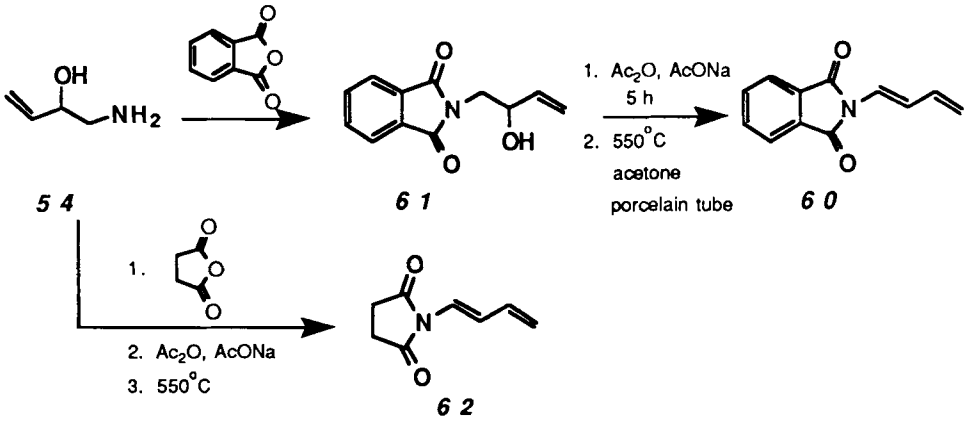
(a) 180°C/sealed tube/24 h (b) 30% KOH/sealed tube/150°C/24 h
(c) Ac_2O/NaOAc/100°C/20 h (d) 550°C

drops of 30% KOH. The alcohol from these reactions was acetylated with acetic anhydride (sodium acetate, 20 hr, water bath, 58%). The *N*-(1,3-butadienyl)-2-pyrrolidinone product (***56***) was formed in 29% yield when an acetone solution of the acetate was dropped through a porcelain tube at 550°C (over 1.5 hour with nitrogen). The overall yield of this process was 11% from γ–butyrolactone. The difficulty of the procedure and its low yield precluded significant development of other derivatives of ***56***.



57 *58* *59* *60*

A slightly different synthetic route was required when imides were substituted for lactams in the preparation of imido-1,3-butadiene derivatives.[34] 1-Phthalimido-1,3-butadiene (***60***)[35] was prepared by reaction of phthalic anhydride with allyl amine to give ***57*** in 96% yield. Reaction with paraformaldehyde in the presence of tosic acid gave dioxane ***58*** in 22%. Acetylation with acetic anhydride gave 1-phthalimido-2,3-diacetoxy butane (***59***) in 22% and pyrolysis at 600°C through a porcelain tube

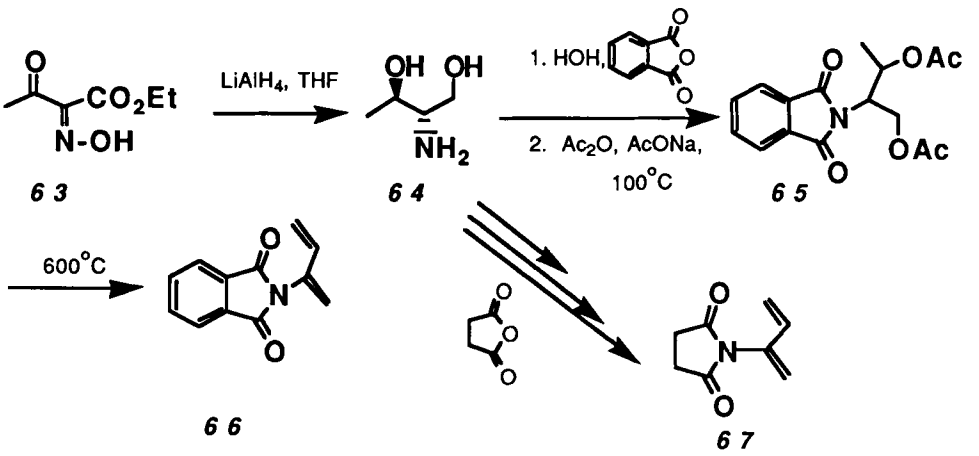


54 *61* *60* *62*

gave ***60*** in 28% yield (1.3% from allyl amine).[35a] This method was improved by reacting ***54*** with phthalic anhydride to give ***61*** in 78% yield.[35b] Acetylation of the allylic alcohol was nearly quantitative and pyrolysis at 550°C gave ***60*** in 64% yield (overall yield was about 50%).[35b] The use of succinimide rather than phthalimide

in the latter sequence produced ***62*** in an overall yield of 22% (the acetate pyrolysis gave 29% of ***62***)[35b]

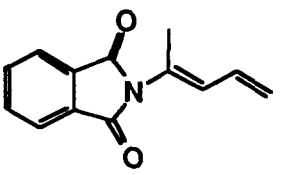
The sequence was again modified for preparation of the 2-imido derivatives, 2-phthalimido-1,3-butadiene (***66***) and 2-succinimido-1,3-butadiene (***67***). *dl-Erythro*-2-amino 1,3-butadiene (***64***) was prepared by lithium aluminum hydride reduction of ethyl 2-oximino-3-oxo-butanoate (***63***, 43%) and condensation with phthalic anhydride gave 2-phthalimido-1,3-butanediol. The crude diol was acetylated to give ***65*** in 63% overall yield. Pyrolysis at 600°C in a porcelain tube gave ***66*** in 28% yield (18% from the amino diol).[36] Diene ***67*** was prepared in a similar manner by using succinimide in place of phthalimide in this sequence[36] Both 1-phthalimido-2-methyl-1,3-butadiene (***68***)[37] and 1-succinimido-2-methyl-1,3-butadiene (***69***.)[38] were prepared. Although this methodology was used for several types of dienyl



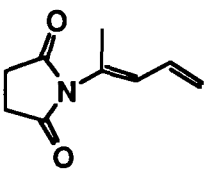
63 ***64*** ***65*** ***66*** ***67***

lactams and imides, the yields were low. Expansion of the method for the synthesis of other derivatives was limited by availability of the appropriate amino alcohol, alkenyl oxirane or halo-alkenol.

An alternative and more direct preparation of *N*-dienyl lactams was reported by Heck[39] in which *N*-vinyl-2-pyrrolidinone (***70***) reacted with *trans*-2-bromostyrene (***71***) in the presence of a palladium catalyst to give ***72*** in 25% yield. The catalyst

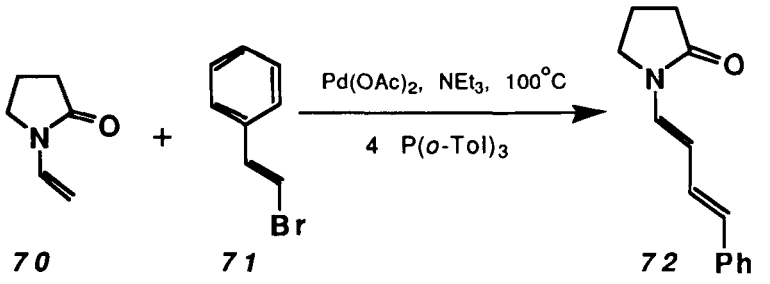


68



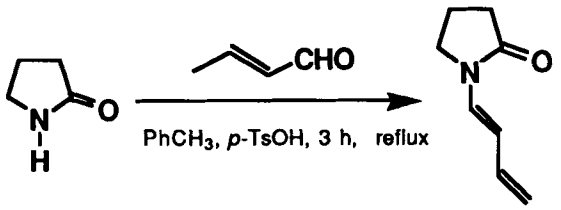
69

was palladium acetate with the ligand tri-*o*-tolyl phosphine. Reaction with triethylamine at 100°C for four days gave ***72***, exclusively as the terminal methylene adduct. This method has not been expanded to other derivatives and does not appear to be general in scope.



70 *71* *72*

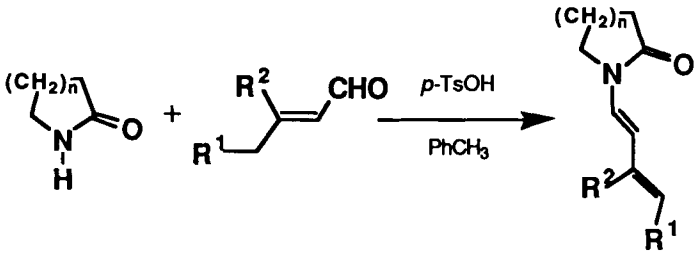
While exploring the preparation of *N*-alkenyl lactams from condensation of aldehydes and lactams[40], based on modification of previous work which reacted acetaldehyde[41] and 2-pyrrolidinone, we found that reaction of crotonaldehyde with 2-pyrrolidinone in refluxing toluene (catalytic *p*-TsOH) gave ***56*** in 41%. The water formed during the reaction was collected in a Dean-Stark trap via azeotropic distillation with benzene or toluene. The reaction was facile and reaction of several lactams with a variety of α,β-unsaturated aldehydes gave the corresponding dienyl lactam in yields ranging from poor to good (see Table 7).[42] The lower yields were obtained when volatile aldehydes with a propensity for polymerization were used in the reaction. The boiling point of crotonaldehyde for example is 104°C, requiring benzene rather than toluene as a solvent. The longer reaction times required with benzene lead to greater polymerization. We observed that as the boiling point of the aldehyde increased (accompanied by substitution at the terminal carbon of the



56

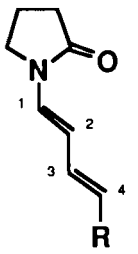
conjugated system) the yields improved. 3-Methyl-2-butenal, for example, gave 66% of the corresponding diene and 2-octenal gave 56% of *N*-octadienyl 2-pyrrolidinone. When R^1 of the aldehyde was hydrogen (Table 7) the diene generated was the *trans*-isomer, as confirmed by ^1H and ^{13}C NMR. When R^1 was methyl or butyl, however, there was an 81:19 and 75:25 mixture of *trans-trans:trans-cis* isomers, respectively. The double bond conjugated to nitrogen was *trans*, by analogy with ***56*** as shown in Table 7.

Table 7. Preparation of *N*-Dienyl Lactams from Lactams and Aldehydes.



n	R^1	R^2	% Diene
1	H	H	41
	H	Me	66
	Me	H	48
	n-Bu	H	56
2	H	H	34
	H	Me	39
3	H	H	20
	H	Me	46

Table 8. NMR Chemical Shifts of *N*-Dienyl 2-Pyrrolidinones.



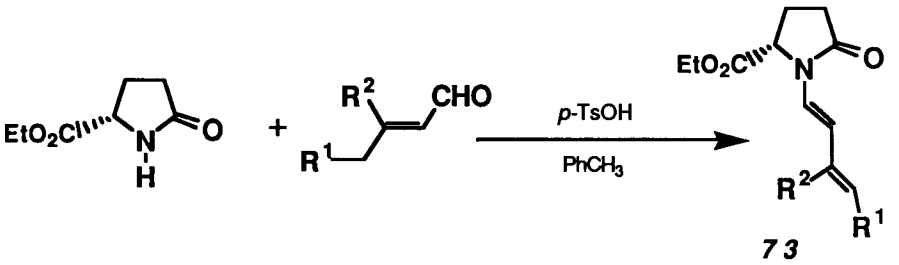
R	Nuclei	Signal	Chemical Shift (ppm)
H	^1H	C_1H	7.03 (d, J = 14.3 Hz)
		C_2H	5.60 (dd, J = 14.2,14.1 Hz)
		C_3H	6.23-6.37 (m, J = 10.4,16.9 Hz)
		cis-C_4H	5.08 (d, J = 16.9 Hz)
		trans-C_4H	4.93 (d, 10.3 Hz)
	^{13}C	C=O	171.7
		C_1	125.5
		C_2	111.2
		C_3	133.8
		C_4	112.7
n-Bu (*E,E*)	^{13}C	C=O	172.6
		C_1	127.7
		C_2	112.6
		C_3	132.6
		C_4	124.2
n-Bu (*E,Z*)	^{13}C	C=O	172.8
		C_1	126.0
		C_2	107.9
		C_3	130.0
		C_4	126.0

As shown in Table 8, C_3 of ***56*** appears at 133.8 ppm and the butyl derivative (entry 4 in Table 7) at 133 ppm.[42] This is similar to and consistent with the 134-135 ppm chemical shift of C_3 for the dienyl carbamates in Table 3 with the *trans*-regio-chemistry. The spectroscopic properties of the dienyl lactams were essentially the same as the dienyl amides. The proton NMR data can, therefore, be compared directly with that of the dienyl amides and carbamates in Table 4. The *trans*-dienyl carbamate derivative (***22***) showed a signal at 6.87 ppm for the C_1 hydrogen and the

cis-derivative ***21*** showed that signal at 6.60 ppm. The 7.03 ppm chemical shift for C_1 of ***56*** is clearly analogous to ***22*** and all dienyl protons are consistent with this assignment. The dienyl hydrogen coupling constants for ***54*** (10.3, 14.3 and 16.9 Hz) are also similar to those in ***22***.

We have recently reported the only preparation of an optically active dienyl lactam (***73***) by reaction of *S*-ethyl pyroglutamate with α,β-unsaturated aldehydes.[43] We made use of the chiral lactam, S-ethyl pyroglutamate (S-5-carboethoxy-2-pyrrolidinone) in the diene forming reaction. Pyroglutamate proved to be less reactive, requiring longer reaction times and more vigorous conditions (refluxing toluene). The longer reaction times and reduced reactivity led to very poor yields with crotonaldehyde but several chiral dienes could be prepared from other aldehydes in reasonable yields. Pyroglutamate was prepared from the *L*-glutamic acid

Table 9. Preparation of Chiral Dienyl Lactams from Pyroglutamate



73

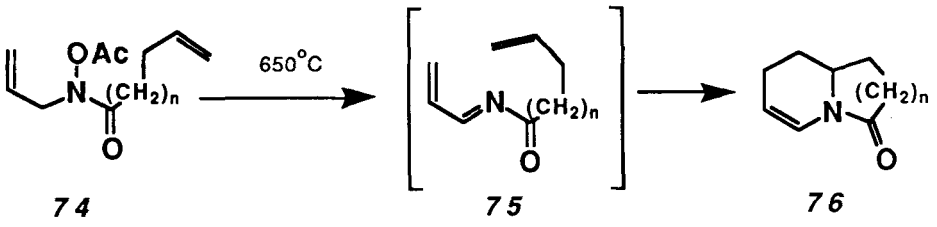
R^1	R^2	% ***73***
H	H	39
H	Me	42
Et	H	72

by the method of Silverman.[44] The several chiral dienyl lactams prepared by this method are shown in Table 9. An alternative synthesis reacted ethyl pyroglutamate with 4-bromobutanal to give the *N*-(4-bromo-2-butenyl) lactam. Subsequent reaction with DBU gave the *N*-butadienyl derivative in 56% overall yield. This is a useful alternative for the poor yields observed by direct condensation with croton-

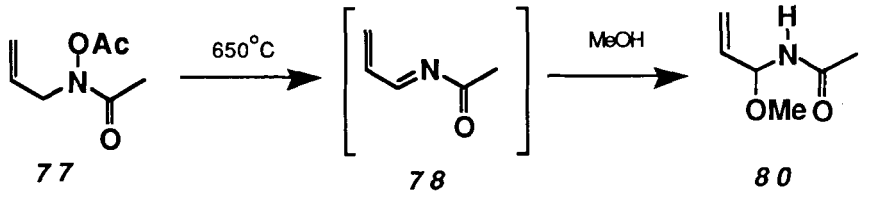
aldehyde.

1d. *N*-Acyl-1-Azadienes

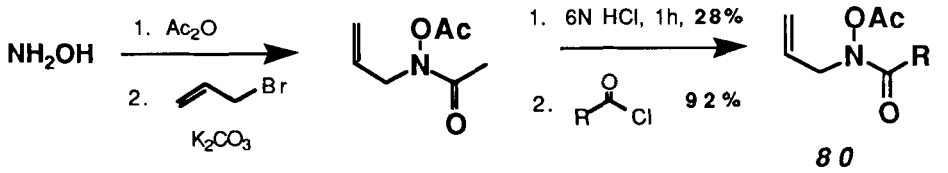
1-Azadienes are distinctly different species from dienyl amides but the *N*-acyl derivatives are rather close analogs and are included here. A straightforward, albeit transient, preparation was reported by Fowler in which thermolysis (650°C) of *N*-acyl-O-acetyl-*N*-allylic hydroxylamines (***74***) produced the corresponding *N*-acyl-1-aza-diene (***75***) *in situ*.[45] Under thermolysis conditions ***75*** could not be isolated but spontaneously gave an intramolecular Diels-Alder reaction, leading to ***76*** (see section 3c). In no instance was the azadiene (***75***) isolated or observed although



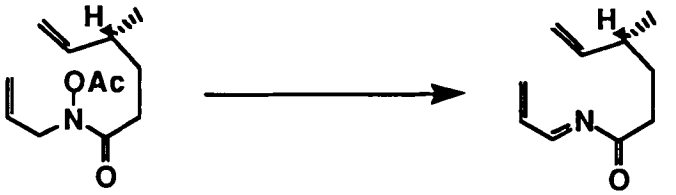
pyrolysis of ***77*** generated acyl azadiene (***78***), which was trapped by addition of methanol to give ***79***. *N*-Acyl derivatives such as ***74*** were prepared by acylation of



hydroxylamine with acetic anhydride, followed by reaction with allyl bromide and potassium carbonate.[45] Acid hydrolysis and trapping with an acid chloride gave the desired acetoxy derivative, ***80***.

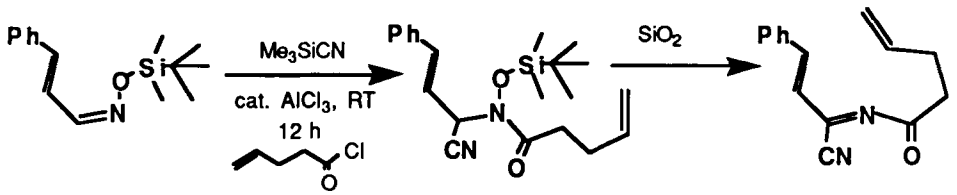


The chiral *N*-acyl-1-azadiene ***82***, formed by pyrolysis of ***81***, was initially reported in the review of Fallis,[46] as a private communication from the author, with no details. Fowler has now described the preparation of ***82***, which was used in a synthesis of (-)-deoxynupharidine.[47] Acyl amide ***81*** was prepared from the chiral precursor dihydro-myrcene via the acid chloride[48] and condensed with *N*-methallyl-O-acetyl-hydroxyl-amine.[47]



81 ***82***

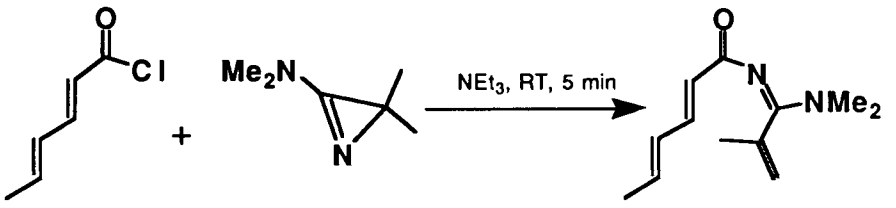
Fowler also reacted the O-dimethyl-*t*-butylsilyl imine (***83***) with 4-pentenoyl chloride to give ***84***, but chromatography on silica gel induced elimination. The resulting *N*-acyl-α-cyano-1-azadiene (***85***)[49] was quite stable and could be isolated and purified. It gave small amounts of the internal Diels-Alder cyclization product as a contaminating by-product.



83 ***84*** ***85***

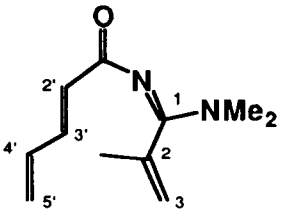
Acyl azadienes are generally unstable to isolation, as described above. Incorporation of heteroatom substituents, however, can stabilize this functional group. In a synthesis of tetrahydro-1-(1H)-isoindolones, Heimgartner prepared a stable 2-amino-*N*-acyl-1-azadiene derivative (***88***) by condensation of the acid chloride of dienoic acid (***86***) with 3-dimethylamino-2,2-dimethyl 2H-azirene ***87***.[50] Azadiene ***88*** was isolated in 77% yield. The proton NMR (see ***89***) revealed the expected dienyl amide signals and the C_3 hydrogens of the azadiene moiety absorbed at

4.82 and 5.02 ppm.[50] The carbon NMR data was not reported. The infrared showed the acyl amidine C=C moiety at 1615, the conjugated amidine at 1545, the



86 **87** **88**

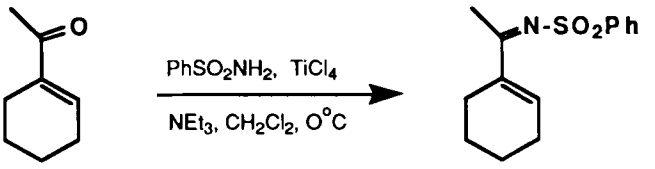
trans-conjugated alkenyl moiety at 1009 and the terminal vinyl group at 912 cm^{-1}.



89

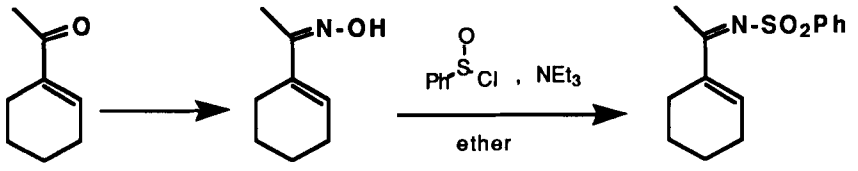
C_3H, 7.02 ppm (dd, $J_{2'3'}$ = 15.0, $J_{3'4'}$ = 10.6 Hz)
C_4H, 6.40 ppm (dt, $J_{4'5'}$ = 11.4 (*trans*), J4'5' = 10.6 (*cis*), $J_{4'3'}$ = 10.6 Hz)
C_2H, 5.91 ppm (d, $J_{2'3'}$ = 15.0 Hz)
trans-C_5H, 5.42 ppm (d, $J_{5'4'}$ = 16.4 Hz)
cis-C_5H, 5.27 ppm (d, $J_{5'4'}$ = 10.2 Hz)
C_3H, 5.02 and 4.82 ppm (m)

Boger developed a *N*-sulfonyl-1-aza-1,3-butadiene derivative which was stabilized by the electron withdrawing benzenesulfonyl group.[51] Reaction of 1-acetyl-1-cyclo-hexene (***90***) with benzenesulfonamide, in the presence of $TiCl_4$, gave the *N*-benzene-sulfonyl-1-azadiene derivative, ***91***.[52]



90 **91**

An alternative preparation converted ***90*** to its oxime (***92***) and reaction with phenyl sulfinyl chloride[53] at ambient temperatures (via homolytic rearrangement of the inter-mediate O-phenyl sulfinyl oxime) gave ***91***.



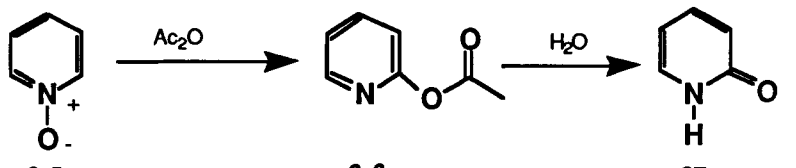
90 ***92*** ***91***

1e. 2(1H)-Pyridones

2-(1H)-Pyridones (***93***) are an unusual class of dienyl lactams which can be viewed as tautomeric forms of 2-hydroxypyridinium salts. They are, however, well-known compounds and give Diels-Alder reactions similar to other dienyl lactams. The most common method for the preparation of 2-(1H)-pyridones (***93***) is by oxidation of pyridinium derivatives such as ***94***. Many oxidizing conditions have been reported and several useful reagents are shown in Table 10. In many cases

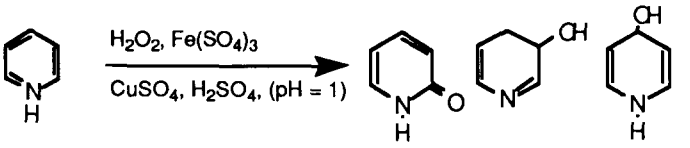
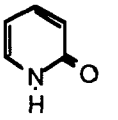
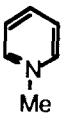
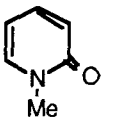
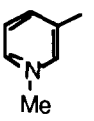
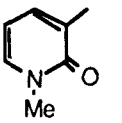
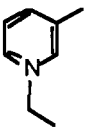
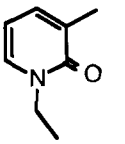
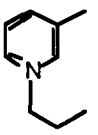
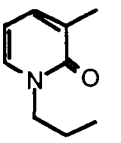
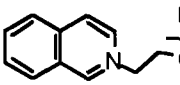
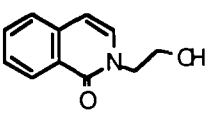
93 ***94***

the yields are rather poor and potassium ferricyanide appears to be the superior reagent, giving moderate to good yields in many cases (entries c,h,i,j,k in Table 10).



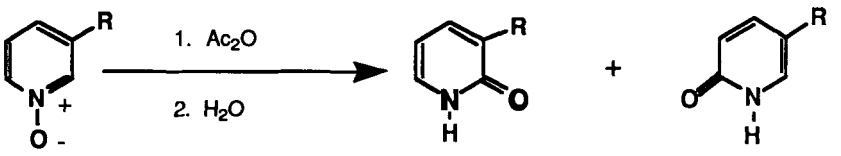
95 ***96*** ***97*** R = H

Table 10. Oxidation of Pyridine Derivatives to 2 (1H)-Pyridones.

Entry	Pyridinium	Oxidant	Pyridone	%
a		H_2O_2, $Fe(SO_4)_3$; $CuSO_4$, H_2SO_4, (pH = 1)	16 : 70 : 14	5[56]
b		$CuSO_4$, 180-250°C		30[54]
c		$K_3Fe(CN)_6^{-3}$, NaOH		49[54]
d		AgO		7[55]
e				0[54]
f		H_2O_2		18[54]
g		$KMnO_4$		20[54]
h		$K_3Fe(CN)_6^{-3}$, NaOH		70[54]
i		$K_3Fe(CN)_6^{-3}$, NaOH		45[55]
j		$K_3Fe(CN)_6^{-3}$, NaOH		52[59]
k		$K_3Fe(CN)_6^{-3}$, NaOH		64[56]

Oxidation of *N*–methyl-pyridinium iodide to 2-(1H)-pyridone ***93*** (R = Me), for example, proceeds in 49% yield with potassium ferricyanide ($Fe[CN]_6^-$).[57] Oxidation with silver oxide was reported by Tschitschibabin in 1921, but this reagent gave very poor yields.[58] Fenton's reagent (Fe^{+2}, H_2O_2) gave poor yields and also mixures of isomeric pyridones.[59]

An alternative synthetic route to pyridones involves reaction of pyridine *N*-oxides (***95***) with acetic anhydride to give 2-acetoxy pyridine ***96***. This is a well-known reaction and an early example of "heteroaromatic *N*-oxide rearrangements with acetyl-ating reagents".[60] Rearrangement of ***96*** to the pyridone (***97***) is facile in water and reactions of pyridine *N*-oxides have become an important synthetic source of 2-pyridones. When the pyridinium salt is unsymmetrical, as in ***98***, mixures of the 2-alkyl (***99***) and 5-alkyl (***100***) pyridones result.[61] When R is methyl, equal amounts of ***99*** and ***100*** are formed.[61] When R is an electron withdrawing substituent, however, ***99*** is the major isomer (R = CO_2H[61a], CO_2Me[62], halogen,[63] nitro[64]). The rate determining step is nucleophilic attack of the acetate at C_2 or C_6 in ***95*** or ***98***. Heating ***95*** with $(ClCH_2CH_2O)_2C{=}O$ (chloroethyl pyrocarbonate) at 60-70°C also gave ***93*** directly, in 50% yield.[65] Yields of the pyridone are greatly improved by a modification of this reaction which heated the antimony chloride salt of a pyridine *N*-oxide (***101***), inducing rearrangement to ***102***. Hydrolysis gave the pyridone, as shown in Table 11[66]

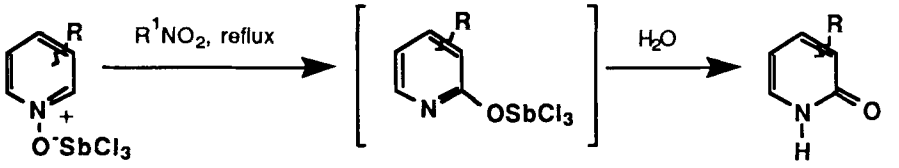


98 ***99*** ***100***

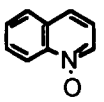
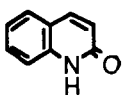
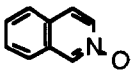
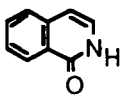
A number of related rearrangement or hydrolysis processes are known with 2-substituted pyridinium salts when the substituent is an alkoxy or ammonium moiety. 2-Ethoxy-pyridine, for example, was pyrolyzed at 400°C to give ***93*** and ethylene.[67]

2-Benzyloxypyridine reacts with ethanolic sodium ethoxide and Pd/C to give ***93*** and benzyl alcohol.[68] Katrikzky also showed that pyridinium salts such as ***103*** rearrange to ***104*** on treatment with dilute sodium hydroxide at ambient temperature. Heating to reflux liberated 5-chloro-2-pyridone (***105***) in 58%,[69] via saponification of the amide moiety. 2-Chloropyridines are rather labile and subject to nucleophilic displacement by hydroxide. Heating ***106*** with 50% sodium hydroxide at 130°C in

Table 11. Thermal Rearrangement of Antimony Salts of Pyridine *N*-Oxides.



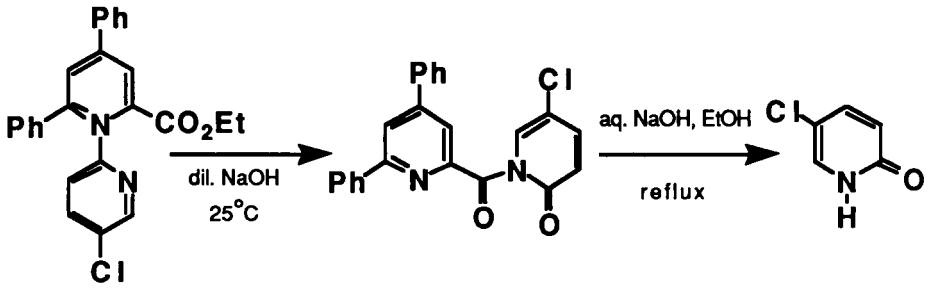
101 ***102***

R	R^1	Reaction Conditions	% Pyridone
H	Me	reflux, 5 h	81
	Ph	90°, 5h	40
2-Me	Me	reflux, 5 h	44
		reflux, 10 h	70
3-Me	Ph	180°C, 2 h	30
		reflux, 10 h	81
4-Me	Me	reflux, 6 h	78
4-NO_2	Me	reflux, 3 h	60
		reflux, 10 h	86
	Me	reflux, 10 h	 72
	Me	reflux, 10 h	 94

the presence of a phase transfer agent gave ***107*** in 96% yield.[70]

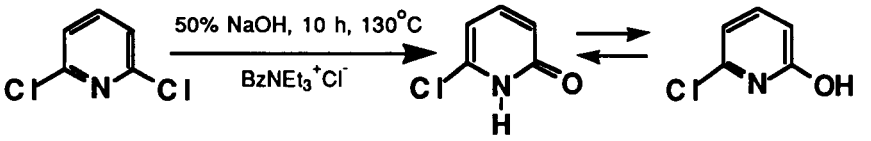
A very common method for the preparation of 2-pyridones involves cyclization of

ketoamides or other keto-acid derivatives. Nucleophilic acyl substitution of the amide



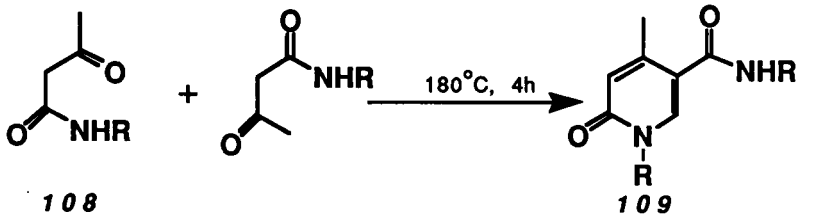
103 ***104*** ***105***

is followed by an intramolecular attack of the second amide moiety and elimination to generate the pyridone. The low nucleophilicity of the amide moiety requires vigorous conditions for reaction to occur. 3-Oxobutanamide (***108***), for example,



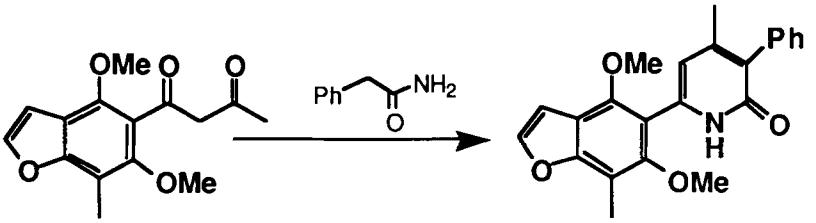
106 ***107***

was heated to 180°C in order to form the corresponding 5-acyl-2-pyridone, ***109***.[71] The difficulty with this reaction is apparent in the 19% yield of resulting product, pyridone ***109*** (R = Me or Et). A similar condensation was reported for the conversion of ***110*** to ***111***.[72] In this case the phenyl group facilitated the second condensation



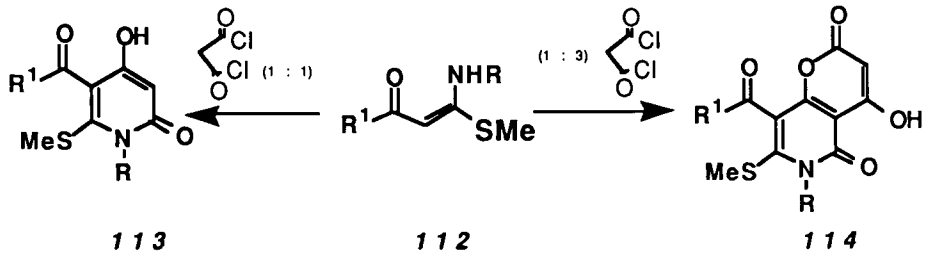
108 ***109***

to complete formation of the ring but no yield was reported.[72] Another variation of this condensation is shown for the conversion of ***112*** to ***113*** in 71-91% yield via condensation with malonyl dichloride.[73] A 1:1 mixture of ***112*** and malonyl dichloride gave ***113*** but a 1:3 reaction mixture led to the 4-pyranopyridone derivative (***114***) in 35-44% yield. The improved yield of pyridone was, in part, a result of the increased reactivity of the acyl chloride derivatives.

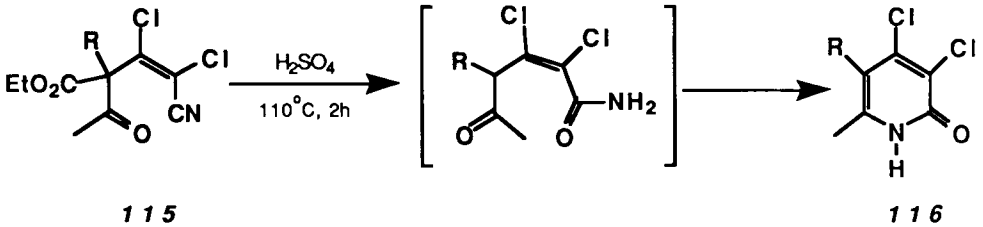


110 ***111***

An acid catalyzed ring closure of cyano-ketone ***115*** was also reported but is related to the previous condensations. Initial hydrolysis leads to decarboxylation and conversion of the nitrile to the amide. The amide undergoes condensation with the ketone (analogous to the preparation of ***109*** and ***111***) to give ***116*** in 94% yield.[74]

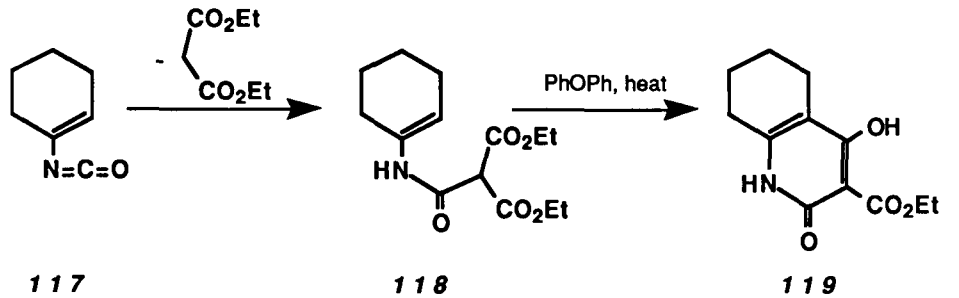


113 ***112*** ***114***

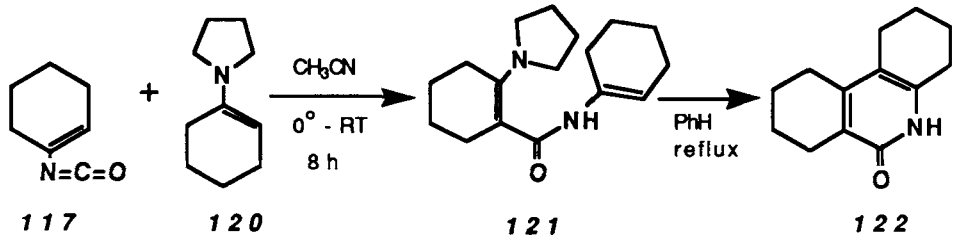


115 ***116***

Rigby has identified two methods for the preparation of 2-pyridones from isocyanates. Reaction of 1-isocyanato-1-cyclohexene (***117***) with the enolate of diethyl malonate gave ***118*** and heating in diphenyl ether gave 72% of 4-hydroxy-2-(1H)-pyridone ***119***.[75] A similar reaction occurred with enamines such as 1-pyrrolidino-1-cyclo-hexene (***120***), which reacted with ***117*** to give ***121***.[76] Heating in refluxing benzene or toluene afforded the pyridone (***122***) in 73%.

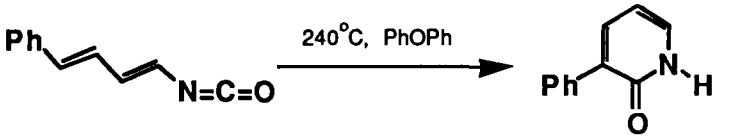


117 ***118*** ***119***



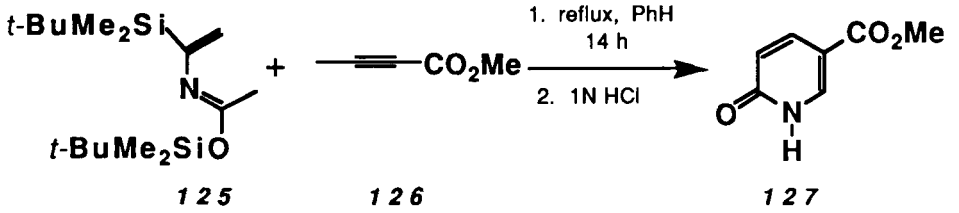
117 ***120*** ***121*** ***122***

An alternative procedure which uses isocyanates involves thermolysis of dienyl isocyanates such as ***123***, generating ***124*** in 66% yield.[77] A Diels-Alder approach was reported by Ghosez in which azadiene derivative ***125*** cyclized in the presence



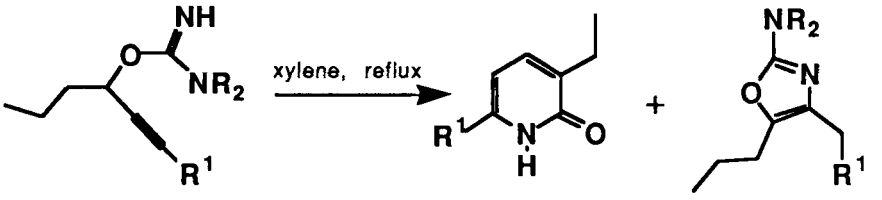
123 ***124***

of methyl propiolate (***126***), to give pyridone ***127***.[78] Rigby also generated pyridones via a 4+2 cycloaddition of benzyne and vinyl isocyanates, as in the reaction of ***117*** with ***128*** (which gives benzyne in the presence of lead tetraacetate) to give ***129*** in 58%.[79]



125 *126* *127*

Table 12. Conversion of Propargylic Pseudoureas to 2-Pyridones.



130 *131* *132*

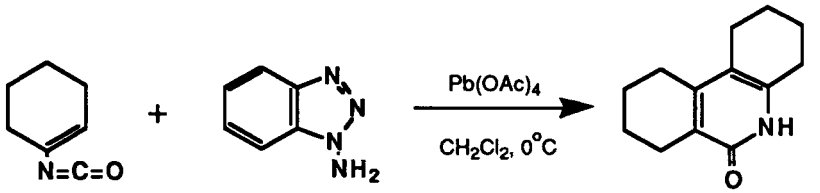
NR_2	R^1	Temp (ºC)/hr	%*131*	%*132*
$N(CH_2)_4$	Ph	140/20	54	38
NMePh	Ph	140/28	69	11
$N(CH_2)_4$	H	140/24	13	31
NMePh	H	140/20	41	27
$N(C_6H_4)_2$*	H	205/36	28	-
$N(CH_2)_4$	2,4-diMeC_6H_3	140/24	14	16
NMePh	"	140/24	46	39
$N(C_6H_4)_2$	"	205/12	-	73

* carbazole

Thermal rearrangement of propargylic pyrrolidine pseudoureas (***130***) also led to good yields of the 2-pyridone (***131***) along with a substituted oxazole (***132***).[80] The product distribution was dependent on the nature of the dialkylamino group, as shown in Table 12.[80a]

The proton and carbon NMR spectral characteristics of 2-pyridones has been

reported,[81,82] and NMR data for representative pyridones is shown in Table 13. The aromatic-like chemical shifts of the protons and carbons is apparent. The

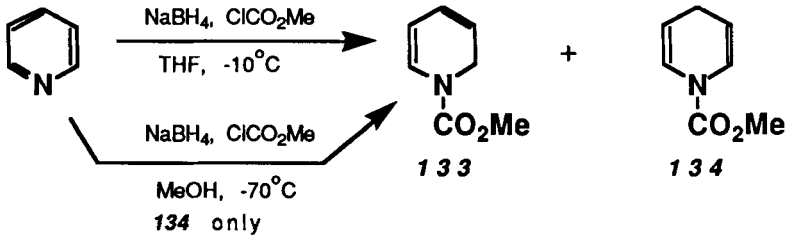


117 *128* *129*

infrared is characterized by strong absorptions at 1680, 1665 and 1650 cm^{-1} for the conjugated lactam moiety.

1f. *N*-Acyl-1,2-Dihydropyridines

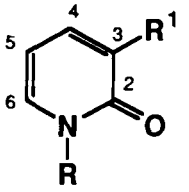
A related and useful class of dienyl lactams are the *N*-acyl 1,2-dihydropyridines. Fowler showed that reduction of pyridine with sodium borohydride, in the presence of methyl chloroformate, led to a mixture of *N*-carbomethoxy-1,2-dihydropyridine (***133***) and *N*-carbomethoxy-1,4-dihydropyridine (***134***).[83] When the reaction is done in THF



133 *134*

at less than 10°C, a mixture of ***133*** and ***134*** is obtained in about a 60:40 ratio. If the reaction is done in methanol at -70°C, however, only 2-4% of ***134*** is obtained and the reaction becomes a preparatively useful route to ***133***.[83] These derivatives are relatively stable, but slowly decompose when exposed to atmospheric oxygen at ambient temperature.

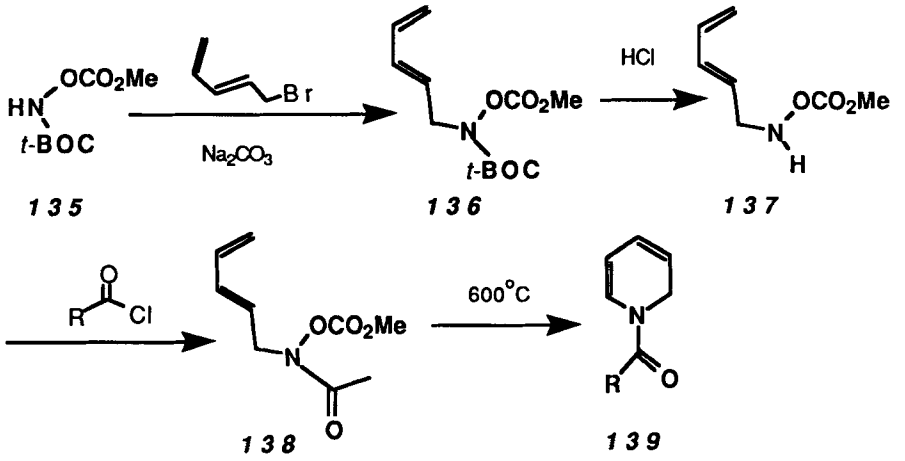
Table 13. NMR Spectral Data for Representative 2-Pyridones.



R	R^1	Nuclei	Signal	Chemical Shift (ppm)
H	H[81]	^1H	NH	12.93
			C_3H	6.60
			C_4H	7.47
			C_5H	6.30
			C_6H	7.43
		^{13}C	C_2	165.40
			C_3	120.33
			C_4	141.54
			C_5	106.85
			C_6	134.35
Et	Me[59]	^1H	$CH_2\mathbf{CH_3}$	1.39 (t, 3H)
			CH_3	2.03 (s, 3H)
			$\mathbf{CH_2}CH_3$	3.89 (q, 2H)
			C_5H	6.06 (t, 1H)
			C_4H	7.15 (m, 1H)
			C_6H	7.36 (m, 1H)
Me	H[82]	^{13}C	C_2	163.2
			C_3	120.54
			C_4	139.66
			C_5	106.07
			C_6	138.47
			N-CH_3	37.60

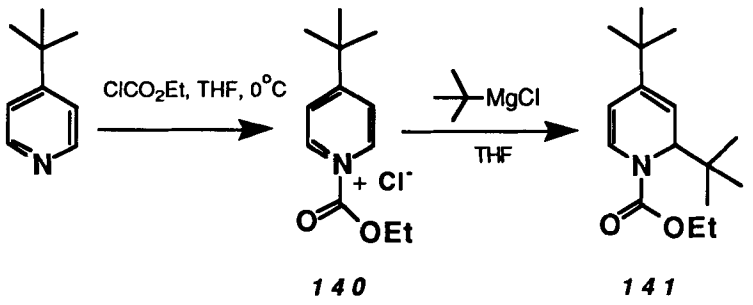
They can be stored indefinitely under argon at -30°C.[83] One drawback in this procedure is the limited availability of *N*-acyl derivatives other than the *N*-carboalkoxy derivatives. Reduction of intermediate *N*-acyl pyridinium salts, obtained by reaction of pyridine with an acyl chloride other than chloroformate derivatives, gives poor yields of the dihydropyridine. Fowler introduced a cyclization procedure, based on the methodology described for synthesis of *N*-acyl azadienes (see section 1d).[45] In this procedure 5-bromo-1,3-pentadiene reacts with hydroxamic acid ***135*** to give ***136*** and removal of the BOC protecting group gave ***137***.[84] Reaction with

Table 14. Preparation of Acyl 1,2-Dihydropyridines Via Cyclization of *N*-Acyl Azadienes.



R	% 139
OMe	43
-CH_2Ph	45
Me	32
Ph	41
-$(CH_2)_3CH{=}CH_2$	58

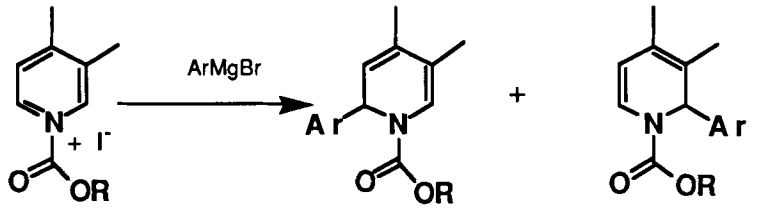
an acyl halide generates the *N*-acyl hydroxamide derivative, ***138***. Pyrolysis through a hot tube at 550-600°C gave the desired *N*-acyl 1,2-dihydropyridine (***139***) in moderate to good yield, as shown in Table 14.[84]



Fink and co-workers reported a synthesis of 2-alkyl-*N*-acyl-1,2-dihydropyridines

via reaction of Grignard reagents with *N*-acyl pyridinium salts.[85] 4-*t*-Butylpyridine reacts with ethyl chloroformate to give ***140*** and subsequent reaction with *t*-butylmagnesium chloride led to a 55% yield of ***141***.[85]

Table 15. Reactivity and Selectivity of Grignard Addition to Acyl Pyridinium Salts.



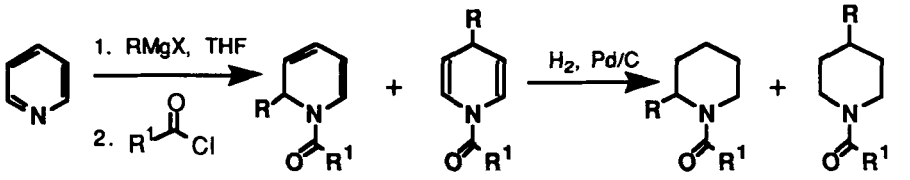
142 ***143*** ***144***

R	Ar	Solvent	%	***143:144***
Et	Ph	ether	31	78:22
iBu	Ph	THF	27	75:25
iPr	Ph	ether	32	90:10
Ph	Ph	THF	35	92:8
Et	*p*-ClC_6H_4	THF	40	62:38
Ph	*p*-ClC_6H_4	THF	55	95:5
Et	o-$CH_3C_6H_4$	THF	46	95:5
Et	*o*-$CH_3C_6H_4$	THF	56	>95

Lyle and Comins later showed that this Grignard addition showed some selectivity for addition to the less sterically hindered position at C_2 or C_5.[86] Addition of aryl magnesium bromide to ***142***, for example, gave a mixture of ***143*** and ***144*** in modest to good yield (see Table 15).[86]

It is noteworthy that a catalytic amount of cuprous iodide gives primarily the 1,4-dihydropyridine on reaction with the Grignard.[87] When unsubstituted pyridine is used, both 1,2- and 1,4-addition of the Grignard reagent can occur. Addition of a Grignard to pyridine followed by addition of an acyl chloride led to ***145*** and ***146***. These products were not purified but were hydrogen-ated to the acyl piperidines ***147*** and ***148***.[87b] The extent of attack at C_4 (see Table 16)[87b] depends on the steric encumbrance at C_2. Increasing steric hindrance at C_2 is a function of the group on the acyl carbon as well as the 'incoming' organometallic.

Table 16. 1,2- vs.1,4-Addition of Grignards to *N*-Acyl Pyridinium Salts.

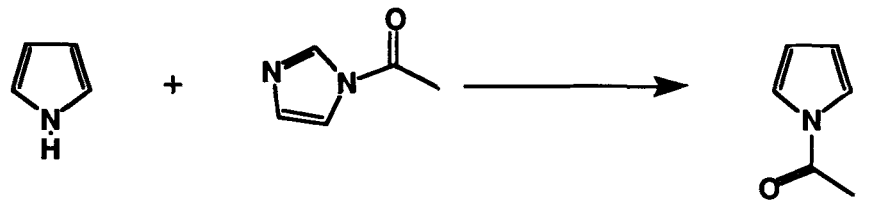


145 *146* *147* *148*

R	R^1	%	*147:148*
EtMgBr	Me	76	70:30
EtMgBr	EtO	73	64:36
EtMgBr	*t*-Bu	73	52:48
PhMgCl	Me	70	93:7
PhMgCl	EtO	80	93:7
PhMgCl	Ph	77	73:27
PhMgCl	*t*-Bu	66	52:48
iPrMgCl	Me	56	51:49
iPrMgCl	EtO	82	41:59
iPrMgCl	*t*-Bu	80	13:87

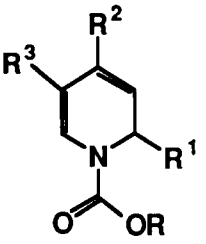
Only the proton NMR and infrared data were reported for the *N*-acyl-1,2-dihydropyridines, as shown in Table 17.[84,85,86] It is clear that the hydrogen adjacent to the nitrogen is further downfield, but the hydrogen on the sp^3 hybridized carbon at C_2 is also far downfield (4.34, 4.57 and 5.68 ppm). The infrared shows the urethane carbonyl at 1720, 1700 and 1705 cm^{-1}.

A related aromatic acyl dienyl 'lactam' is *N*-acetyl pyrrole (***150***). Reaction of pyrrole with acetic anhydride usually leads to a mixture of ***150*** and 2-acetylpyrrole. Reaction of pyrrole with *N*-acetyl imidazole (***149***), however, gave at least 90% of ***150*** in 90 minutes.[88]



149 *150*

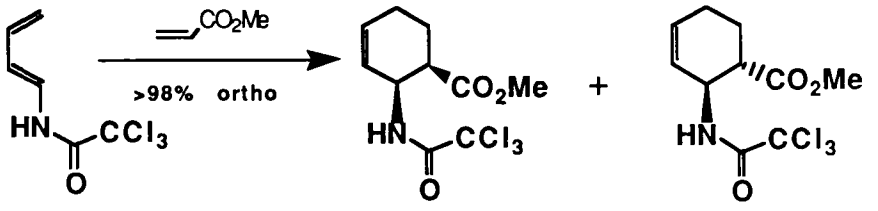
Table 17. Spectral Characteristics of *N*-Acyl 1,2-Dihydropyridines.



R	R^1	R^2	R^3	Signal	Chemical Shift (ppm)
H	H	H	H[84]	CH_3	3.75 (s, 3H)
				C_2H	4.34 (dd, 2H, J = 4.2 Hz)
				C_3	5.11 (t, 1H, J = 7 Hz)
				C_4H, C_5H	5.35 (m, 2H)
				C_6H	6.55-6.80 (m 1H)
Et	*t*-Bu	t-Bu	H[85]	C_2H	4.57 (J'2,3 = 6.0 Hz)
				C_3H	4.30
				C_5H	5.30
				C_6H	6.73
Ph	*p*-ClC_6H_4	Me	Me[86]	CH_3	1.70-2.08 (2s, 6H)
				C_2H	5.68 (d, 1H)
				C_3H	6.03 (d, 1H)
				C_6H	6.92 (br s, 1H)
				Ar	7.08-7.80 (m, 9H)

2. INTERMOLECULAR DIELS-ALDER REACTIONS

The dominate reaction of dienyl amides and lactams is the Diels-Alder cyclization. Both inter- and intramolecular versions of the reaction are known, each leading to somewhat different synthetic uses. We will begin with the intermolecular



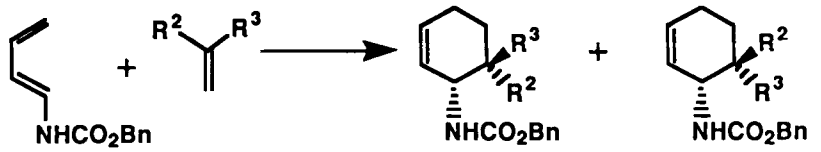
25 *151* *152*

cyclization reactions.

2a. Dienyl Amides

Overman and Houk reported the photoelectron spectra of *N*-acylamino-1,3-dienes as well as the stereochemistry and regiochemistry of their intermolecular Diels-Alder reaction.[89] The diene shows high regioselectivity (> 98%) for the 'ortho'-product and 75:25→80:20 stereoselectivity for the *endo*- (*cis-)* adduct. This is illustrated by

Table 18. Diels-Alder Cyclization of 1-Aminoacyl-1,3-butadienes.

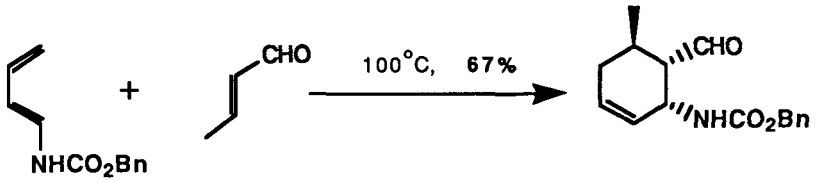


153 *154* *155*

R²	R³	%	154:155
Ph	H	quant	93:7
4-nitroPh	H	quant	90:-
4-OMePh	H	95	85:15
piperonyl	H	70	100:0
piperonyl	CO_2Et	64	64:21
piperonyl	COMe	69	100:-
piperonyl	CN	40	3:2
CO_2Et	Ph	91	71:20[90]
E-$PhCH_2OCH_2CH$=CHCHO		90	90:- [91]

reaction of *N*-trichloroacetyl-1-amino-1,3-butadiene (***25***) with methyl acrylate, which gave 76.9% of ***151*** and 23.3% of ***152***. The Diels-Alder cyclization of ***25*** showed cyclization of ***25*** showed higher *ortho*-selectivity than a similar reaction with *trans*-pentadienoic acid, which gave 83% *ortho*-selectivity and a 74:26 *endo:exo* mixture.[89] Overman and Houk showed that *endo*-selectivity for the dienyl amides and carbamates increased with increasing facility of cyclization (faster rate of reaction) and as the ionization potential of the diene decreased. The *endo*-selectivity was attributed to attractive secondary orbital interactions,[89,92] considering only the diene donor HOMO and the dienophile acceptor LUMO.[93] As shown in Table 18,

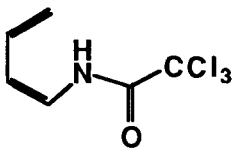
endo-selectivity in the cycloaddition of diene ***153*** is apparent in the preference of ***154*** over ***155***.in the cyclohexene adducts. The regiochemistry of the dienophile is



153 ***156***

reflected in the final product, as expected. *trans*-2-Butenal, for example, gave 67% of ***156*** on reaction with ***153***.[91]

The stereochemistry and regiochemistry of the cyclohexene adduct was determined by ^{1}H and ^{13}C NMR analysis. Inspection of the ^{13}C data for ***157*** (in Table 19)[89] revealed the signal for the proton at C_1 appeared at about 4.75 ppm (broad multiplet) for both *cis*- and *trans*- isomers. The C_6 hydrogen, however, showed a downfield shift for the *cis*-adduct with the pseudo equatorial hydrogens appearing as an unsymmetrical four-line absorption. Both C_1 and C_6 in the carbon



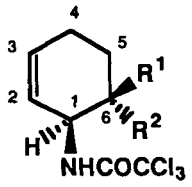
24

spectrum absorbs at higher field for the *cis*-adduct. "An equatorial carbon with substituent deshields the α- and β-carbons more than the axial one.".[89] Data for the carbobenzoxy adduct (***158***) are also shown in Table 19.[93] The same downfield shift is observed for C_1 and C_6 for the *Z*-adduct ($R_2 = CO_2Et$).

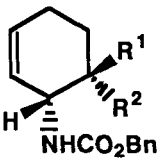
It is interesting to note that although *trans-N*-trichloroacetamido butadiene ***25*** reacts with methyl acrylate at 100°C to give a 3:1 mixture of ***151:152***, the *cis*-derivative (***24***) gave the same mixture at 110°C. This was attributed to slow isomer-

ization of the unreactive *cis*- isomer (***24***) to ***25***.[91]

Table 19. NMR Data for the Cycloadducts of Dienyl Carbamates.



157

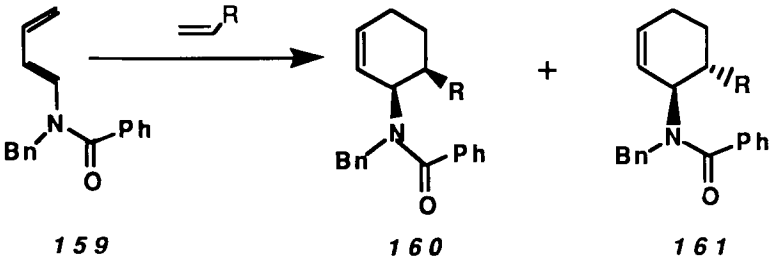


158

	R^1	R^2	Nuclei	Signal	Chemical Shift (ppm)
157	CO_2Me	H[82]	^1H	C_1H	4.77
				C_6H	2.98 ($J_{1,6}$ = 4.5 Hz)[93]
			^{13}C	C_1	47.3
				C_2	130.8
				C_3	125.7
				C_4	22.4
				C_5	22.9
				C_6	42.3
157	H	CO_2Me	^1H	C_1H	4.74
				C_6H	2.69 ($J_{1,6}$ = 6.8 Hz)[93]
			^{13}C	C_1	49.5
				C_2	49.5
				C_3	125.4
				C_4	23.6
				C_5	23.6
				C_6	44.9
158	CO_2Et	Ph	^{13}C	C_1	49.7[90]
				C_4	23.0
				C_5	24.0
				C_6	53.5
158	Ph	CO_2Et	^{13}C	C_1	53.7
				C_4	23.5
				C_5	30.9
				C_6	54.7

In similar work, Oppolzer prepared the *N*-benzyl benzamide derivative ***159*** which also showed *endo*- (*cis*-) selectivity in the Diels-Alder cyclization, as shown in Table 20[94]

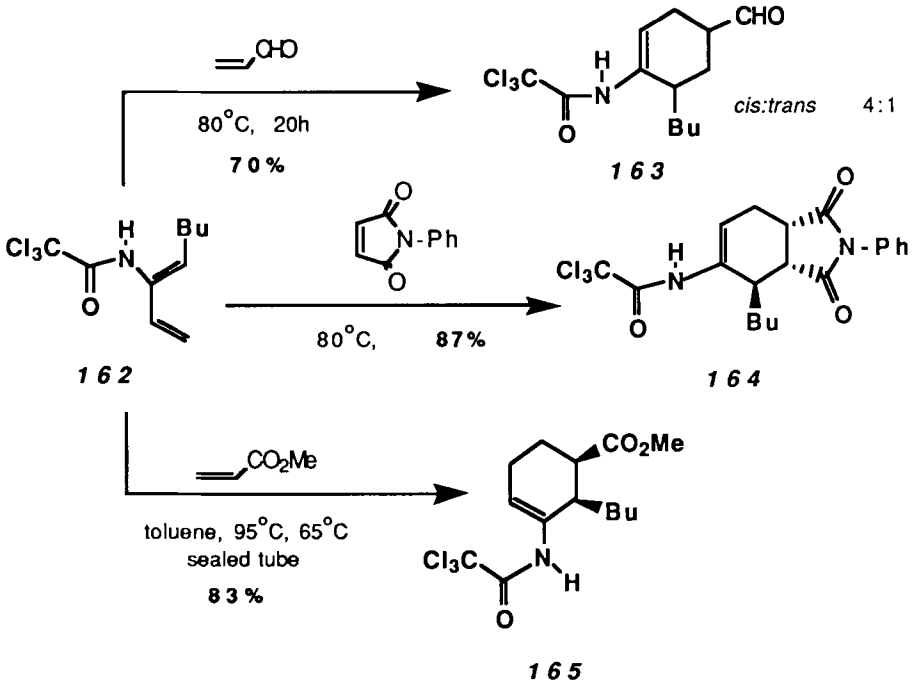
Table 20. Diels-Alder Cyclization of *159*



159 *160* *161*

R	Conditions	% *160*	% *161*
CO_2CH_3	80°/3d	73	18
CO_2tBu	100°/10h	71	15
CN	80°/40h	74	24

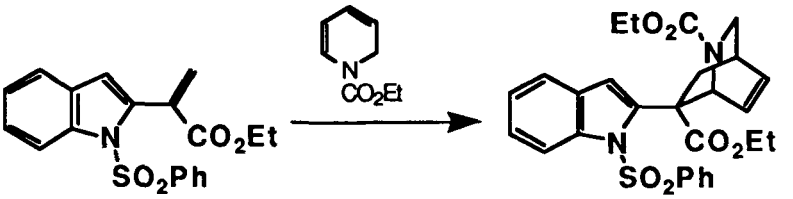
The 2-amidobutadiene derivatives also show excellent selectivity in the Diels-Alder reaction. The *N*-trichloroacetyl-2-amino-1,3-butadiene derivative ***162*** reacted



with acrolein to give ***163*** in 70% as a 4:1 *cis*:*trans* mixture.[95] Similar reaction of

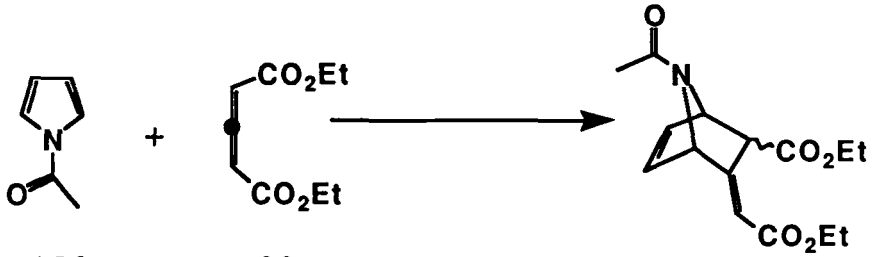
162 with *N*-phenylmaleimide gave ***164*** in 87%. In separate work, reaction of ***162*** with methyl acrylate gave ***165*** in 83%.[96]

Other dienyl amides show similar reactivity, but the course of the reaction is dependent on the structure of the diene. Sundberg reported the cyclization of ***166*** with 1-carboethoxy-1,2-dihydropyridine (100°C, 48h, neat) to give ***167***.[97] It is clear that ***166*** reacts as a dienophile rather than as a 2-aminodiene.



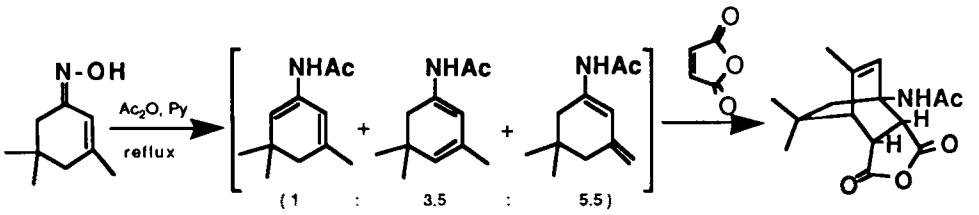
166 ***167***

Kozikowski showed that *N*-acetyl pyrrole (***150***) undergoes Diels-Alder reactions to produce bicyclic adducts in good yield. Specifically, the reaction of ***150*** with 1,3-dicarboethoxy allene (***168***) gave ***169*** in 70% yield.[98] Another acylamino butadiene derivative was reported by Boar and Barton[99] to give an *endo*-Diels-Alder adduct on reaction with maleic anhydride. This dienyl amide was prepared from the



150 ***168*** ***169***

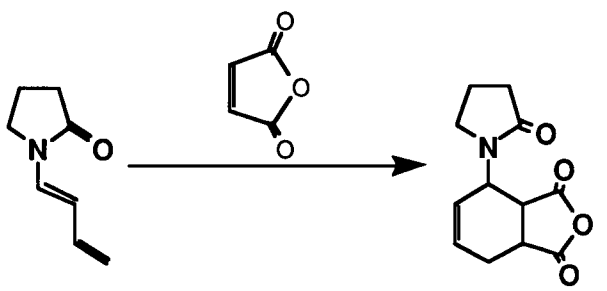
oxime of isophorone (***170***) was converted to a mixture of three dienyl amides, including the 1-acylamino derivative, ***171***. Reaction with maleic anhydride, however, led to a single Diels-Alder adduct (***172***) in 63%, clearly showing that a thermal isomerization of the dienyl amide accompanied the Diels-Alder reaction and favored ***171***.



170 171 172

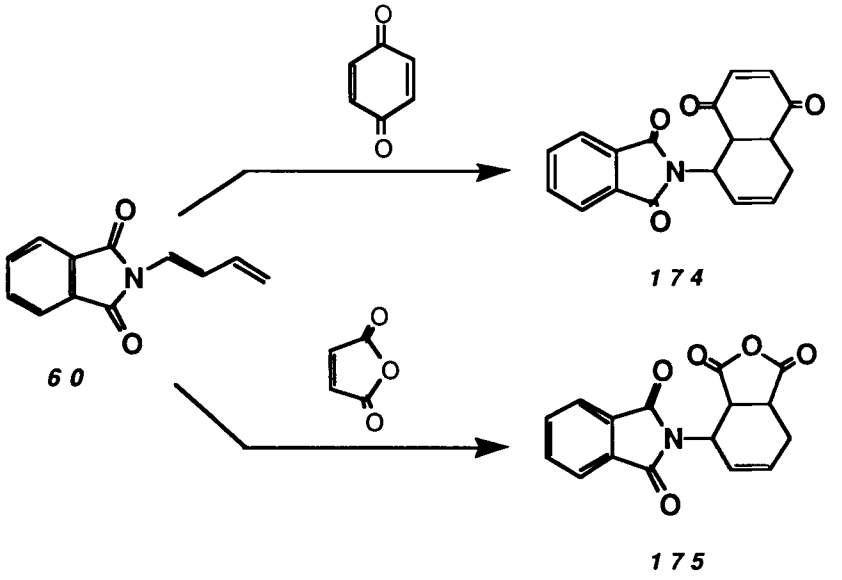
2b. Dienyl Lactams

The similarity of dienyl amides and dienyl lactams suggests a similar analogy in their reactions with dienophiles. Murata and Terada first reported the Diels-Alder



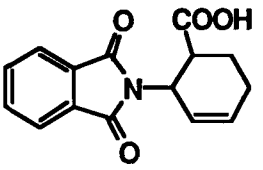
56 173

reaction of a dienyl lactam (***56***) with maleic anhydride to give ***173*** in 70% yield.[33]

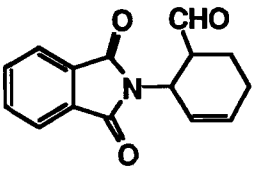


60 174 175

The stereochemistry of the cycloadduct was not indicated. They also prepared the corresponding dienyl imides and showed they give Diels-Alder adducts with a variety of alkenes. Reaction of ***60*** with *p*-benzoquinone, for example, gave ***174*** and reaction with maleic anhydride gave ***175***.[34] Similar reaction with acrylic acid gave ***176*** and acrolein gave ***177***. Although the regiochemistry was reported as that shown in the diagram, there was no structural proof and the relative stereochemistry was not discussed for the imides or the lactams.

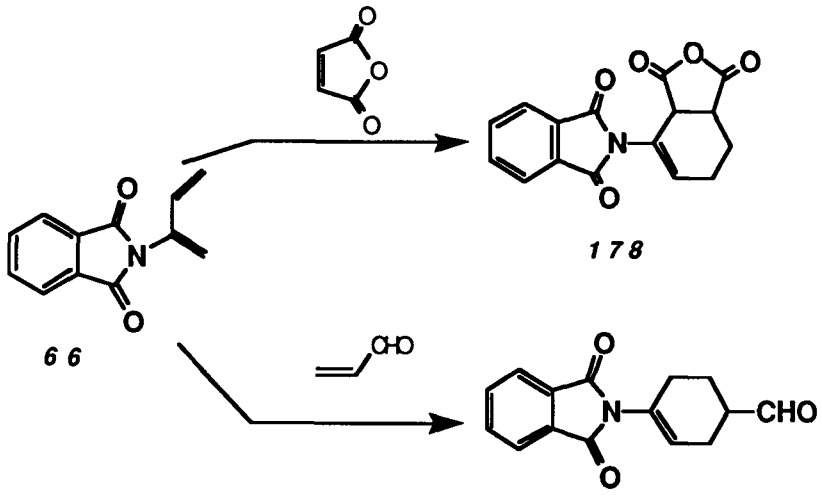


176



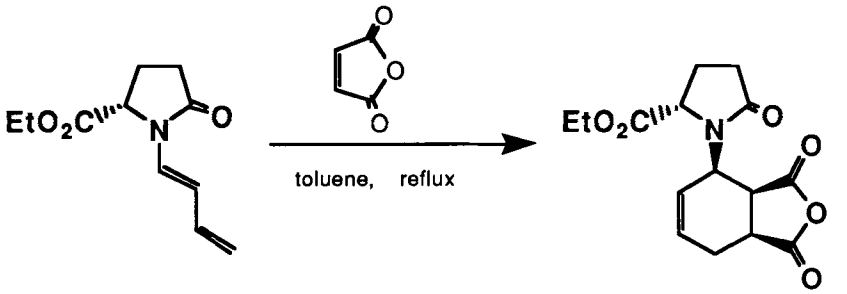
177

2-Phthalimido butadiene derivatives such as ***66*** were also prepared and reaction of ***66*** with maleic anhydride gave ***178***. Similar reaction with acrolein gave ***179***.[34] Once again, the regiochemistry was not discussed but reported to be that shown. We prepared 1,3-butadiene-2-pyrrolidinone derivatives such as ***56*** by reaction of lactams with conjugated aldehydes. This is a more general route and



66 ***178*** ***179***

Diels-Alder reaction with maleic anhydride and ethyl acrylate[42] confirmed the selectivity to be *cis-* and *ortho-*. The *cis:trans* selectivity for C_1-C_2 was about 80:20 in all cases. There was a slight decrease in selectivity (to about 70:30 with piperidone derivatives and 60:40 for capro-lactam derivatives) as the size of the lactam ring increased. The initial thermal cyclization was rather sluggish but the use of highly polar solvents increased the rate of reaction and gave a slight improvement in selectivity (see Table 21).[42] The optimum cyclization conditions employed 50% aqueous ethanol and decreased the reaction time by about 60%. The cycloadduct derived from reaction with ethyl acrylate (***181*** in Table 21) gave the expected downfield shift for the C_6 hydrogen in the *cis*-adduct (2.78-2.87 for the *cis-* vs. 2.45-2.61 ppm for the *trans-*). In the case of the C_1 hydrogen, the signal for the *cis*-adduct was downfield (5.04-5.09 ppm) of the *trans*-adduct (4.80-4.91 ppm). The ^{13}C NMR (see Table 22) for the *cis-* adduct shows absorbances similar to those observed for dienyl carbamate ***157***, which showed ^{13}C NMR signals: [C_1 (47.3 ppm), C_6 (42.3 ppm), C_2 (130.8 ppm), C_3 (125.7 ppm) and $C_{4/5}$ (22.4/22.9 ppm)]. These compare favorably with the chemical shifts reported in Table 22 for the lactam cycloadduct. The analogous cycloadduct derived from maleic anhydride (***180***) is also shown in Table 21 and the yields were also quite good.

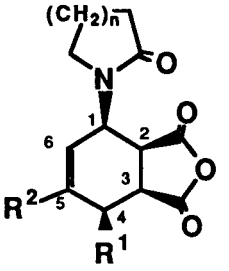


182 ***183***

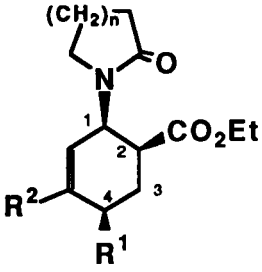
We reported the preparation and Diels-Alder cyclization of ***182***, the only example of a chiral dienyl lactam.[43] *S*-Ethyl pyroglutamate was converted to ***182*** by reaction with crotonaldehyde (see part 1c). The Diels-Alder cyclization proceed-

ed smoothly to give a single product (***183***) with maleic anhydride. The relative stereochemistry of the cyclohexene ring was determined to be 'all *cis*-' but the absolute stereochemistry has not been determined due to the inability to obtain crystalline derivatives. Similar reaction with ethyl acrylate gave a 93:7 mixture of *cis*:*trans* adducts ***184:185*** in 91% yield. Analysis by gas chromatography/mass

Table 21. Diels-Alder Cyclization of Dienyl Lactams



180

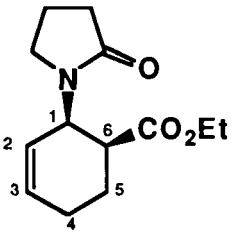


181

R^1	n	R^2	% *180*	% *181*	*cis:trans*	Solvent
H	1	H	70	41	70:30	toluene
				72	82:18	dioxane
				95	85:15	aq. EtOH
		CH_3	50	78	82:10	toluene
CH_3		H		95	91:9	aq. EtOH
n-C_4H_9		H		92	98:2	aq. EtOH
H	2	H	67	93	79:21	aq. EtOH
				74	74:26	toluene
				82	76:24	dioxane
				86	78:22	EtOH
				80	80:20	aq. THF
		CH_3	64	77	78:22	toluene
H	3	H	67	95	74:26	aq. EtOH
				72	61:39	toluene
		CH_3	55	91	60:40	aq. EtOH
				55	56:44	toluene

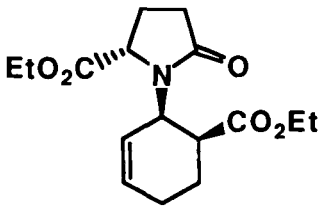
spectrometry showed the *cis*- adduct favored one diastereomer by at least 91.5:1. The reaction mixture favored the *trans*- adduct by at least 6.5:0.1 although the latter diasteromer was present in such small amount that its ratio could only be estimated. Reactions with methyl vinyl ketone showed reduced *cis*- selectivity (82:18) and

Table 22. Spectral Data for The Cycloadduct of *N*-Dienyl Lactam *56* and Ethyl Acetate.



Isomer	Nuclei	Signal	Chemical Shift (ppm)
Z-	^1H	C_1H	5.04-5.09 (m, 1H)
		C_6H	2.78-2.87 (m, 1H)
	^{13}C	C_1	45.14 or 43.66
		C_2	131.84
		C_3	123.94
		$C_{4,5}$	23.66
		C_6	43.66 or 45.14
E-	^1H	C_1H	4.80-4.91 (m, 1H)
		C_6H	2.45-2.61 (m, 1H)

the diastereoselectivity was also reduced to 40:1 for the *cis*- adduct.



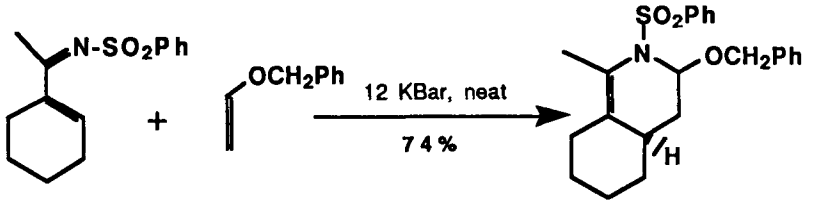
184

185

2c. Acyl Azadienes

Boger reported an intermolecular Diels-Alder reaction for the *N*-benzenesulfonyl-1-azadiene ***91***. Under pressure (12 KBar) ***91*** reacts with electron rich alkenes such as benzyl vinyl ether to give cycloadduct ***186***, in 74% yield.[51] This reaction was *endo*-selective, with an *endo:exo* ratio of >20:1. The electron withdrawing sulfonyl group accentuates the electron rich nature of the azadiene leading to

"reaction with electron rich dienophiles in $LUMO_{diene}$-controlled Diels-Alder reactions".[51,1] The cycloadducts are stable to chromatography on Fluorisil but are

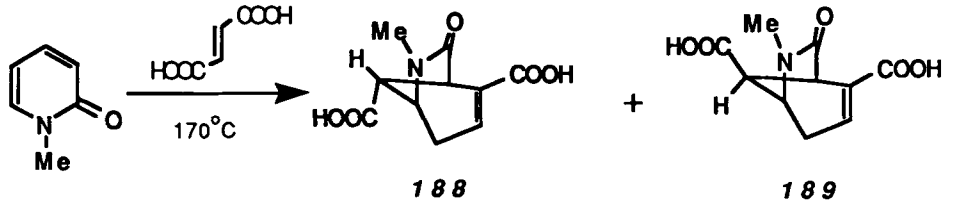


91 *186*

somewhat unstable to silica gel. There is no epimerization at C_2, however, and the products are configurationally stable. Several examples of this reaction are shown in Table 23.[51] In the general case, cycloaddition leads to the *N*-sulfonyltetrahydropyridine derivative, ***187***.

2d. 2-(1H)-Pyridones

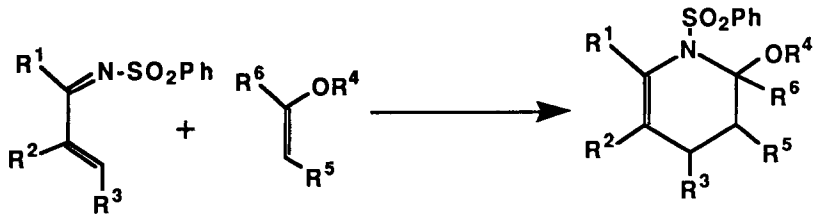
The Diels-Alder reaction is perhaps the best known and most studied reaction of pyridones. Table 24 shows the bicyclic amides obtained with a variety of dienophiles. Good yields of cycloadduct are obtained only with highly reactive dienophiles. Reactions with maleic anhydride usually give modest yields of cyclic product with a preference for the *endo*-adduct. Fumaric acid and its esters give extremely poor yields of the cycloadduct with the geometry of the double bond preserved, as expected. The acid appears to give somewhat better yields than the ester. It was noted that prolonged heating of *N*-methyl-2-pyridone and fumaric acid (170°C) gave a mixture of the rearranged products ***188*** and ***189*** in 8 and 12% yield, respectively.[100,105,101]



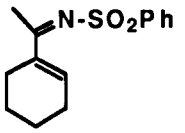
188 *189*

The reaction with dimethylacetylene dicarboxylate gave the expected cycloadduct in poor to good yield, but the adducts are subject to a retro 4+2 reaction on heating. Reaction of *N*-4,6-trimethyl 2-pyridone with dimethylacetylene dicarboxylate, for example, gave cycloadduct ***190*** in 71% yield,[106] but prolonged heating at 80°C gave the aromatic retro Diels-Alder product (***191***) in 75% yield along with extruded methyl isocyanate. *N*-Phenyl maleimide reacts with the pyridone to give the cycloadduct in poor to moderate yield, as a mixture of *endo*- and *exo*-isomers.

Table 23. Inverse Electron Demand Diels-Alder Reactions of N-Sulfonyl-1-aza-1,3-butadienes.



187

R^1	R^2	R^3	R^4	R^5	R^6	n	Conditions	% *187*
Me	H	H	Et	H	H	10	60°/12h[b]	73[a]
Me	H	Ph	Et	H	H	5	12 KBar/80h[c]	69[a]
Ph	H	Ph	Et	H	H	5	12 KBar/45h[c]	77[a]
H	H	Ph	Et	H	H	5	12 KBar/45h[c]	72[a]
			Bn	H	H	5	6 KBar/144h[c]	72[a]
H	H	H	Et	H	H	10	40°/11h[c]	82[a]
								
			Et	H	H	5	12 KBar/87h[c]	89
"			Et	H	H	5	110°/48h[d]	79
"			Bn	H	H	5	12 KBar/70h[b]	74[a]
"			Bn	Me	H	2	12 KBar/72h[c]	28[a]
"			Me	H	Me	5	12 KBar/76h[c]	82[a]
"			Me	H	OMe	5	12 KBar/96h[c]	63

[a] *endo:exo* >20:1 [b] neat [c] CH_2Cl_2 [d] $PhCH_3$

Table 24. Diels-Alder Cyclization of 2-Pyridones

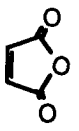
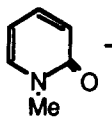
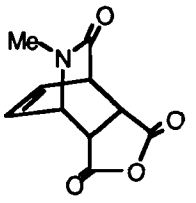
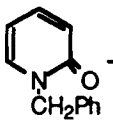
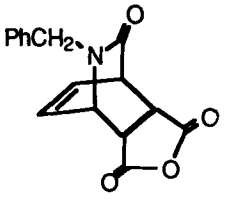
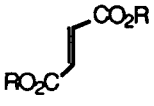
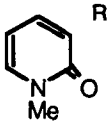
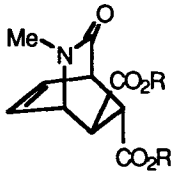
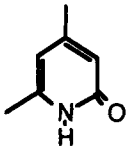
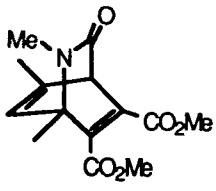
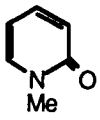
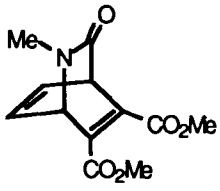
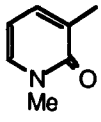
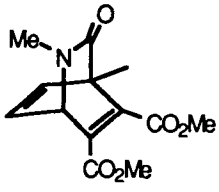
Dienophile	Pyridone	Cycloadduct	%
			42[100,102,103]
			31[104]
	 R = Me, $PhCH_3$, reflux		4[100,107,105]
	R = Et, $PhCH_3$, reflux		4
	R = H, H_2O, reflux		13
	 PhH, reflux, 72h		71[106]
	10 KBar, 12h, 70°C		16[107]
	15 KBar, 15h, 60°C		22[107]

Table 24 Cont.

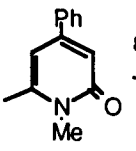
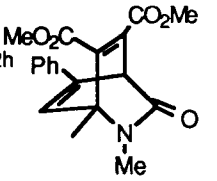
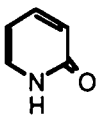
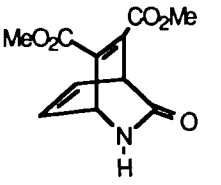
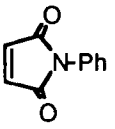
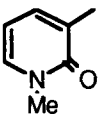
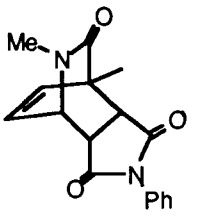
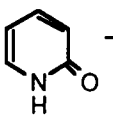
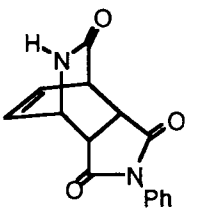
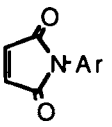
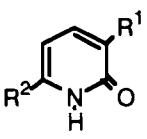
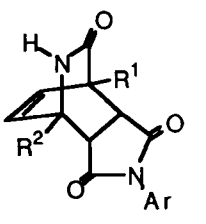
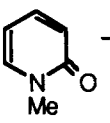
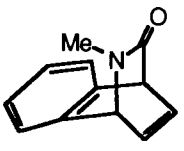
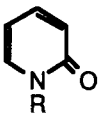
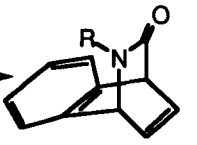
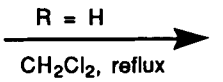
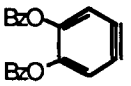
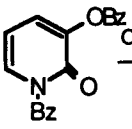
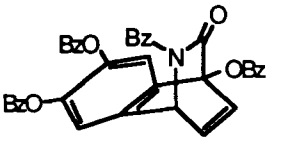
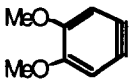
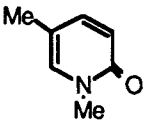
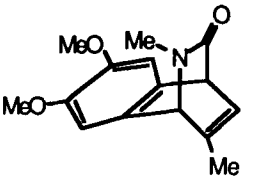
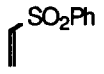
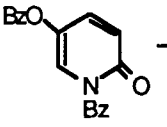
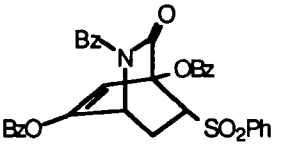
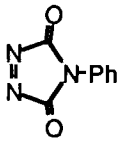
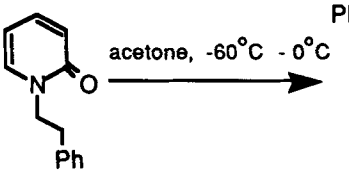
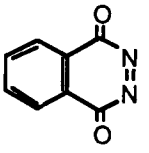
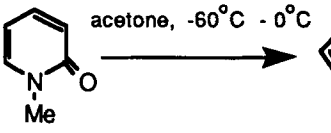
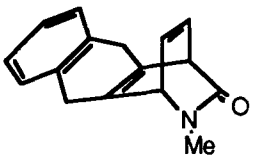
Dienophile	Pyridone	Cycloadduct	%
			70[108]
			(-)[109]
			a32[60,110,111] b(-) c(-)
			a30/b20[112]
			a35/b22[112]
	R^1 = H, R^2 = Me		a5/b41[112]
	R^1 = Me, R^2 = H		a7/b40[112]
			10[113]

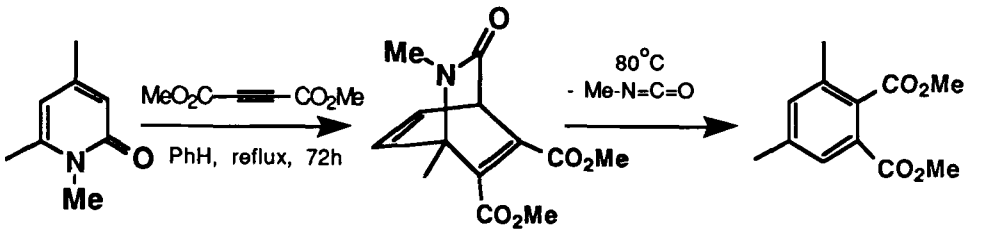
Table 24 Cont.

Dienophile	Pyridone	Cycloadduct	%
			7[113]
			(-)[114]
			17[115]
			17[116]
			(-)[117]
			68[118]
			17[119]

[a] *endo* [b] *endo* + *exo* [c] *exo*

At lower temperatures the *endo*-adduct (***192***) predominates but at temperatures

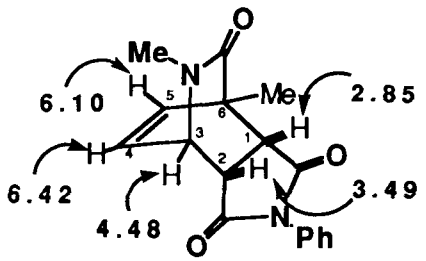
greater than 160°C the *exo*-product (***193***) is favored.[59] The *exo/endo* adducts were identified via proton NMR (shown for ***192*** and ***193***). It is apparent that the C_2 hydrogen for the *endo*-adduct



190 ***191***

(***192***) is closer to the bridging lactam nitrogen and is further downfield (3.49 ppm)[59] than in the *exo*-adduct ***193*** (3.19 ppm). The C_3 hydrogen in ***192*** is somewhat upfield relative to ***193***, probably due to the deshielding effect of the imide moiety. The coupling constant for the hydrogens on C_2 and C_3 ($J_{2,3}$) is also diagnostic. In ***192***, $J_{2,3}$ is 4.0 Hz but only 2.5 Hz in ***193***.

Benzyne, generated by several different routes, generally gives poor yields of the cycloadduct on reaction with pyridones.[113-116] Complete NMR data including COSY analysis was presented for the cycloadducts.[115] Triazolenes have been used as dienophiles and led to 17-70% yields of cycloadduct.[118,119] More



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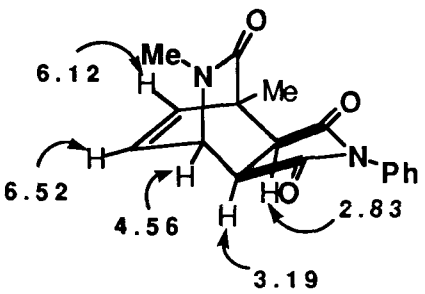
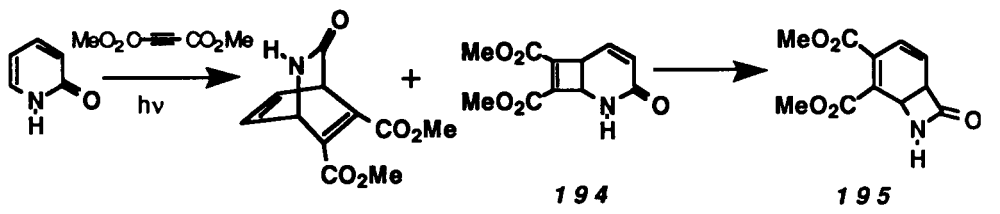
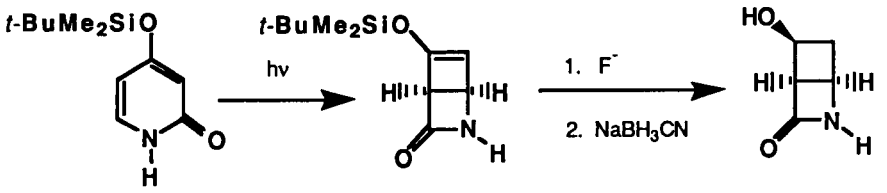


193

recently, vinyl sulfones have been used as a dienophile and gave 46% of the *endo*-sulfone and 20% of the *exo*-sulfone.[117]

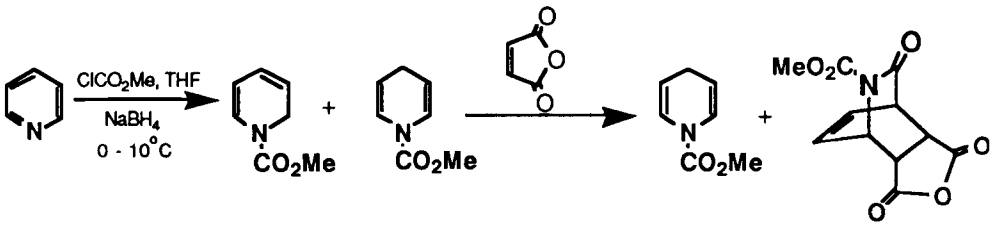


The photochemical reaction of dialkylacetylene dicarboxylates and 2-pyridones led to a mixture of the 4+2 and 2+2 cycloadducts.[109] In the entry cited in Table 23, the initially formed 2+2 cycloadduct (***194***) rearranges to the β-lactam, ***195***.[109] In the context of this reaction, it is interesting to note that 2-pyridones undergo an internal 2+2 pericyclic reaction photochemically. Irradiation of ***196***, for example, gave ***197***.[120,121] Conversion of ***197*** to alcohol ***198*** allowed a straightforward synthesis of synthetically important β-lactams.



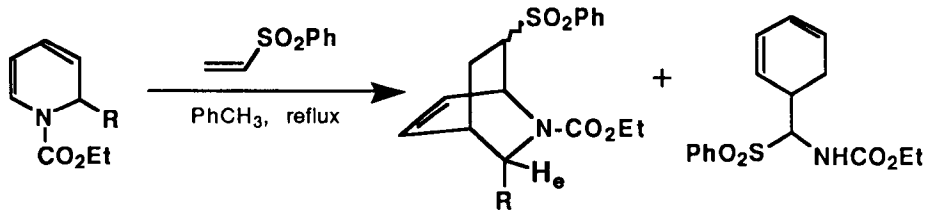
2e. *N*-Acyl-1,2-Dihydropyridones

In his initial study of the preparation of *N*-acyl 1,2-dihydropyridines via reduction of *N*-acyl pyridinium salts,[83] Fowler found that a mixture of 1,2- and 1,4-dihydropyridines was produced. Reaction of this mixture with maleic anhydride converted the 1,2-dihydropyridine to ***199***. This adduct could be chromatographically removed and this technique was used to 'purify' the 1,4-dihydropyridine. More synthetically interesting 1,2-dihydropyridines have been prepared and the Diels-Alder reaction has been used for the synthesis of important natural targets. Krow showed that ***200*** reacted with phenyl vinyl sulfone to give cycloadduct ***201*** with minor amounts of a diene cleavage product, ***202***.[122] As shown in Table 25[122] the adduct with an



endo-substituent and an *exo*-C3 hydrogen (H_e in ***201***) appeared downfield relative to the *endo*-C_3-hydrogen. The *exo*-alkyl adduct with an *endo*-C_3 hydrogen was readily apparent if present (it was prepared independently for comparison) but was not observed in any case. This reaction showed high selectivity for the adduct bearing an *exo*-hydrogen.

Table 25. Cycloaddition of *N*-acyl-1,2-Dihydropyridines and Phenyl Vinyl Sulfone.



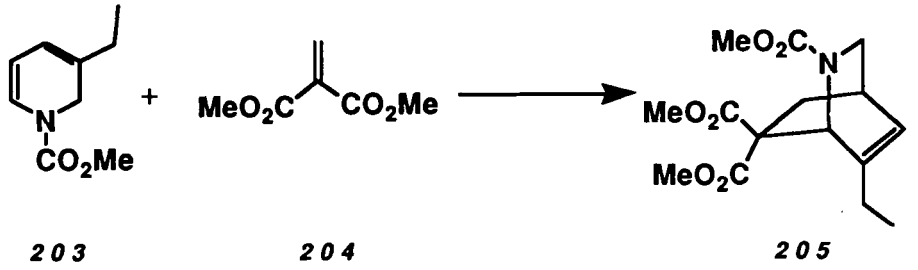
200 ***201*** ***202***

R	% *201*	H_e (ppm)	*endo* H (ppm)
H	28	3.26 (dd)	2.94 (d)
Me	50	3.61 (dq)	3.32
Et	24	3.40 (br	3.08
Pr	32	3.55 (dt)	3.18
iPr	37	3.43 (br)	3.03

In separate work, Raucher showed that ***203*** reacted with dienophile ***204*** to give ***205*** in 68% yield. This cycloadduct was used as an intermediate in the synthesis of catharanthine.[123]

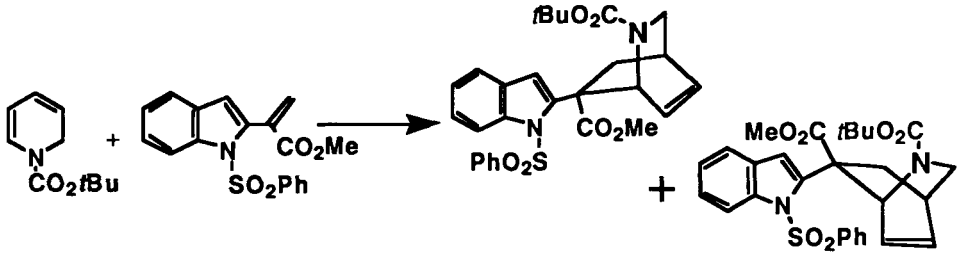
Another synthetic application of this methodology was for the preparation of isoquinolines from dihydropyridine derivatives.[124] Sundberg used this route in a

synthesis of catharanthine in which ***206*** reacted with methyl-1-benzenesulfonyl



203 ***204*** ***205***

indole-2-acrylate (***53***) to give 65% of a 1:1 mixture of adducts ***207*** and ***208***.[125] In another application, Mariano used a dihydropyridine strategy for a synthesis of reserpine.[126]



206 ***53*** ***207*** ***208***

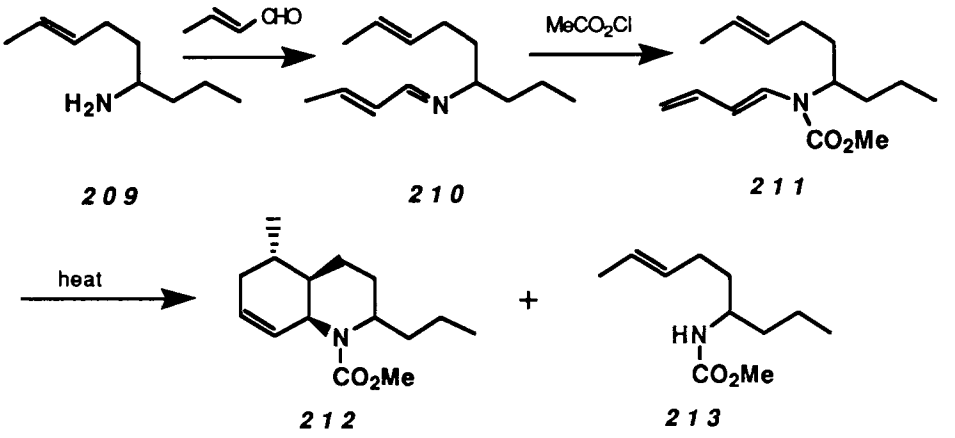
3. INTRAMOLECULAR DIELS-ALDER REACTIONS

The excellent review of intramolecular Diels-Alder cyclizations by Fallis[9] encompasses virtually all types of dienes, both carbon and heterosubstituted. Many examples of dienyl amides, acyl azadienes and pyridones were reported. Some intramolecular cyclizations for selected dienes will be repeated here with the emphasis on dienyl amide and lactam derivatives.

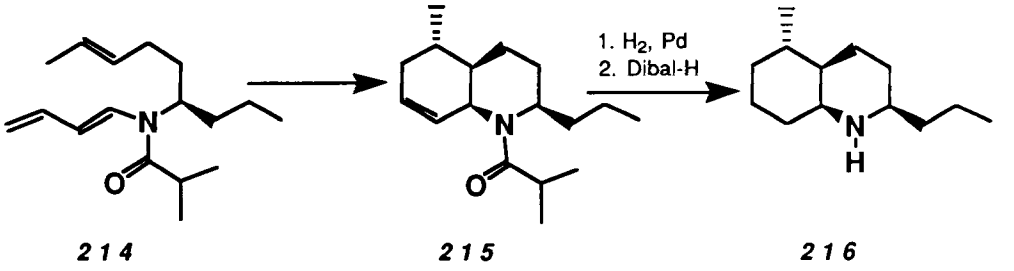
3a. Dienyl Amides

Oppolzer showed that amine ***209*** was converted to imine ***210*** and, thereby, to

dienyl carbamate ***211.*** Thermal cyclization (toluene, 5% solution, sealed ampoule, 215°C, 20 h) gave ***212*** in 25% yield,[30b] along with an elimination product, ***213***. Carbamate ***212*** was converted to ±-pumilotoxin. Oppolzer later improved the

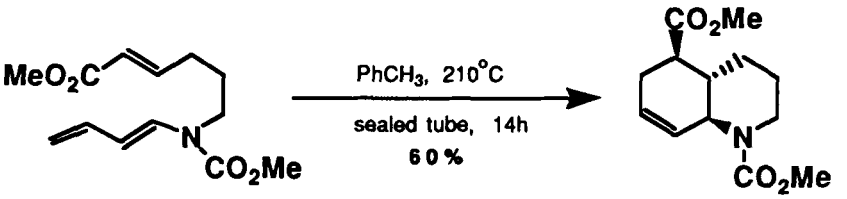


synthesis by preparing *R*-***214*** from *R*-norvaline.[30a] Conversion to *R*-***214*** was followed by cyclization to ***215***. The sequence was modified to use an amide as the



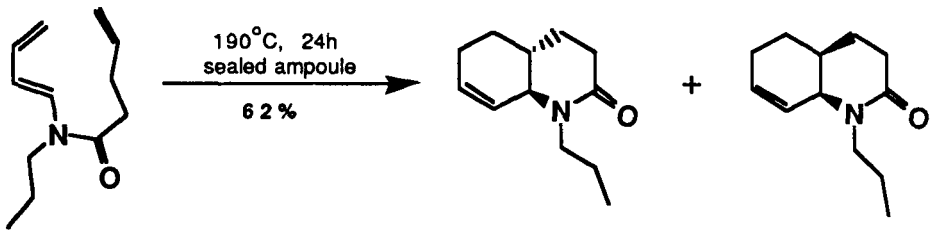
nitrogen protecting group rather than the carbamate. Another improvement was in the thermolysis technique used for conversion of ***214*** to ***215***, which was again accomplished in a sealed tube at 230°C (toluene/16 h) but in the presence of 2% *bis*-(trimethylsilyl) acetamide. Little elimination was observed and ***215*** was formed in 60% yield along with minor amounts of the diastereomeric product. Hydrogenation and reductive cleavage with diisobutylaluminum hydride gave 2*R*-pumiliotoxin C, ***216***. A similar strategy was used by Witiak in which a dienyl amide possessing a pedant acrylate moiety (***217***) was cyclized to ***218*** in 60% yield (sealed tube,

toluene, 210°C, 14 h). [127] These conditions were virtually identical to those reported by Oppolzer.



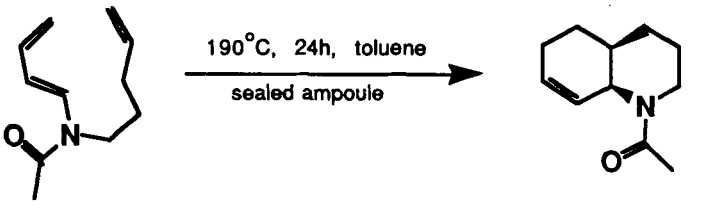
217 ***218***

Oppolzer also showed that allylic amide ***219*** was cyclized to a mixture of ***220*** and ***221*** in 62% yield.[128] The modification in this procedure was the use of an amide rather than a carbamate, as in the pumiliotoxin synthesis (*vide supra*). The dienophile is attached to the 'arm' containing the amide carbonyl rather than to the *N*-alkyl 'arm' (as in ***214*** and ***217***).



219 ***220*** ***221***

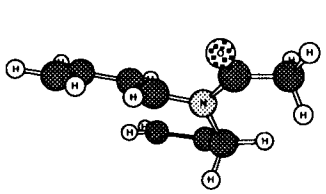
Oppolzer also studied the differences in the internal cyclization of two types of dienyl amides: those with the amide carbonyl *exocyclic* to the ring being formed (as in ***214*** and ***217***) and those with the carbonyl within that ring (as in ***219***). Oppolzer



222 ***223***

showed[124] these two different types of trienes gave opposite stereochemical

results. Cycloaddition of the external carbonyl derivative ***222***, for example, gave ***223*** in 59% yield as the *cis*-adduct. The cyclization of the previously mentioned, internal carbonyl derivative ***219***, however, gave a mixture of the *cis*-cycloadduct ***220*** (25%) and the *trans*-adduct ***221*** (37%). Oppolzer rationalized these results by a preference for an *endo*-transition state (***224*** for ***222***) in which there was overlap of the amide π orbitals with the diene π system. The *endo*-transition state for ***219*** (***225***) and the *exo*-transition state (***226***) show that only ***226*** is reasonably stabilized by conjugation and that formation of the products is dependent on a competition between overlap of the π orbitals vs. the *endo*-transition state.[128] The *cis-trans-*



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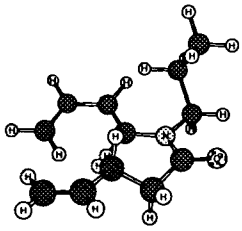

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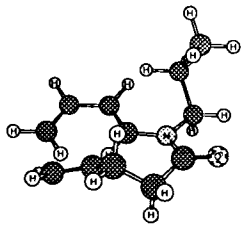
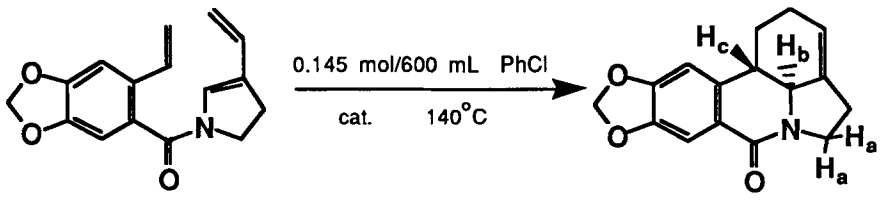


226

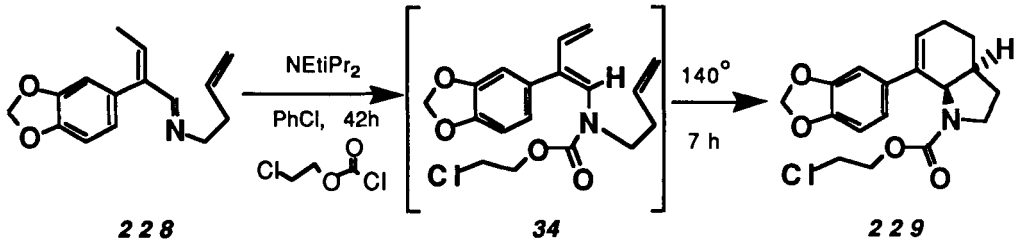
trans configuration in cycloadducts ***220*** and ***221*** was assigned by reduction to the corresponding amine with lithium aluminum hydride. The amine derived from ***220*** shows a coupling constant ($J_{1,2}$) of 12.2 Hz whereas $J_{1,2}$ for the amine derived from ***221*** was 3.5 Hz. The large coupling constant was indicative of a *trans*- ring juncture in ***220***.[128]

Stork used this internal Diels-Alder strategy for a synthesis of lycorane in which ***29*** was cyclized to ***227*** in 51% yield.[25] This cyclization was more sensitive to the

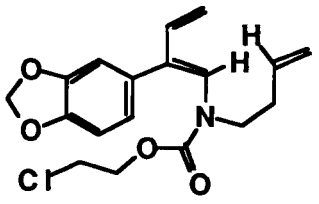


29 ***227***

reaction conditions than the examples reported by Oppolzer. Catalytic amounts of 3-*t*-butyl-4-hydroxy-5-methyl phenylsulfide and O,*N*-*bis*-(trimethylsilyl)-acetamide were required. The use of ammonia treated glassware was necessary to obtain the reported yield. Determination of the stereochemistry for the ring juncture was possible by proton NMR analysis in d_6-benzene, in which the signals for H_a were separated from those for H_b and H_c. The coupling constant ($J_{a,b}$) was shown to be 12 Hz, consistent with the *trans*-ring juncture.[25] This is analogous to Oppolzer's analysis which suggests the *exo*-transition state (***226***) is required for ***29*** to give the observed *trans*-ring juncture.



228 ***34*** ***229***



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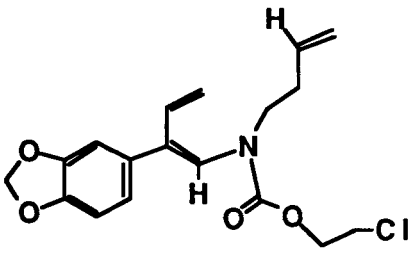
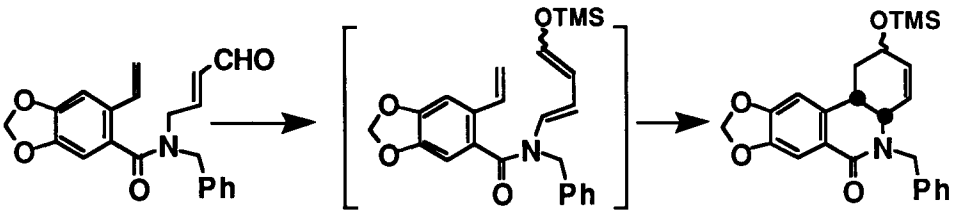


230

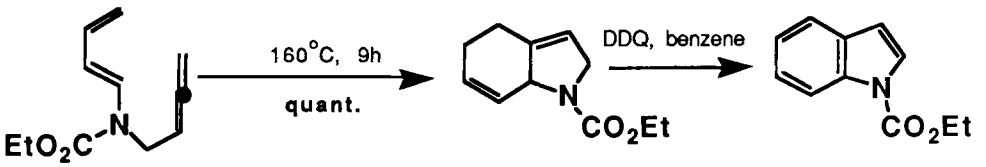
This sensitivity to conjugation and π orbital interactions in the transition state is further illustrated by treatment of ***228*** with an appropriate chloroformate to give ***34***.[26] Subsequent heating to 140°C for seven hours gave ***229*** in 53%, with a *trans*- ring juncture, in contrast to Stork's observation. This difference in selectivity appears to result from the geometry of the diene. In ***34***, the *cisoid*-transition state required for the *trans*-adduct has a severe steric interaction of the aromatic ring and

the carbamate.[26] The *trans*- geometry in the *cisoid* transition state ***230*** relieves this interaction and was suggested to rationalize the observed *cis*-adduct. This interaction appears to dominate the reaction, despite the loss of conjugation of the



231 ***232*** ***233***

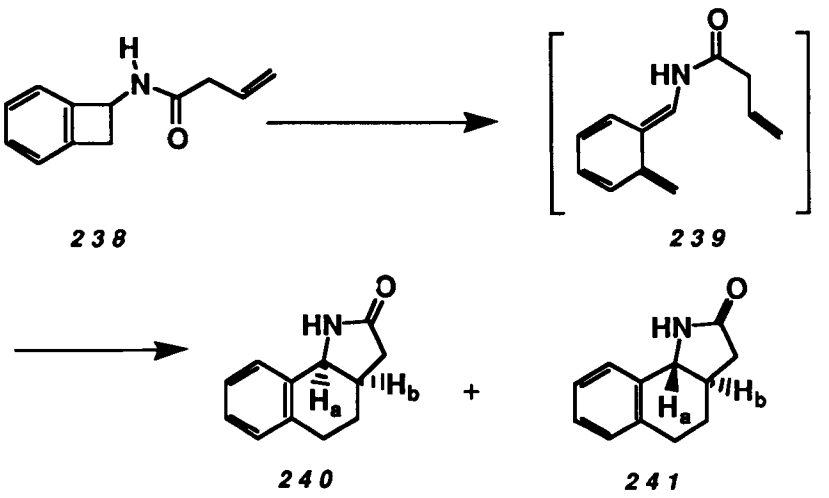
nitrogen lone pair and the diene π orbitals. In similar work relating to a synthesis of *cis*- dihydrolycoridine, Keck showed that ***231*** cyclizes to ***233*** via ***232***.[129] Treatment of ***231*** with triethylamine and chlorotrimethylsilane in DMF at 160°C generated ***232***, *in situ*, and cyclization gave ***233*** in 65% yield. The ring juncture was shown to be *cis*- rather than *trans*-, presumably via an *exo*-transition state.



234 ***235*** ***236***

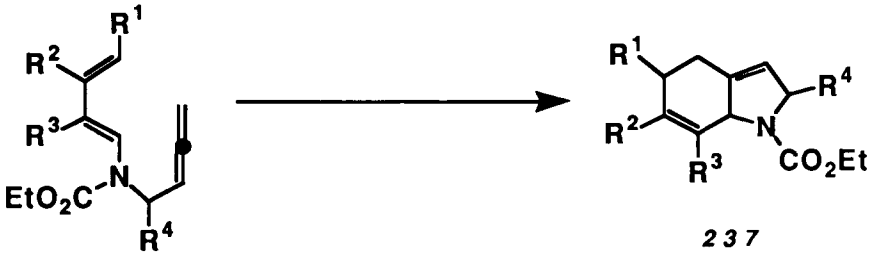
An extension of this work utilized an allene as the dienophile. Kanematsu described an intramolecular Diels-Alder reaction of allenic dienyl amide ***234*** for the synthesis of indoles.[130] Oxidation of the initial cycloadduct (***235***) to the indole (***236***) was accomplished with DDQ. A variety of indoles were synthesized in this manner via derivatives ***237*** in Table 26.[130]

An interesting and well-known variation of the reaction generates a transitory dienyl lactam via thermolysis of azabenzocyclobutane derivatives. Oppolzer showed that ***238*** opened to ***239*** on heating in refluxing toluene (16 h) to give a 4.7:1 mixture of the *cis*- and *trans*-cycloadducts, ***240*** and ***241***, respectively, in 96%



yield.[131] The proton NMR confirmed the geometry of the adduct. Cycloadduct ***240*** showed a signal for H_a at 4.76 ppm (d, J = 6.5 Hz) whereas H_a in ***241*** appeared at 4.26 ppm (d, J = 8.5 Hz). The two isomers were not interconverted in boiling toluene.

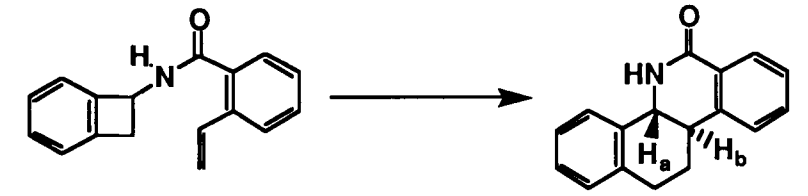
Table 26. Cyclization of Allenic Dienyl Amides.



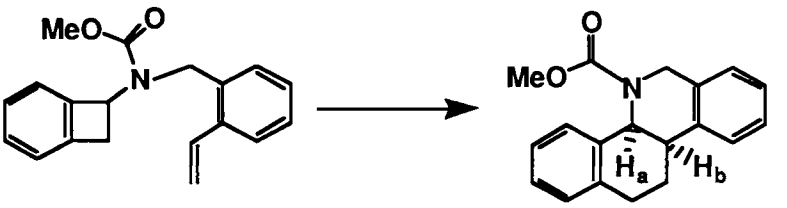
R^1	R^2	R^3	R^4	Conditions	% *237*
H	H	H	H	160°/9h	100
Et	H	H	H	200°C/16h	76
H	Me	H	H	160°C/8h	100
$-CH_2CH_2CH_2CH_2-$		H	H	160°C/12h	100
H	H	Et	H	100°C/10h	>75
H	H	H	Bn	100°C/5h	>74

As previously noted for dienyl amides, the carbamate alkenes showed the opposite stereochemistry from the alkyl amides.[28,29] Cyclization of amide ***242*** in

refluxing bromobenzene (16h) gave ***243*** in 90% yield with a *trans*-ring juncture. Cyclization of urethane ***37***, however, gave the *cis*-adduct (***244***) in 78% yield. The coupling constant ($J_{a,b}$) for ***243*** was 12.5 Hz and $J_{a,b}$ for ***244*** was 6 Hz. This methodology was used in a synthesis of *dl*-chelidonine.[28]



242 ***243***

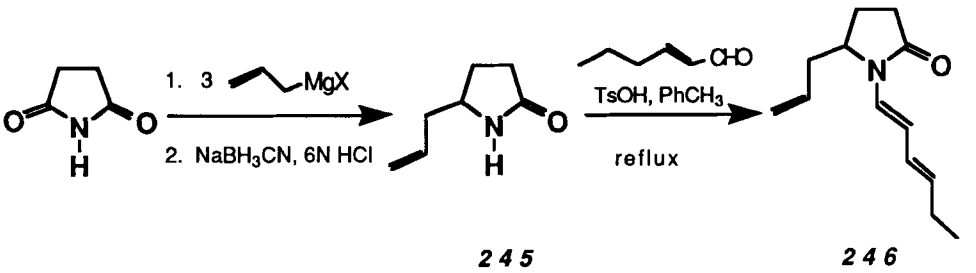


37 ***244***

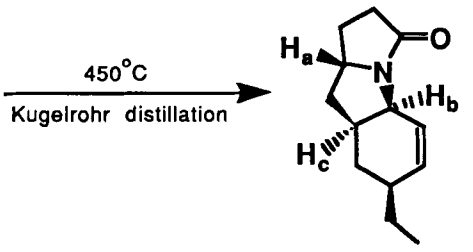
3b. Dienyl Lactams

The only reported example of an internal Diels-Alder cyclization with dienyl lactams was accomplished in our laboratories.[132] Initially, succinimide was reacted with excess allylic magnesium bromide, followed by reduction with sodium cyanoborohydride to give ***245*** in 43% yield. Subsequent reaction with 2-hexenal gave ***246*** in 72% yield. This triene was cyclized by two methods. First, ***246*** was heated in toluene (sealed tube, 235°C, *bis*-(trimethylsilyl) acetamide) using Oppolzer's conditions to give ***247*** in 53% yield. Passage of ***246*** through a hot tube (450°C, Kugelrohr distillation) and trapping at -78°C also gave ***247*** in 55%. Analysis of the ^{1}H NMR and COSY spectra indicated a *cis*- relationship for the lactam nitrogen and the 'arm' of ring b, as shown in ***247***. The COSY NMR spectrum showed no long range (W type) coupling between H_a-H_b or between H_a-H_c. There was strong coupling between H_b and H_c, however, suggesting a *cis*- relationship ($J_{b,c}$ = 6.5

Hz). Additional work with a chiral derivative is in progress. Attempts to convert dienyl pyroglutamates such as ***182*** to ***S-245*** failed due to the great steric hindrance to attack at the C_5 methylene. Similar attempts with *N*-protected derivatives gave mixed, but generally poor results. We are currently examining the preparation of alkenyl and alkynyl derivatives at C_5 via protected glutamic esters (open chain compound).

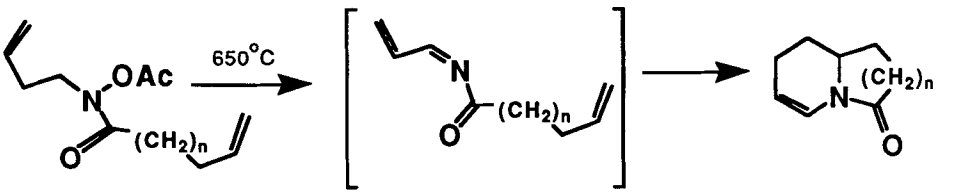


245 ***246***



247

3c. Acyl Azadienes

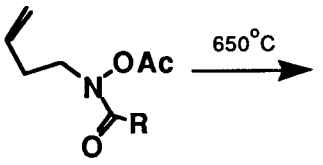


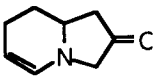
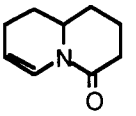
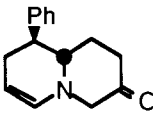
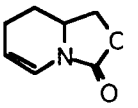
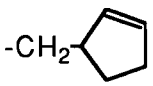
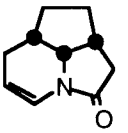
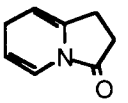
74 ***75*** ***76***

Fowler showed that O-acetyl-*N*-allyl amides undergo thermolysis at 650°C (hot tube, =1 μs contact time) to generate the corresponding indolizidinone.[45] Thermolysis of ***74*** (n = 2), for example, generated the acyl 1-azadiene ***75***, *in situ.* This

azadiene was not isolable but gave an internal Diels-Alder cyclization and the cycloadduct ***76*** in 75% yield.

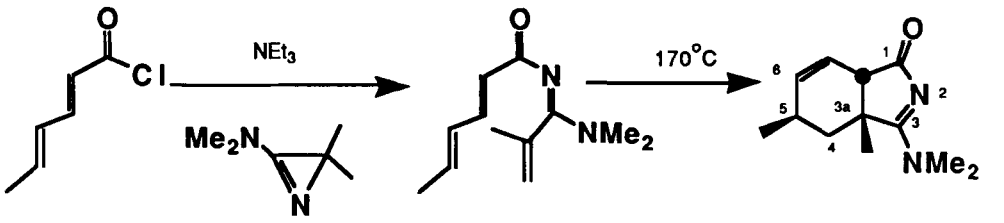
Table 27. Generation and Cyclization of *N*-Acyl Azadienes



R	Product	% *76*
$CH_2CH_2CH=CH_2$		75
$(CH_2)_3CH=CH_2$		69
$CH_2CH=CHPh$		74
$OCH_2CH=CH_2$		70
-CH_2- 		69
$CH_2CH_2C\equiv CH$		90

A variety of derivatives were been prepared by this method, as shown in Table

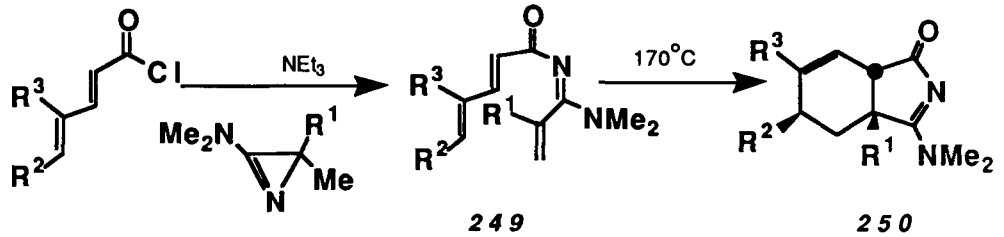
27.[45] A related acyl azadiene was prepared by Widmer and Heimgartner in a synthesis of tetrahydro-1-(1H)-isoindolones.[49] In this work the acid chloride of a dienoic acid (***86***) was treated with 3-dimethylamino-2,2-dimethyl-(2H) azirine (***87***)



86 ***87*** ***88*** ***248***

to give acyl amidine derivative ***88***. Thermolysis at 170°C gave the 3a,4,5,7a-tetrahydro-1-(1H)-isoindolone, ***248*** in 78% yield. The major diasteromer possessed a C_5 methyl as shown. Several examples of this reaction were given, as shown in Table 28,[49a] in which ***249*** was an intermediate to the cyclized product, ***250***.

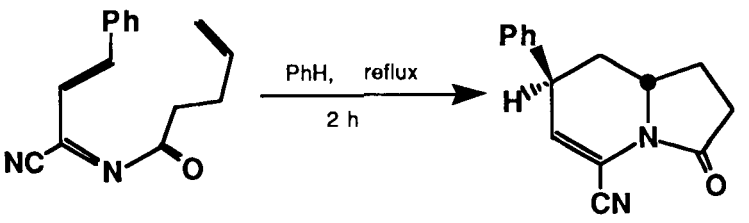
Table 28. Diels-Alder Cyclization to Tetrahydro-1-(1H)-isoindolones.



249 ***250***

R1	R2	R3	% *249*	% *250*
Me	Me	H	77	78
Me	H	H	65	70
Me	H	Me	61	63
Ph	Me	H	88	66

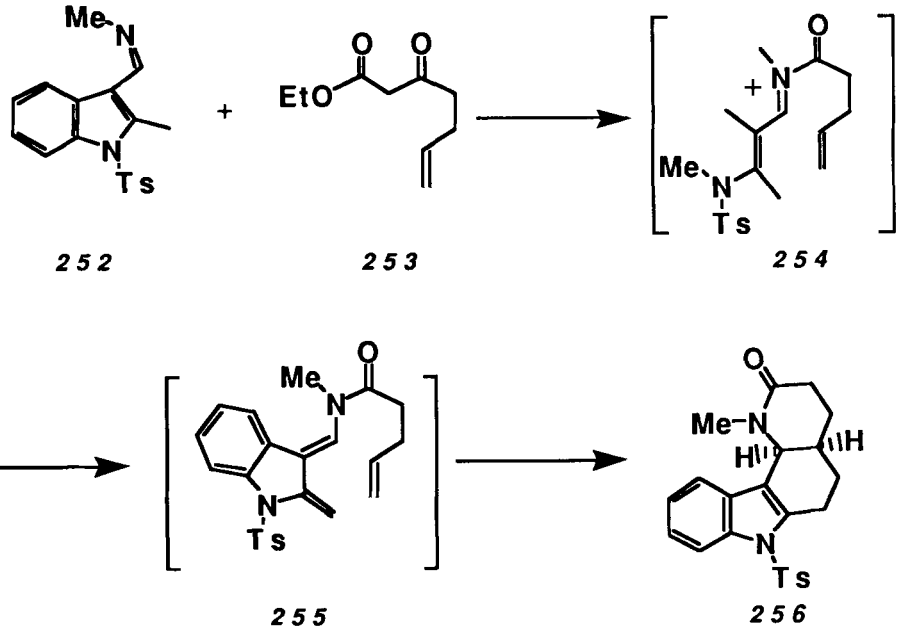
The *N*-acyl-α-cyano-1-azadiene prepared by Fowler (***85***)[49] also undergoes an internal Diels-Alder cycloaddition in refluxing benzene (2 hours) to give ***251*** in 54% overall yield from the dimethyl-*t*-butylsilylhydroxylamine derivative. The major product (>25:1) is ***251*** in which the phenyl substituent is *cis*- to the bridgehead



85 *251*

hydrogen (this is presumably the less stable isomer). The cyano group may increase the activation energy of the *endo*-transition state, leading to a preference for the *exo*-transition state and ***251***. There may also be a temperature effect and there is a general effect of substituents at the 3-position of the diene, which is known to increase the percent of *exo*-product.[49,133] The overlap of the nitrogen lone pair and the carbonyl group may also be more favorable in the *exo*-transition state.[49]

A similar acyliminium diene was generated by Magnus in a synthesis of indol-2,3-quinomethanes.[134] In this case imine ***252*** reacted with the mixed carbonic anhydride ***253*** (from ethyl chloroformate and 4-pentenoic acid) by heating to

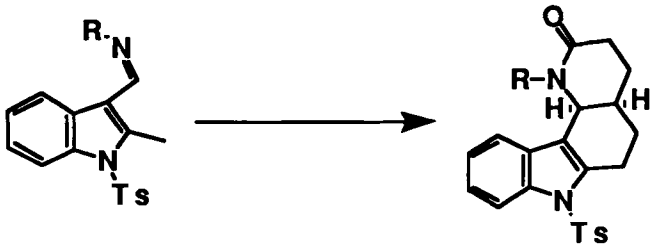


252 *253* *254* *255* *256*

135°C, to give the acyliminium salt ***254***. Rearrangement to ***255*** was followed by

intramolecular Diels-Alder cyclization to ***256*** in 40% yield. As shown in Table 29, cycloadduct ***257*** was formed, in good to moderate yield, in a variety of cases. The major by-product resulted from addition of ethoxide to iminium salt ***254*** and there was also a small amount of a β-lactam.

Table 29. Synthesis of Indol-2,3-quinodimethanes

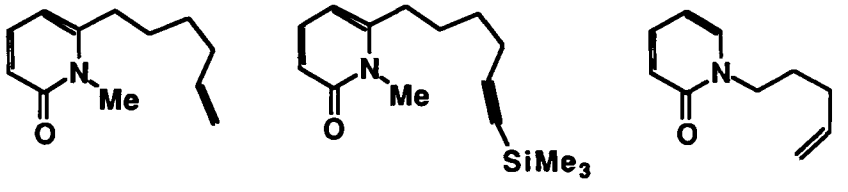


257

R	% *257*
$CH_2CH_2OCH_3$	55
CH_2CH_2SPh	60
CH_2CH_2SePh	22
$CH_2CH(OCH_3)_2$	58
CH2Ph	56
CH_3	40

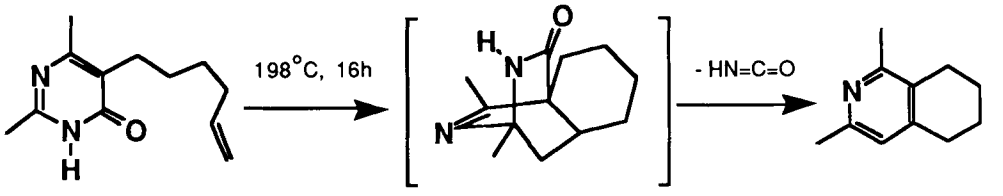
3d. 2-(1H)-Pyridones

Several examples of internal Diels-Alder cyclizations with substituted 2-pyridones were presented in Fallis' review.[9] Substituted alkenyl pyridones do not give an internal cyclization product under a variety of conditions. Pyridones ***258***,[135] ***259***[135] and ***260***,[135] for example, gave no Diels-Alder adduct up to 200°C in DMF. Beyond 200°C extensive decomposition was the predominate process.



258 ***259*** ***260***

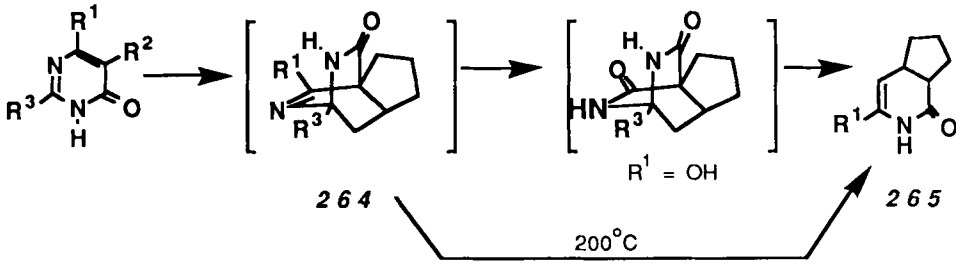
Pyrimidine derivatives such as ***261***, however, gave good yields of the internal cyclization product. Cyclization of pyrimidine ***261*** gave the transient Diels-Alder adduct ***262***, which thermally eliminated isocyanic acid (198°C/16h) to generate an annelated pyridine derivative ***263*** in 56% yield.[136]



261 ***262*** ***263***

This was a general reaction, in which prolonged heating of the initially formed cycloadduct ***264*** (in DMF) resulted in elimination of isocyanic acid and formation

Table 30. Cyclization of Alkenyl Pyrimidines.



264 ***265***

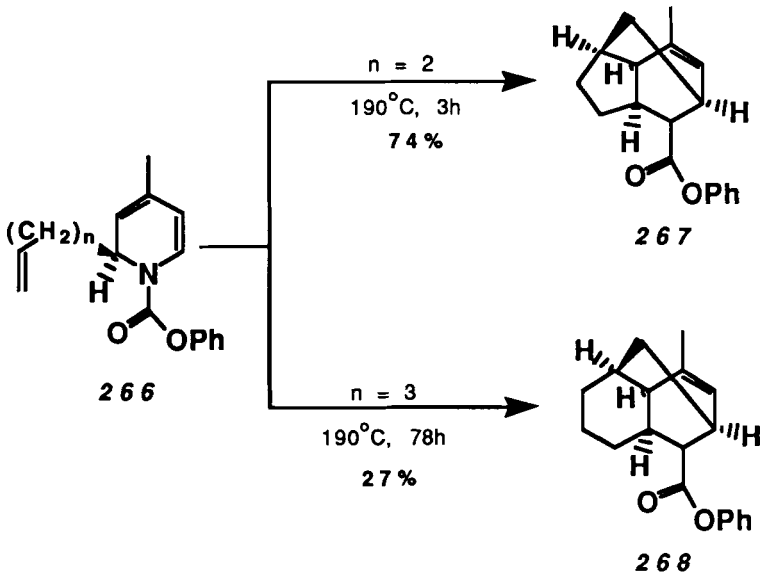
R1	R2	R3	% *265*
OH	$(CH_2)_2CH=CH_2$	Me	98
	"	Ph	59
Me	"	Me	65
Ph	"	Me	51
OH	$(CH_2)_3C\equiv CH$	Me	46
	"	Ph	40
OH	$CHMeCH_2CH_2C\equiv CCH_3$	H	87
OH	$(CH_2)_2C\equiv N$	Me	-
Me	$(CH_2)_4CH=CH_2$	Me	56
OH	$(CH_2)_4CH=CH_2$	Me	44

of a dihydropyridine (***265***).[136] This was a useful intermediate in the synthesis of

actinidine alkaloids.[137] Several examples of this latter cyclization are shown in Table 30.[136,137]

3e. *N*-Acyl-1,2-Dihydropyridines

Although the vast majority of Diels-Alder cyclization reported for this class of diene involves intermolecular reaction with dienophiles, Comins reported the internal cyclization of an *N*-acyl-1,2-dihydropyridine.[138] Heating ***266*** (n=2) to 190°C gave ***267*** in 74% yield. Increasing the chain length of the pedant alkenyl group decreased the propensity for cyclization, and ***266*** (n=3) required 48 hours for

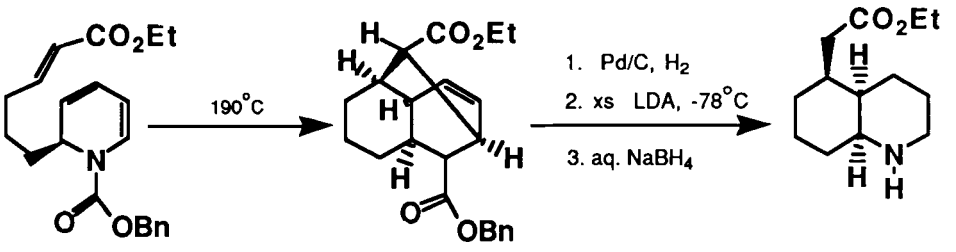


reaction and gave only 27% of ***268***. This method produced *cis*-decahydroquinolines and cyclization of ***269*** gave ***270*** in 55% yield. Hydrogenation and treatment with excess lithium diisopropyl amide opened the ring. Reduction of the resultant imine with aqueous sodium borohydride gave ***271*** in 32% overall yield (from ***269***)

.CONCLUSIONS

The chemistry developed for the preparation of dienyl amides and lactams is

extremely varied. From the formation of 1- and 2-amido butadienes to dienyl lactams, cleaver manipulation of functional groups and interesting condensation or



269 *270* *271*

thermolysis reactions were developed. Acyl azadienes also involved thermolysis of labile pre-cursors and gives a linkage to the chemistry of azadienes. The preparation of pyri-dones required a review of oxidation techniques, thermal rearrangements and a number of cyclization techniques. Reduction and Grignard approaches were used for the preparation of acyl dihydropyridines. A review of preparative routes to dienyl amides and lactams is, therefore, a useful review of a variety of interesting functional group transformations and carbon bond forming reactions.

Although the dienyl moiety in these compounds is expected to give the usual spectral characteristics of heterosubstituted dienes, there are interesting variations with diene type. Inclusion of the characteristic spectral data for each class of dienyl amide or lactam will assist the identification of these structural types.

The primary reaction of dienyl amides and lactams is the Diels-Alder reaction. There are reports of other reactions such as polymerization and alkylation via the amide or lactam enolate. This review focused on the cyclization reaction, however, to show the selectivity and reactivity in an important carbon bond forming process which has important implications to synthesis. Spectral data were again provided to assist the identification of the cycloadduct and especially the regio- and stereochemistry of the products. The internal cyclization showed interesting differences relative to the intermolecular cyclization. Not surprisingly, all classes of dienyl

compounds exhibited similar selectivity although the relative reactivity varied tremendously. A number of synthetic examples were included when appropriate.

Dienyl amides and lactams have become an important class of synthons for the preparation of naturally occurring compounds. The synthesis of heterocyclic compounds with interesting chemical or pharmacological properties is another important application. The intent of this review is to provide a glimpse of the preparation and utility of this class of compounds and to pique the interest of researchers for further development of these interesting dienes.

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