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## HETARYLDIENES: PROMISING BUILDING BLOCKS TO NEW POLYHETARYL DERIVATIVES

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## **Introduction**

Numerous literature data from the recent years reveal that properly substituted dienes bearing a hetaryl substituent can be used as interesting and useful building blocks for several syntheses. This recognition prompted the authors to provide a survey on synthetic methods leading to these compounds and also to summarise the most important application possibilities for their transformations. According to the dual goal of this paper, the first part deals with the synthetic variations classified according to the reaction types and, at the end of the descriptive part of this chapter, a collective table summarises the experimental data and references of the most important synthetic routes to hetaryldienes. The second part, subsequently, describes the most relevant transformations of hetaryldienes.

## **I. SYNTHESIS**

### **A. Syntheses involving compilation of the diene chain**

#### **A.1. Wittig-type syntheses**

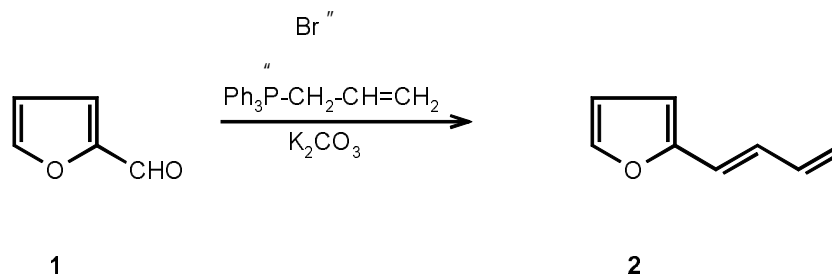
Two main approaches: the classical Wittig reaction (reaction of an aldehyde with a phosphorane) and the Wittig-Horner-Emmons reaction (reaction of an aldehyde with a phosphonic ester) have been widely used for the formation of one of the double bonds of hetaryldienes. Both of these can be classified depending on which functional group (*i.e.* the aldehyde function or the phosphorous reagent) has been provided by the hetarene compound.

##### **A.1.1. Starting from hetaryl aldehydes**

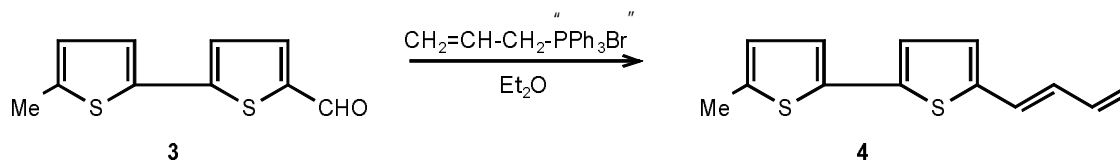
One of the most general routes to hetaryldienes is the Wittig reaction of hetarylaldehydes with allyltriphenylphosphonium bromide under basic conditions. Since the appropriate

aldehydes are often fairly stable and - in some cases - commercially available compounds, this procedure is highly suitable for the synthesis of various hetaryldienes.

Scheme 1



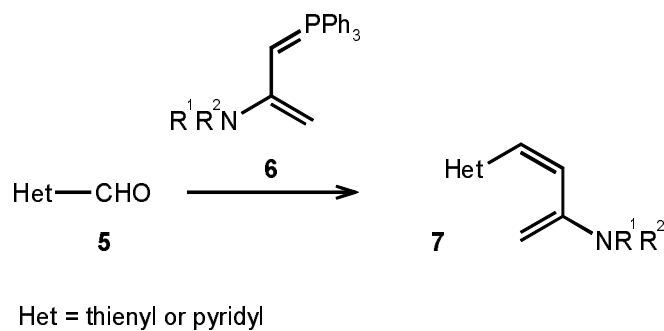
Scheme 2



Thus, 2-furanaldehyde (1) leads to 1-(2-furyl)butadiene (2) in high yield [1] and, similarly, the bithienyl aldehyde 3 affords the corresponding diene 4 [2] which is in fact a naturally occurring compound isolated from *Bidens radiata* [3].

A special application of this synthesis to piperidyl substituted dienes has also been reported [4]: the thienyl and pyridyl aldehydes 5 when treated with the amino substituted triphenylphosphorane derivative 6 afforded the 1-hetaryl-3-aminodienes 7 in good yield.

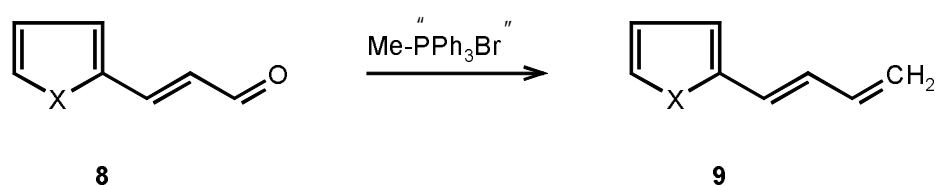
Scheme 3



### A.1.2. Starting from hetaryl acroleins

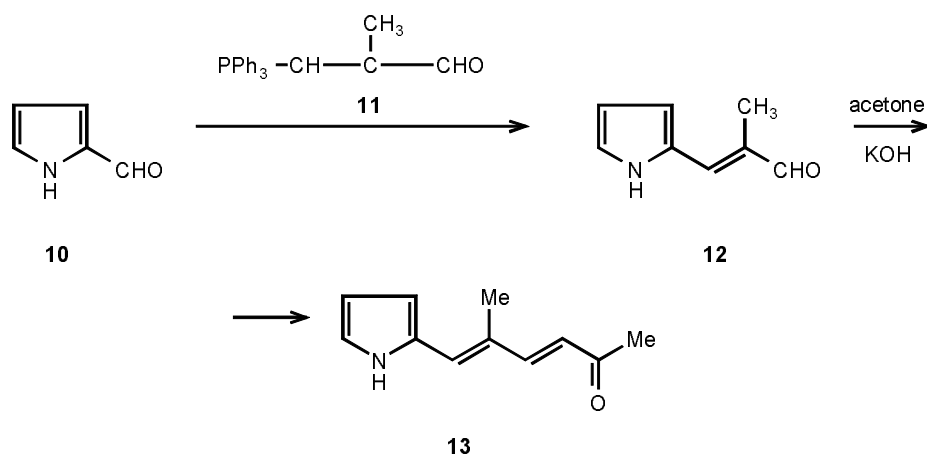
In contrast to the above procedures where one of the double bonds of the diene chain was delivered as a substituent of the Wittig reagent, numerous applications starting from hetaryl acrylaldehydes have been elaborated. Thus, in this synthetic strategy one double bond is provided by the hetarene-ring-containing component and the second one is formed by the Wittig reaction with the phosphorane-containing single carbon atom unit.

Scheme 4



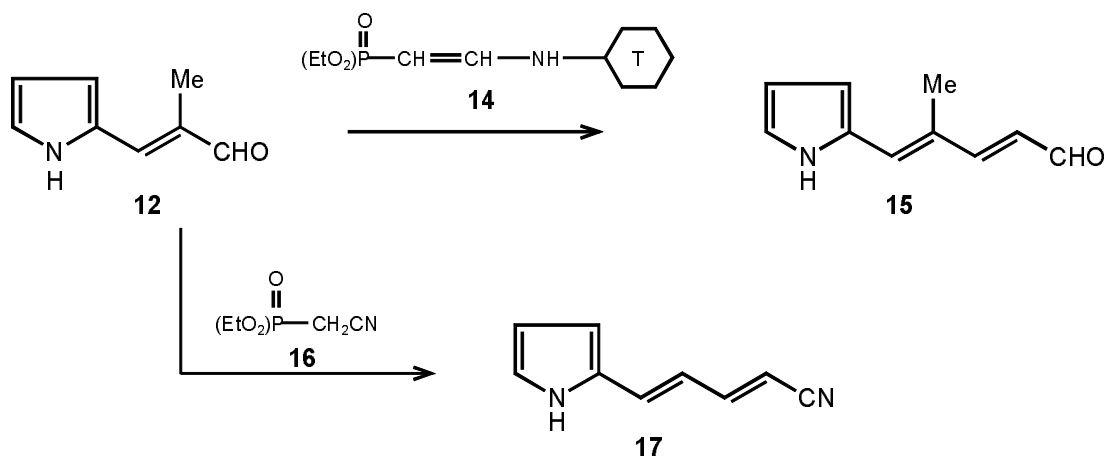
Thus,  $\beta$ -(2-furyl)- and (2-thienyl)acroleine (**8**, X = O, S) when reacted with methyltriphenylphosphonium bromide under basic conditions afforded 1-(2-furyl)- and 1-(2-thienyl)butadiene (**9**) in moderate yield [5]. Synthesis of the pyrrolyl substituted diene **13** has also been accomplished in a similar manner: the starting aldehyde **10** was converted first with formylpropylidene phosphorane (**11**) - also by a Wittig reaction - to the methacrylaldehyde analogue **12** which with a second molecule of the reagent was converted to the diene product **13** [6].

Scheme 5

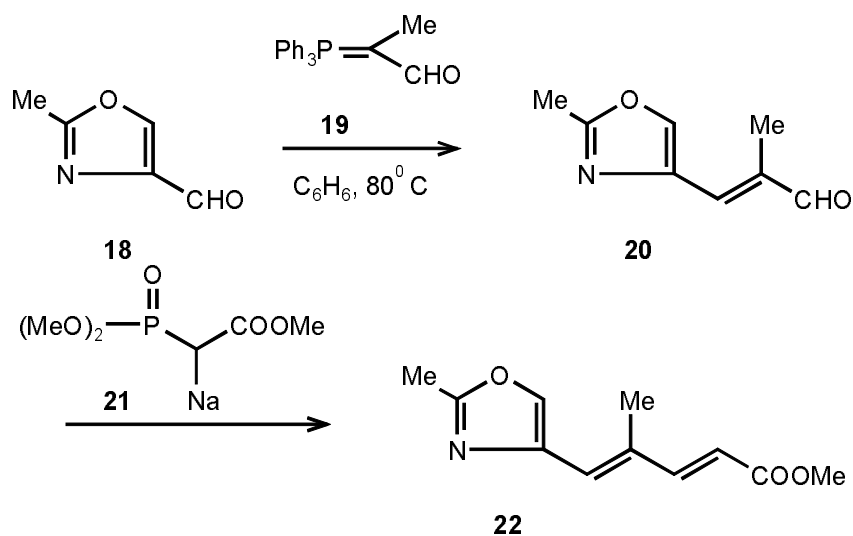


The intermediate methacrylaldehyde derivative **12** can also be treated with different reagents. Thus, reaction with the diethylphosphonate **14** gave the dienylyl aldehyde **15**, whereas use of reagent **16** led to the formation of the cyano-substituted diene **17**. [7]

Scheme 6



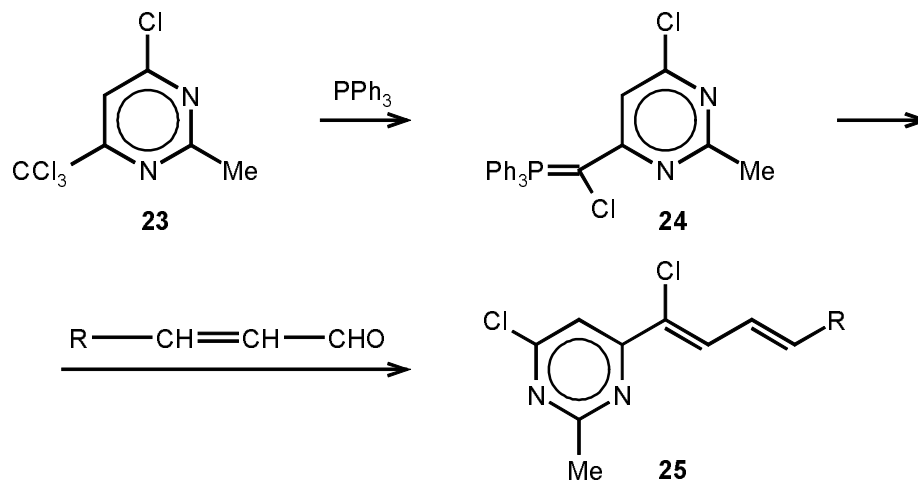
Scheme 7



A similar synthetic strategy as above has been applied for the synthesis of the oxazolyldiene carboxylic ester **22**: reaction of the starting aldehyde **18** and phosphorane **19** gave first the hetarylmethacrylaldehyde derivative **20** which upon treatment with the phosphonic ester (**21**) afforded **22** in high yield [8].

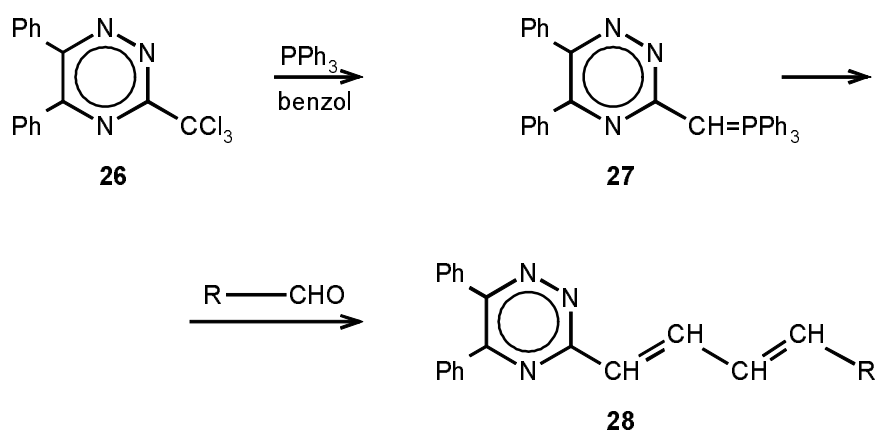
## A.1.3. Starting from hetarylphosphoranes

Scheme 8



Several synthetic approaches to hetaryldienes have been described where the Wittig reaction was carried out by starting from a hetarylphosphorane. Such derivatives can generally be obtained from trichloromethyl substituted hetarenes. Thus, 4-chloro-2-methyl-6-trichloromethylpyrimidine (**23**) was transformed by triphenylphosphine to the phosphorane **24** first which upon reaction with an unsaturated aldehyde gave the end product **25** [9].

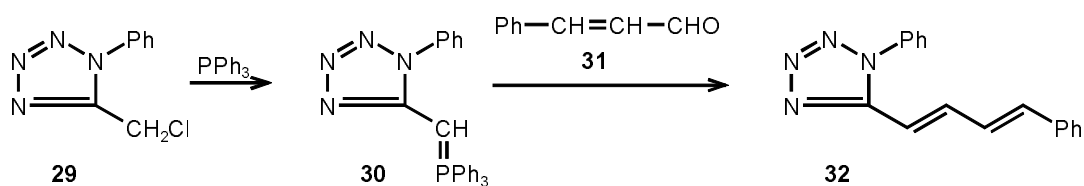
Scheme 9



A similar method has been applied for the synthesis of two *as*-triazinyldiene derivatives (**28**, R = Me and Ph): 5,6-diphenyl-3-trichloromethyl-[1,2,4]triazine (**26**) was

transformed - by using two molar equivalents of triphenylphosphine - to the phosphorane **27** which reacted with the appropriate aldehyde to give the final product **28** [10]. The method also proved to be suitable for the synthesis of five membered hetarene derivatives: the chloromethyl substituted tetrazole **29** easily gave the phosphorane **30** which was reacted with cinnamic aldehyde (**31**) under mild conditions to yield the phenyl substituted tetrazolyldiene **32**.

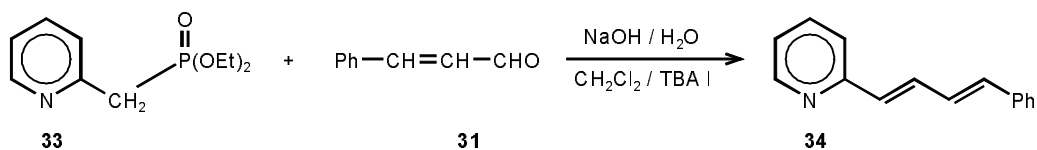
Scheme 10



#### A. 1.4. Starting from hetarylmethylene phosphonic esters

As mentioned in the introductory part, the Wittig-Horner-Emmons synthesis of hetaryldienes can also be accomplished by the reaction of a hetarylphosphonic ester and an aldehyde. The following three examples convincingly show that this methodology can be usefully applied to the synthesis of various hetarene derivatives

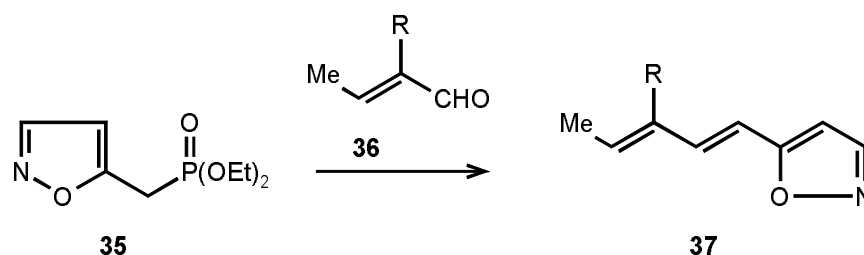
Scheme 11



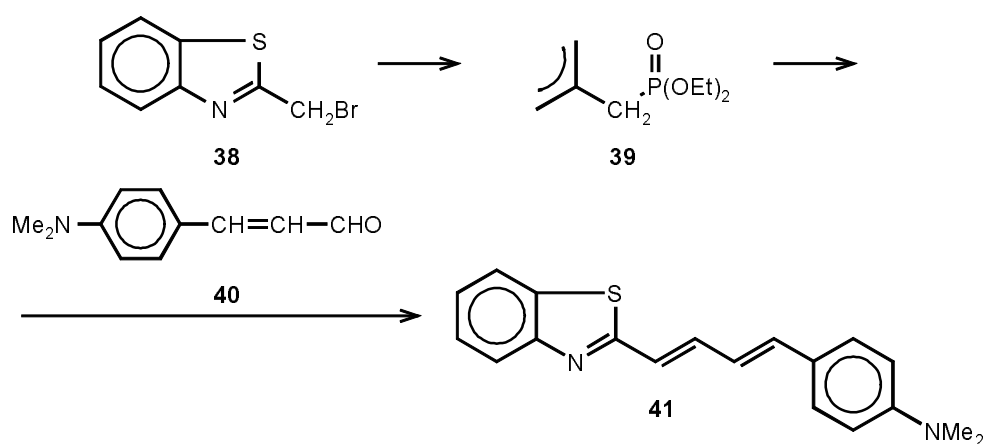
Reaction of cinnamic aldehyde (**31**) with diethyl 2-pyridylmethylphosphonic ester (**33**) under phase transfer conditions gave 1-(2-pyridyl)-4-phenylbutadiene (**34**) [11, 12]. The isoxazolylmethylphosphonic ester (**35**) when reacted with the aldehyde **36** afforded the corresponding isoxazolybutadiene (**37**) [13], whereas the benzthiazolyphosphonic ester **39** - easily obtainable from the bromomethyl compound **38** - was reacted with *p*-dimethylaminocinnamic aldehyde **40** and yielded the deep yellow benzthiazolybutadiene **41** [14].



Scheme 12



Scheme 13

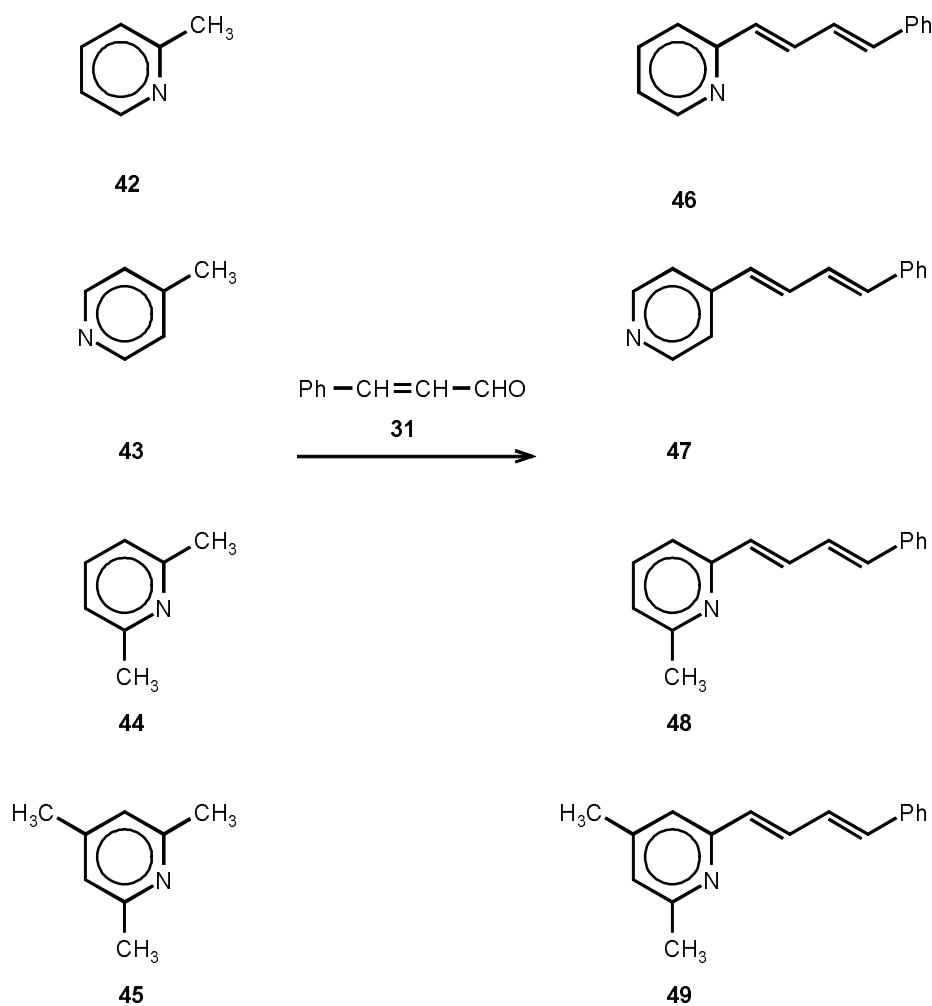


## A.2. Synthesis of the diene chain by the use of other condensation reactions

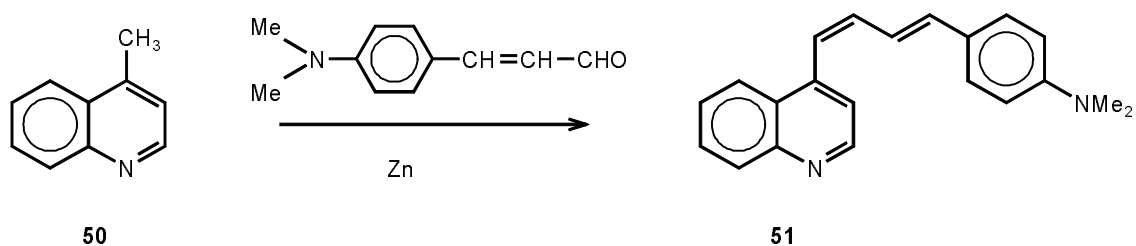
### A.2.1. From methyl substituted hetarenes

$\alpha$ -Methylhetarenes generally undergo condensation reactions with aldehydes under acidic or basic conditions to give olefins. This reactivity can be usefully exploited for the synthesis of hetaryldienes with unsaturated aldehydes as reaction partners. According to this procedure various methylpyridines like 2-picoline (**42**) [15], 4-picoline (**43**), 2,6-dimethylpyridine (**44**) and [2,4,6]collidine (**45**) [16] can be converted to the corresponding substituted 1-pyridyl-4-phenylbutadienes **46**, **47**, **48**, and **49**, respectively. The yields of these conversions are, unfortunately, rather poor in most cases.

Scheme 14



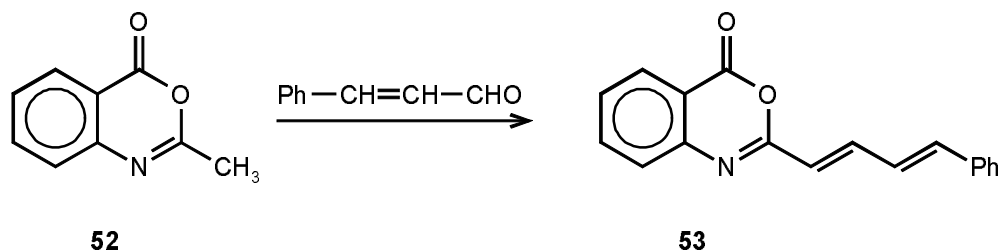
Scheme 15



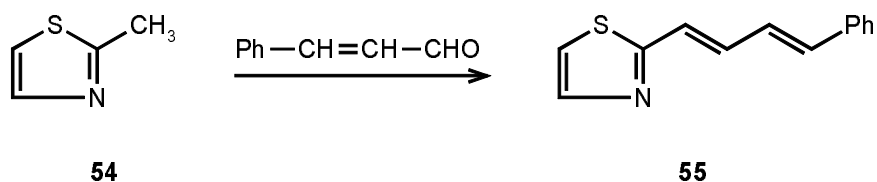
This approach can be applied to benzologues, other six membered heterocycles, and five membered heteroaromatics, too. Thus, 4-methylquinoline **50** leads to the substituted phenyldiene **51** [17], 3-methylbenzoxazinone **52** affords, similarly, the diene **53** [18],

whereas 2-methylthiazole (**54**) can be converted to 1-(2-thiazolyl)-4-phenylbutadiene (**55**) although only in poor yield [19].

Scheme 16

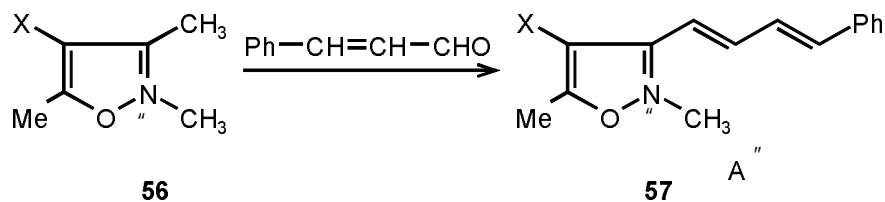


Scheme 17

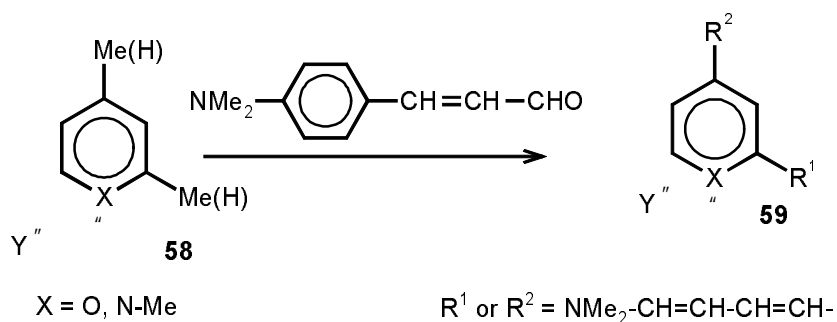


Condensation reaction of the hetarylmethyl group is particularly easy with quaternary compounds. Accordingly, the N-methylated salt **56** reacts smoothly with cinnamaldehyde to give the diene **57** [20], the six membered pyridinium and pyrylium salts **58** ( $X = \text{N}$  or  $\text{O}$ , respectively) can be readily converted to the corresponding dienes (**59**) in high yield [21].

Scheme 18

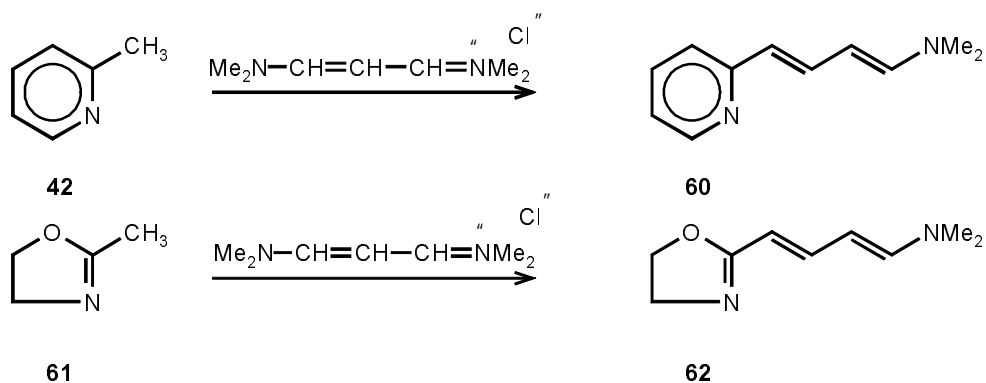


Scheme 19



Instead of aldehydes, masked aldehydes like substituted vinamidinium salts can also be successfully used as reagents in the same transformations. This is nicely demonstrated by the following two examples: both  $\alpha$ -picoline (**42**) and 2-methyloxazolidine (**61**) react with tetramethyl-vinamidinium chloride - which can be regarded as a masked  $\gamma$ -aminoacroleine - to give 1-(2-pyridyl)-4-dimethylaminobutadiene (**60**) and 1-(2-oxazolidinyl)-4-dimethylaminobutadiene (**62**), respectively.

Scheme 20

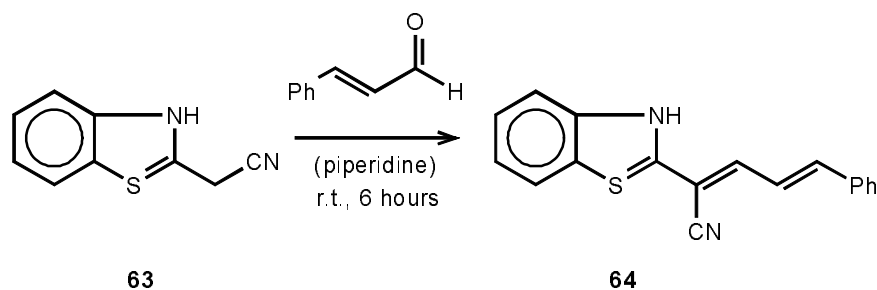


### A.2.2. By miscellaneous condensation reactions

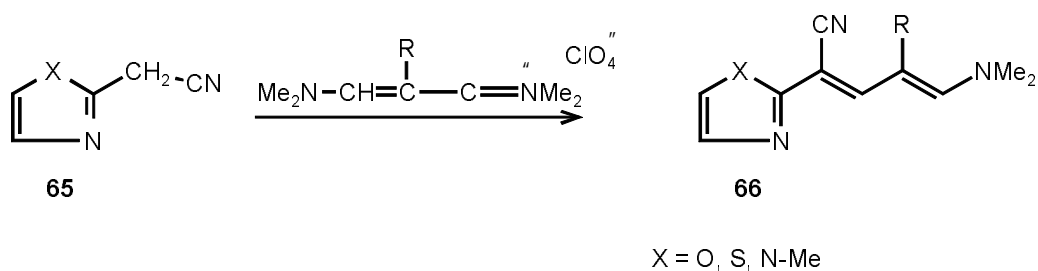
Heteroarenes bearing an active methylene group in the side chain are also suitable starting materials for condensation reactions with unsaturated aldehydes to heteraryldienes. Thus, 2-cyanomethylbenzothiazole (**63**) when reacted with cinnamaldehyde affords 1-benzothiazolyl-1-cyano-4-phenylbutadiene (**64**) in high yield [22]. The same transformation - similar to the previous chapter - can also be carried out by vinamidinium

salts as masked aldehydes. Thus, 2-cyanomethyl substituted azoles (**65**) can easily be transformed to the corresponding 1-azolyldieneamines (**66**) [23].

Scheme 21

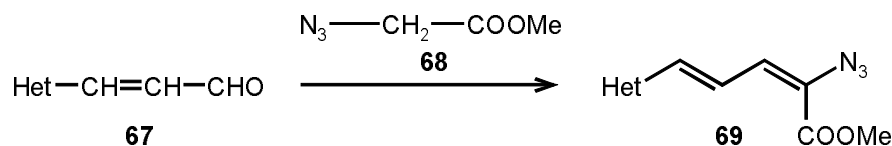


Scheme 22

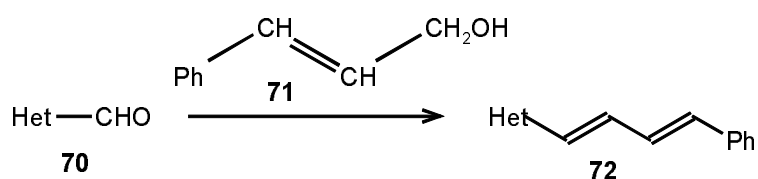


$\alpha,\beta$ -Unsaturated aldehydes attached to a heteroarene can participate in condensation reaction with the active methylene group of methyl azidoacetate (**68**) to give 4-azido substituted 1-hetaryldiene 4-carboxylic esters. Thus, the aldehyde **67** (Het = various five membered heteroaromatics) afforded the diene compound **69** [24, 25].

Scheme 23



Scheme 24



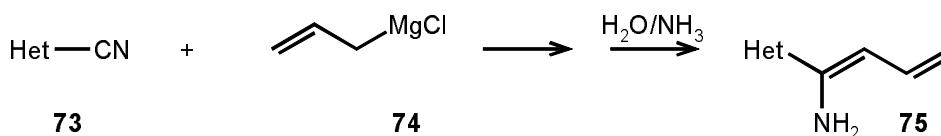
Finally, cinnamic alcohol (71) can react with a hetarene aldehyde (70) to give 1-hetaryl-4-phenylbutadienes 72. This conversion has successfully been applied for 2-furyl-, 2-thienyl- and 3-pyridyl derivatives [24].

### A.3. Synthesis of the diene chain by other methods

#### A.3.1. From a nitrile with Grignard reagent

A special group of hetaryldienes: those bearing also an amino moiety in position 1 is available by the reaction of hetarylnitriles 73 and allylmagnesium chloride (74). The primarily formed complex when worked up with aqueous ammonia affords the 1,1-disubstituted diene products (75) [26].

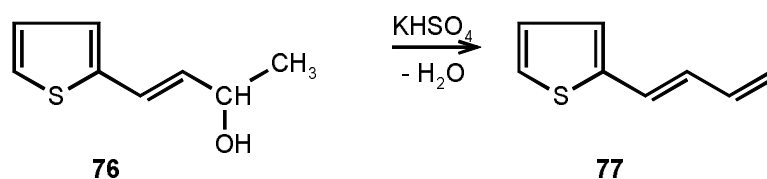
Scheme 25



#### A.3.2. Syntheses utilising dehydration

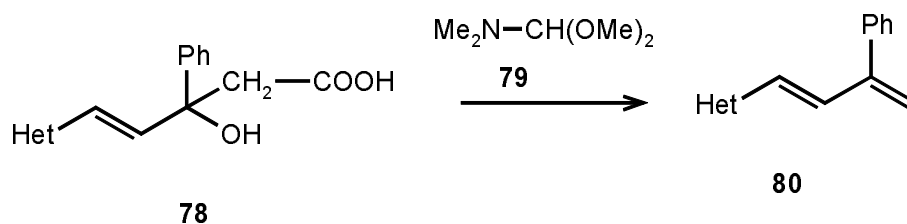
In numerous cases the diene chain of hetaryldienes has been formed by dehydration reaction of a substituted allyl alcohol derivative. The removal of water proceeds in some cases under very mild conditions. Thus, the thienyl derivative 76 can easily be transformed by potassium hydrogensulfate to the thienyldiene 77 [27], which product, however, proved to be rather unstable.

Scheme 26



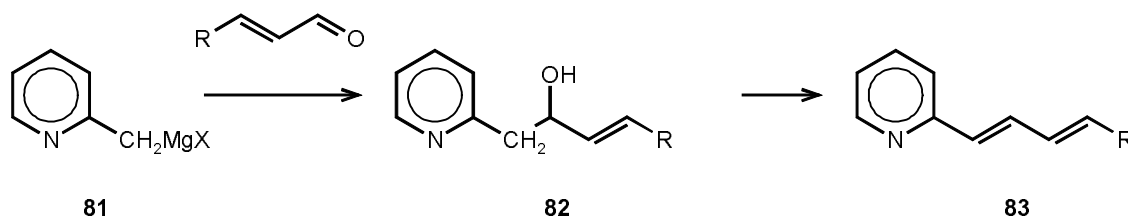
Treatment of **78** (Het = thienyl or furyl) with dimethylformamide dimethylacetal (**79**) leads to similar results, the difference from the transformation **76**  $\rightarrow$  **77** is that a decarboxylation step takes also place and the 1,3-disubstituted diene **80** (Het = 2-furyl and 2-thienyl) is formed [28].

Scheme 27



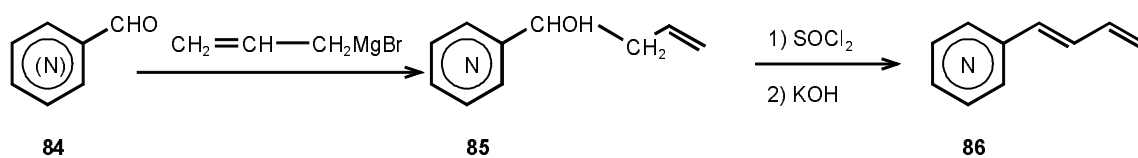
In contrast to the above two starting hetarylethenyl derivatives (**76** and **78**), hetarenes bearing a substituent through a saturated carbon atom can also serve as a precursor to dienes as shown by the following three examples.

Scheme 28

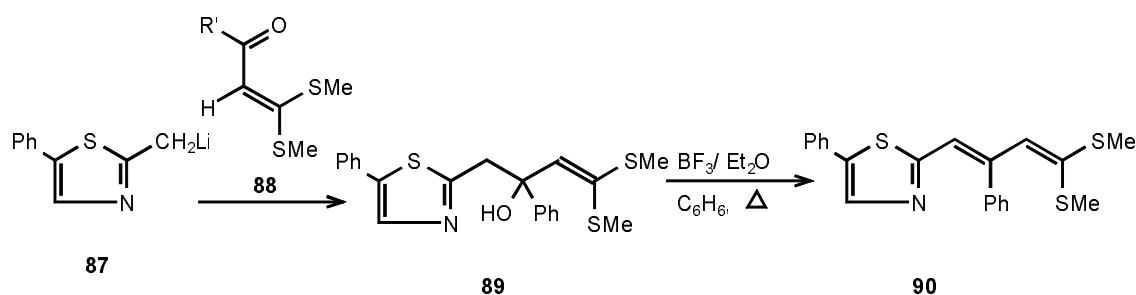


The secondary allyl alcohol **82** which can be synthesised from the pyridyl Grignard reagent **81** and an acrolein derivative undergoes facile elimination to give the corresponding 1,4-disubstituted diene **83** [29]. A similar starting compound (**85**) can be prepared from pyridyl aldehyde **84** and allylmagnesium bromide which upon treatment with thionyl chloride affords pyridyldienes (**86**) unsubstituted at position 4 [30]. An analogous methodology was also successfully applied to the synthesis of a thiazolyldiene (**90**): the lithiated derivative of 2-methyl-5-phenylthiazole (**87**) when reacted with the substituted formylketene dithioacetal (**88**) gave first the secondary alcohol addition product **89** which underwent water elimination on treatment with boron trifluoride etherate to give the thiazolyldiene **90** [31].

Scheme 29



Scheme 30

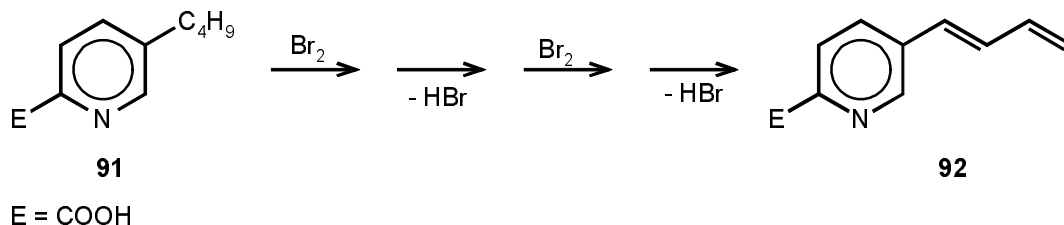


### A.3.3. Synthesis of the diene chain by dehydrobromination

One example is known where the diene side chain of a hetaryldiene has been formed by successive bromination and dehydrobromination steps starting from a butylhetarene: 5-butylpyridine 2-carboxylic acid (**91**, "fusarinic acid") proved to be a suitable starting compound for this purpose and afforded the 3-pyridyldiene derivative (**92**) in 4 reaction steps [32].



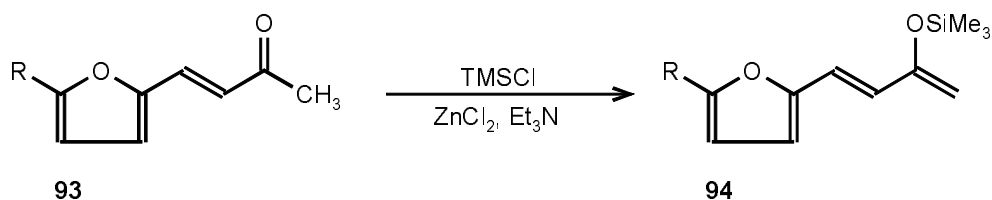
Scheme 31



#### A.3.4. Formation of the diene chain by oxo-enol tautomerism

$\beta$ -Hetaryl- $\alpha,\beta$ -unsaturated ketones can also serve as starting compounds to dienes if the keto function can participate in an oxo-enol tautomerism and undergoes further transformation to a derivative of the enol tautomeric form. This method has been applied in the case of the furyl-ethenylketone **93** which upon trimethylsilylation afforded the trimethylsilyloxy substituted furyldiene **94** [33].

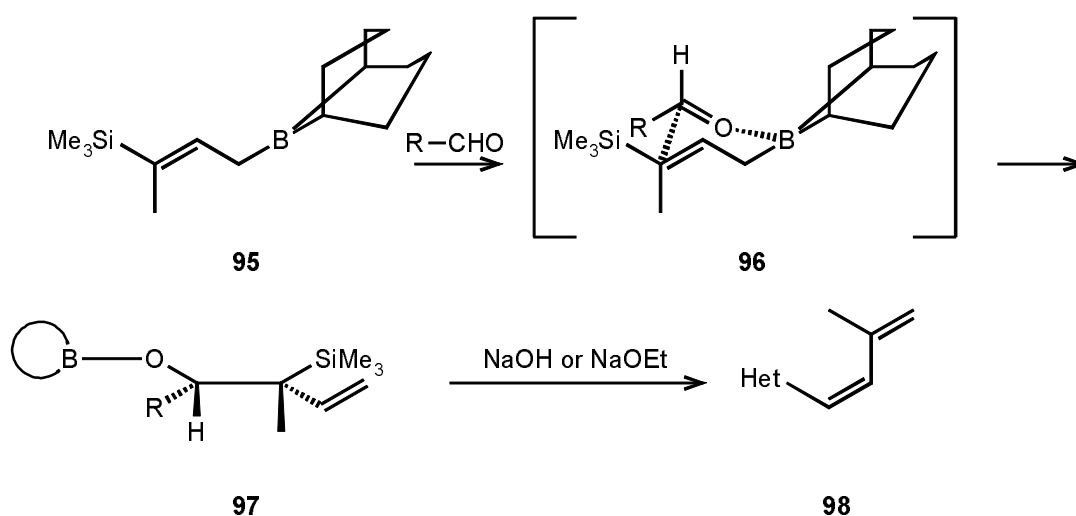
Scheme 32



#### A.3.5. Peterson olefin formation

The "Peterson" olefin formation has also been successfully applied to the synthesis of a series of hetaryldienes. In this procedure the 9-BBN derivative **95** is reacted first with a hetaryl aldehyde to give - *via* formation of the transition state **96** and subsequent rearrangement - the intermediate (**97**). This compound undergoes *syn* elimination in the presence of a base (sodium hydroxide or sodium ethoxide) to give the final hetaryldiene **98**. Because of the *syn* nature of the last elimination step, the product has necessarily a 1-*cis* geometry [34].

Scheme 33



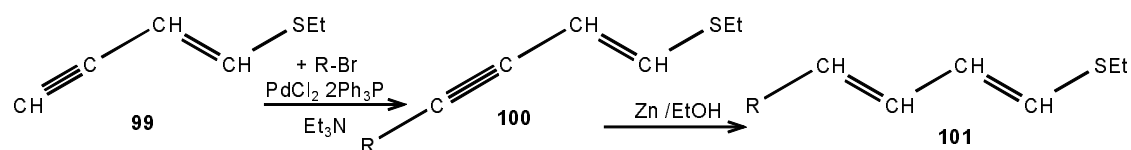
### B. Synthesis of hetaryldienes from other functionalised polyenes

In the following two chapters (B.1. and B.2.) such reactions affording hetaryldienes will be described that start from already existing dienes, and the hetarene side chain is either introduced by a coupling reaction or formed by a ring closure.

#### B.1. Cross-coupling reaction of substituted dienes

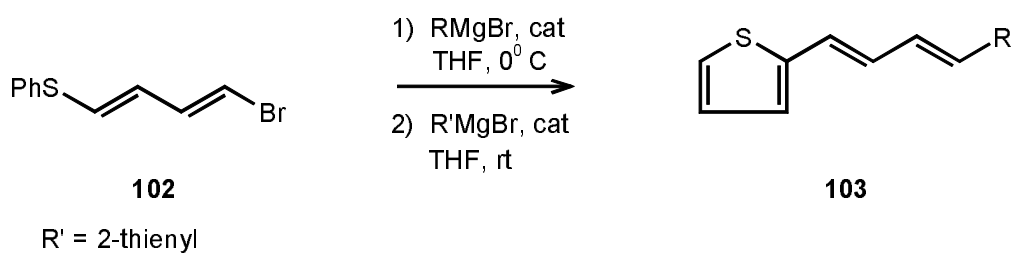
Transition metal catalysed cross-coupling reaction is a straightforward method for attaching a polyene to a hetaryl group. Thus, compound **99** was coupled first with a bromohetarene to give the acetylene-containing product **100** which upon reduction with zinc yields the dienethioether **101**. Both steps take place in good to excellent yields and can be applied to a variety of heteroaromatic (*i.e.* R = 2-furyl, 2- and 3-thienyl, 2- and 3-pyridyl) halides [35].

Scheme 34



A more complicated synthetic strategy taking use of the cross-coupling methodology has been applied to a double coupling of 1-bromo-4-phenylthiodiene (**102**). In this case, two successive couplings have been carried out: the first one taking place at the bromine atom at 0 °C, followed by the coupling at the other terminal of the chain, *i.e.* on the PhS group which can be completed at room temperature to give the final diene **103**.

Scheme 35

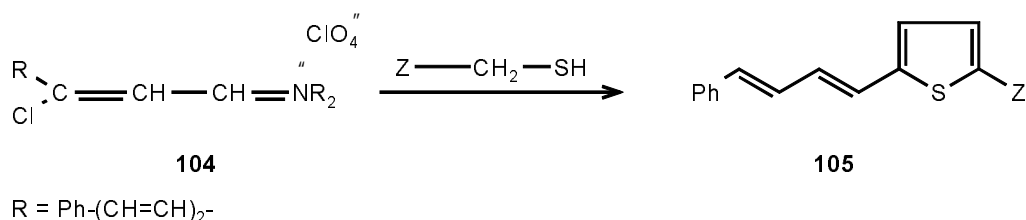


## B.2. Ring closure reaction to hetarenes starting from substituted dienes

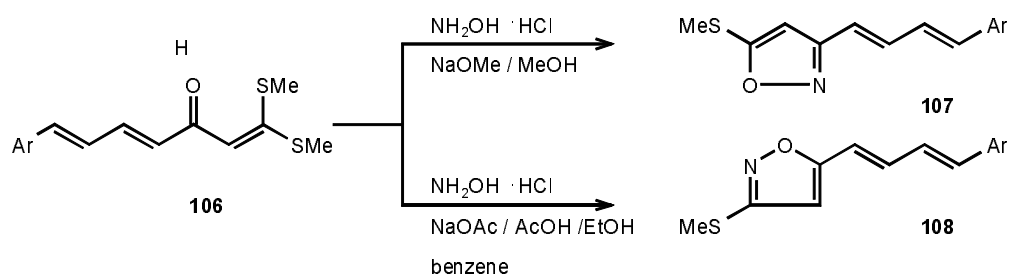
### B.2.1. Formation of 5-membered rings

The iminium salt **104** containing a reactive chlorine atom in the  $\gamma$  position was found to be suitable starting compound for a ring closure to thiophene derivatives. If the R substituent of **104** is a phenyldienyl chain this procedure affords substituted 1-(2-thienyl)-4-phenyldienes (**105**) [36].

Scheme 36

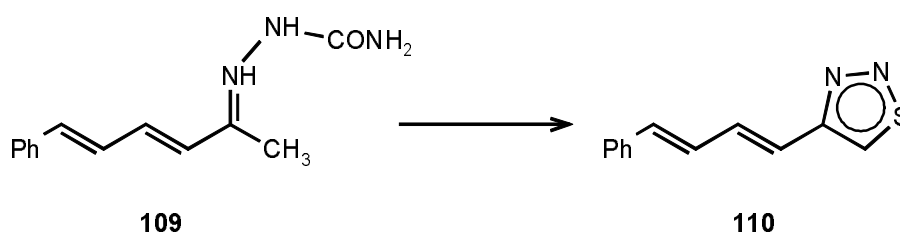


Scheme 37



Ring closure of the side chain of diene **106** with hydroxylamine was carried out under two different reaction conditions: in the presence of sodium methoxide the isoxazolyldiene **107** was obtained, whereas in a mixture of sodium acetate-acetic acid-ethanol-benzene the reaction proved to be regioselective in the other way around and afforded the isomeric **108** product [37].

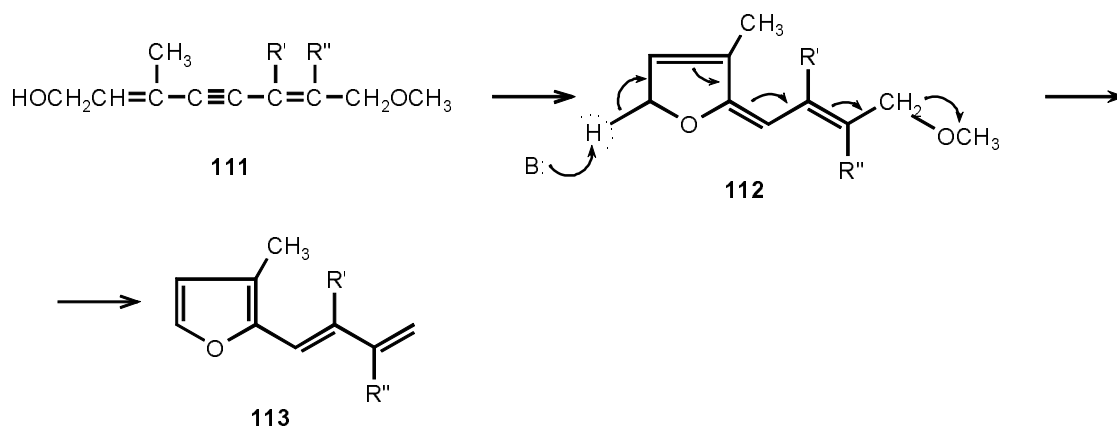
Scheme 38



Ring closure to the 1,2,3-thiadiazole compound bearing a diene side chain (**110**) starting from the semicarbazone **109** has also been reported [38].

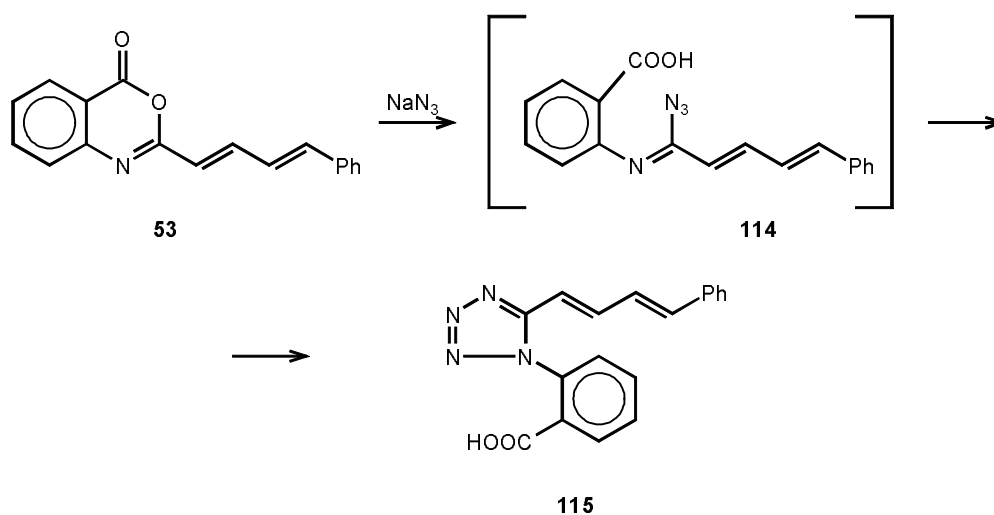
A fairly complicated route starting from the variously substituted polyene **111** to a series of 2-furyldienes has been described: in the first step a ring closure to form the furan ring takes place to afford the intermediate **112**, which by a base-promoted deprotonation (and by the shift of the remaining electrons as shown by the arrows) induces a [1,8] elimination to yield the furyldiene **113**. [63].

Scheme 39



The oxazinyll substituted diene (**53**) discussed already in an earlier chapter (A.2.1.) of this paper underwent a ring opening and subsequent ring closure reaction to yield a tetrazolyldiene: in the first step an azidoazomethine (**114**) was formed which underwent a 1,5-dipolar cyclisation to the final product **115** [18].

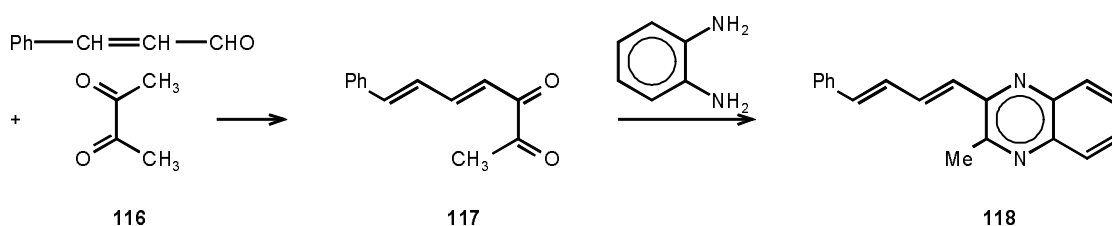
Scheme 40



### B.2.2. Formation of 6-membered rings

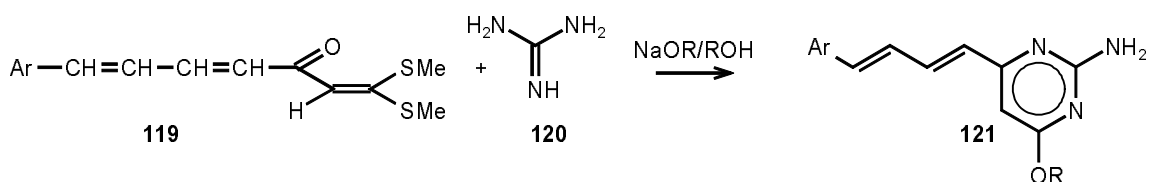
Two examples can be found in the literature where a six membered heterarene is formed by ring closure as a substituent of a diene chain. The first such case was published in the early fifties: the dienyl-methylglyoxal derivative **117** which was obtained from diacetyl (**116**) and cinnamic aldehyde was subjected to a condensation reaction with *o*-phenylenediamine to give the quinoxalyldiene compound **118** [39].

Scheme 41



A more general route has been elaborated for pyrimidinyldienes: the aryldiene bearing an  $\alpha,\beta$ -unsaturated ketone side chain (**119**) was treated with guanidine (**120**) under basic conditions to give 1-(2-amino-4-alkoxypyrimidin-6-yl)-4-aryl diene (**121**) dienes in acceptable yield [40].

Scheme 42

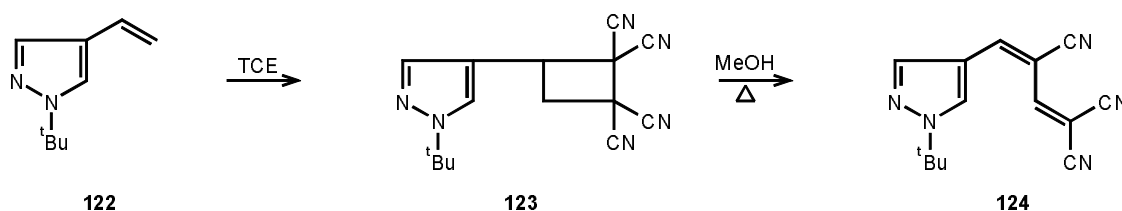


### C. Formation of hetaryldienes by ring opening reactions

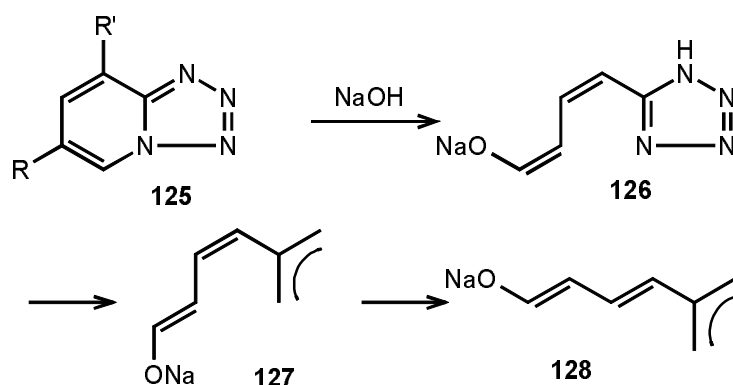
### C.1. Ring opening of neutral systems

The tetracyanocyclobutane derivative **123** which was obtained as a [2+2] cycloadduct of the ethenylpyrazole compound **122** and tetracyanoethylene (TCE) was found to open up in methanol to the tricyanodienylpyrazole **124** in excellent yield. The reaction also involves the elimination of one molecule of hydrogen cyanide [41].

Scheme 43

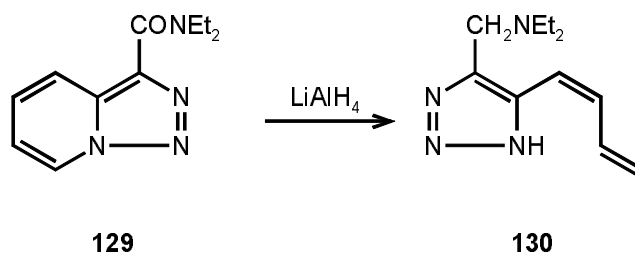


Scheme 44



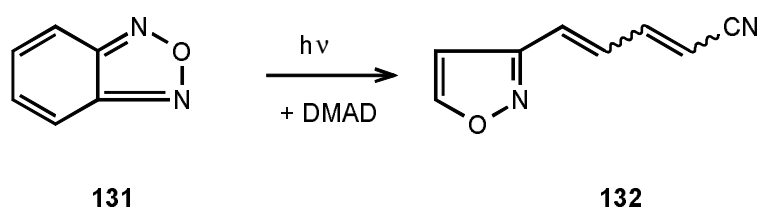
Various substituted tetrazolopyridines (**125**) were found to undergo ring opening to tetrazolyldienes under basic conditions to yield sodium dienolates. Detailed NMR study of this reaction revealed that the ring opening results both in a 1-*cis*-3-*cis*-(**126**) and a 1-*cis*-3-*trans*-diene (**127**), and both can be converted to the more stable 1-*trans*-3-*trans* isomer (**128**). [42]. A similar transformation was found with a [1,2,3]triazolopyridine derivative (**129**): this compound when treated with lithium aluminiumhydride afforded a triazinylidene (**130**) [43].

Scheme 45



An interesting ring opening of benzofurazan **131** to an isoxazolyldiene (**132**) under irradiation has been reported [44]: three different geometric isomers have been found and isolated from the reaction mixture.

Scheme 46



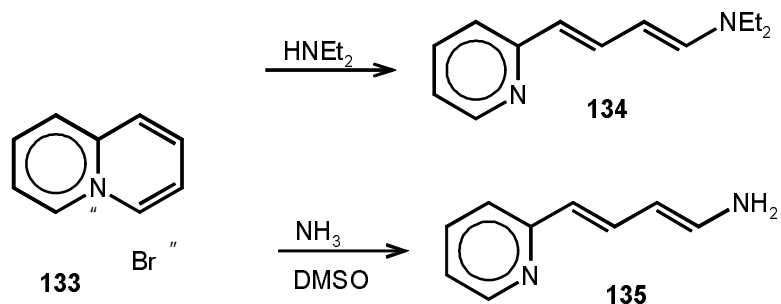
### C.2. Ring opening of positively charged systems with a bridge head nitrogen atom

Numerous examples reveal that fused azinium salts containing a bridge-head nitrogen atom are excellent precursors for heterodylenes. In these reactions a nucleophilic reagent is needed which can attack the azinium moiety to form an addition product first which - via a retroelectrocyclisation - affords the diene bearing the hetero ring fused originally to the particular azine. The below cases convincingly show the general applicability of this procedure.

The ring opening of quinolizinium salts (**133**) to pyridyldieneamines was studied in details. The reaction proceeds in acceptable yield with various secondary amines (derivatives **134** are formed) [45] and is almost quantitative in the case of reactions with ammonia to the free aminodienes **135**, [46]. The reaction has been nicely extended for benzologues yielding quinolyl and isoquinolyldienes [47].

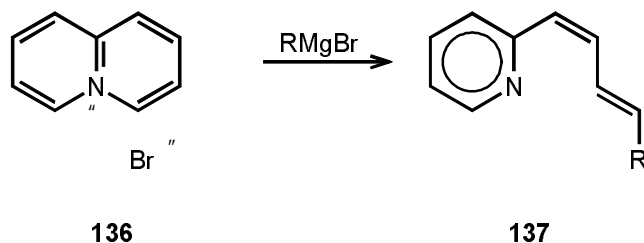


Scheme 47

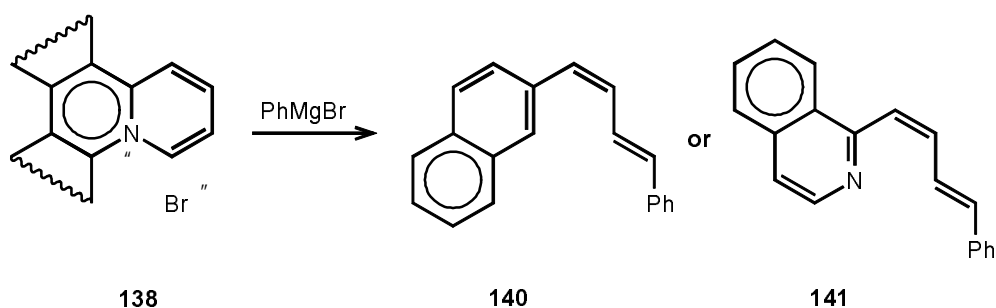


Grignard-reagents as nucleophiles have also been applied to the ring opening reactions of quinolinium salts (**136**) to pyridyldienes. In these transformations the alkyl or aryl group of the reagent acts as a nucleophile to be attached to the terminal position of the diene chain: e.g. 1-hetaryl-4-phenylbutadienes (**137**) have been synthesised by this route [48]. The method was applied to the tricyclic benzologues (**138**) as well affording pyridyl- (**139**), quinolyl- (**140**) and isoquinolyldienes (**141**) [49].

Scheme 48



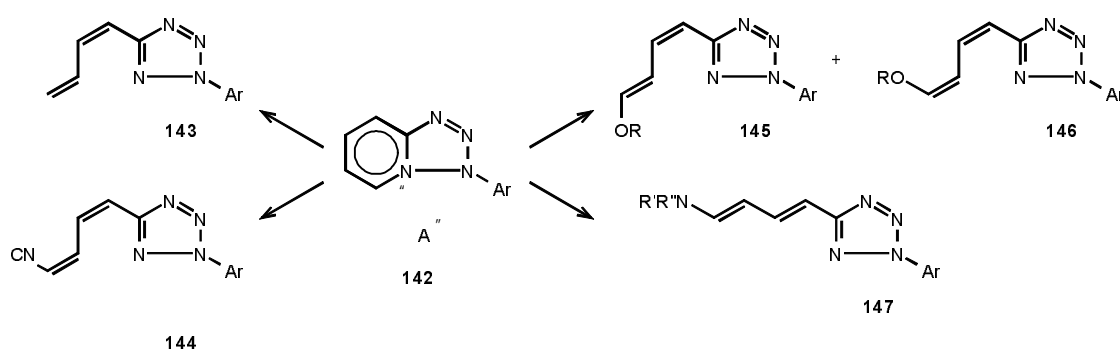
Scheme 49



Similar to the above cases of azinoazinium (*i.e.* 6+6 fused) salts, azoloazinium systems (5+6 fused rings with bridgehead nitrogen atom) behave in an analogous manner when reacted with nucleophilic reagents.

The most extensive studies in this respect have been carried out with tetrazolopyridinium salts (**142**). [50, 51, 52]. As a nucleophile, sodium borohydride, tetraalkylammonium cyanide, sodium alkoxide and various secondary amines have been used. The hydride reagent gave the 1-*cis*-3-*trans* tetrazolyldiene (**143**), whereas a fully *cis* diene (**144**) was obtained as the main product with cyanide anion. In the case of the alkoxide reagent, generally a mixture of the 1-*cis*-3-*trans* (**145**) and 1-*cis*-1-*cis* dienes (**146**) have been obtained. Reaction of the tetrazolium salt **142** with secondary amines resulted in formation of a fully *trans* dieneamine (**147**). If the reaction, however, has been carried out with the sodium salt of the secondary amine, 1-*cis*-3-*trans* dieneamine were formed first which, in most cases in the presence of protic solvents or a trace of acid were transformed to the more stable *trans-trans* isomers.

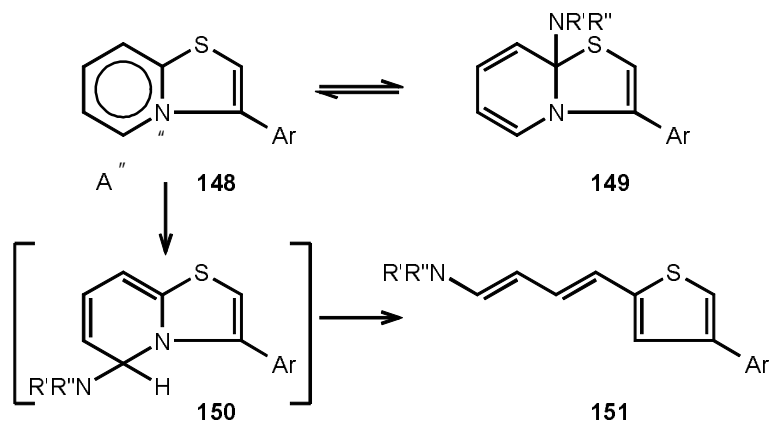
Scheme 50



An interesting behaviour of the thiazolo[3,2-*a*]pyridinium salts (**148**) has been published [53]. This compound reacted with secondary amines (*e.g.* with morpholine) at room temperature to give the addition product **149** which was isolated in crystalline form.

When the reaction was carried out, however, in refluxing acetonitrile, the *trans-trans* thiazolyldieneamine **151** was formed, obviously via the intermediate **150**.

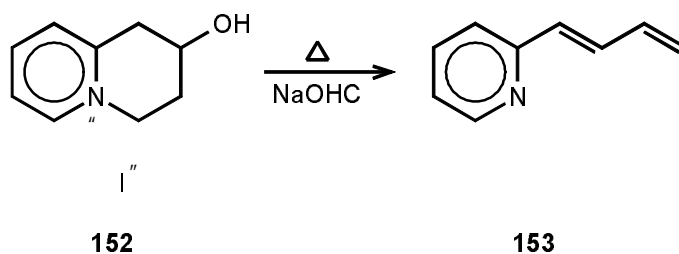
Scheme 51



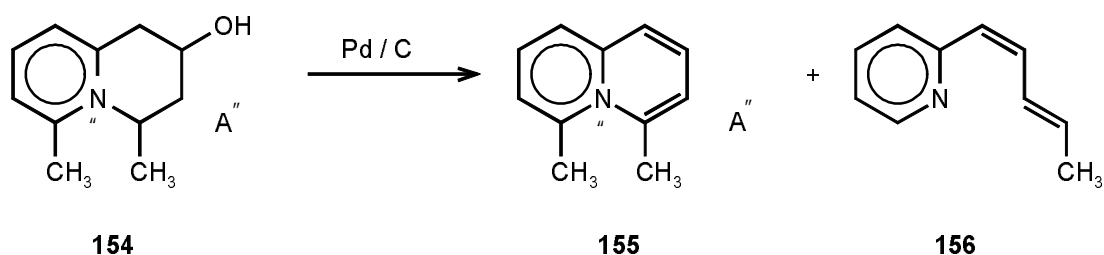
### C.3. Ring opening of partially reduced fused systems with bridge-head nitrogen atom

In contrast to the above cases, partially reduced fused heteroaromatics can also undergo ring opening to yield hetaryldienes. Thus, the tetrahydroquinolizinium salt **152** when treated with sodium acetate at higher temperatures affords pyridyldiene **153** [54].

Scheme 52



Scheme 53

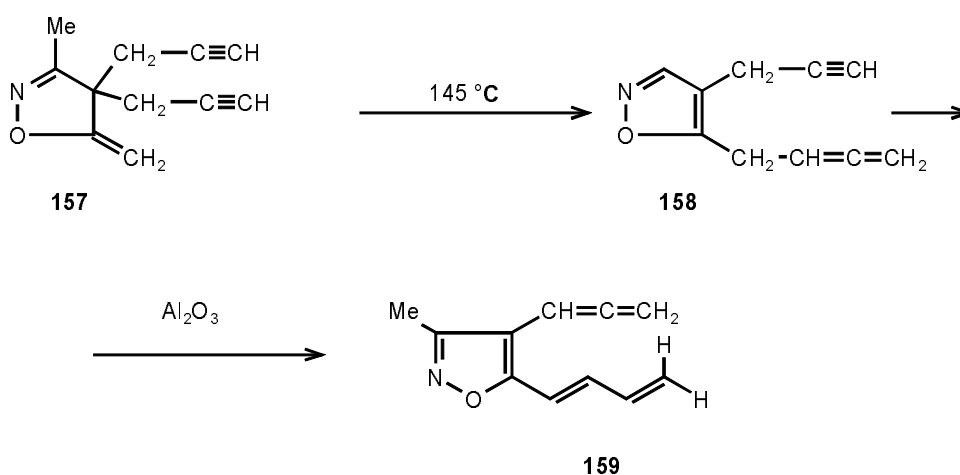


The same type of ring opening was also observed in the case of the dimethyl substituted tetrahydroquinolizinium salt **154** when treated with Pd/C catalyst. Two products: the partially oxidised salt **155** as well as the ring opened diene **156** were obtained [55]

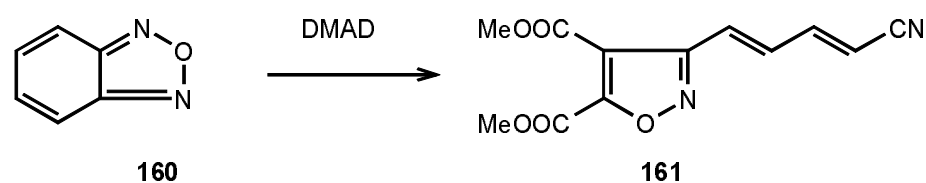
#### D. Synthesis of hetaryldienes by rearrangements.

The isoxazolidine derivative **157** was found to undergo an exothermic reaction when heated to 145 °C to give the **158** isoxazole derivative in very good yield which upon chromatography on alumina underwent a rearrangement to 1-[4-allyl-3-methyloxazolyl-5]diene (**159**) almost in quantitative yield [56].

Scheme 54



Scheme 55



Another and more general rearrangement to hetaryldienes was found with benzoxadiazole **160**: this compound when reacted with dimethyl acetylenedicarboxylate affords - via a fairly unusual addition - the cyano substituted isoxazolyldiene **161** [44, 57]. Similarly, benzoselenodiazoles react with benzyne in an analogous manner and lead to the benzisosenazolyldiene **163**. As indicated by the R substituents the fused benzene ring of the products derived from the reagent, whereas the fused benzene ring of the starting compound **162** undergoes ring opening to afford the diene chain [58, 59].

Scheme 56

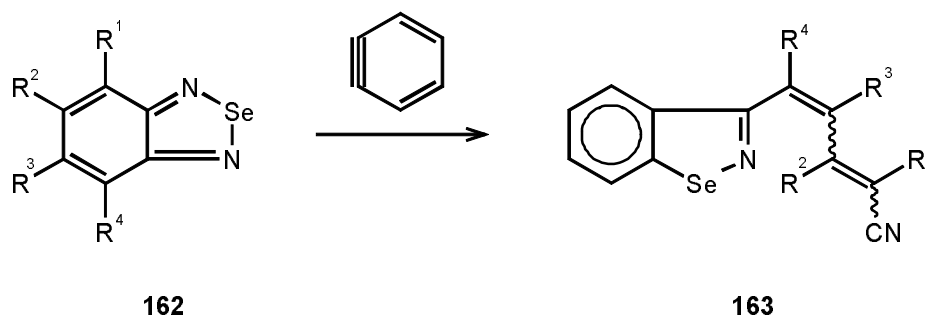
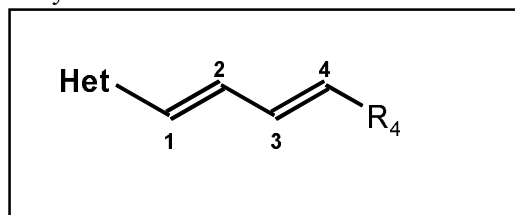


Table 1 cont.

Het	R <sub>1-3</sub>	R <sub>4</sub>	mp	yield (%)	method	ref
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**E. Collective Table**

Table 1 Experimental data and references of hetaryldienes



Het	R <sub>1-3</sub>	R <sub>4</sub>	mp (bp <sup>Hgmm</sup> )	yield (%)	method	ref
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## 5-MEMBERED RINGS WITH ONE HETEROATOM

	-	H	-	87	A1	[1]
	-	H	bp 54 <sup>11</sup>	51	B	[5]
	-	Ph	103-4	84	A2	[12]
	-	Ph	103-4	44	F	[60]
	-	-	4-CN-4-COOMe	44		76 F
	[24]	NMe <sub>2</sub>	-	-	F	[23]
R <sub>1</sub> = NH <sub>2</sub>	H	yellow oil	70	G	[26]	
3-Ph	H	oil	62	G	[28]	
	3-R	H	-	64	G	[61]
	[33]	3-OSiMe <sub>3</sub>	H	bp 73-4 <sup>2</sup>		86 G
		3-OSiMe <sub>3</sub>	H	bp 85 <sup>4</sup>	G	[33]

Table 1 cont.

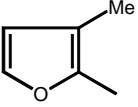
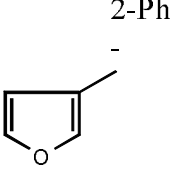
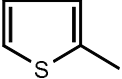
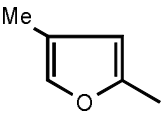
Het	R <sub>1-3</sub>	R <sub>4</sub>	mp	yield (%)	
	----- -----				
	H	-	-	G	[62]
	H	bp 76 <sup>10</sup>	64	H	[63]
	R <sup>2</sup> = Me	H	bp 87 <sup>11</sup>		79
	R <sup>3</sup> = Me	H	bp 92 <sup>17</sup>		74
----- -----					
-	4-CN-4-COOMe	68	52	F	[24]
	----- -----				
[35]		-	SEt		70 <sup>1</sup>
	-	SEt	bp. 121-6 <sup>0.4</sup>		80
	-	H	bp 84 <sup>12</sup>		40
	-	H	oil		57
	4-pentenyl	-	51	H	[65]
	4-CN-4-COOMe	62	72	F	[24]
	Ph	147-9	48	F	[60]
	-	2-(Me <sub>3</sub> Si)-ethenyl	-		50
		3-Ph	H		oil
	[28]				

Table 1 cont.

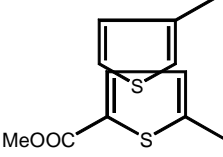
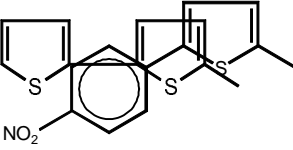
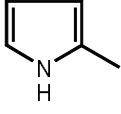
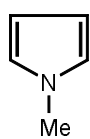
Het	R <sub>1-3</sub>	R <sub>4</sub>	mp	yield (%)	
	R <sub>1</sub> = CN	NMe <sub>2</sub>			
	-	4-CN-4-COOMe	52	78	
	-	SEt	bp 65 <sup>1</sup>	65	
	R <sub>3</sub> =piperidyl	H	oil	80	
	-	H	unmeasurable	61	
-	Ph	130-1	70	H	[36]
-	Ph	193	80	H	[36]



Table 1 cont.

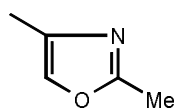
Het	R <sub>1-3</sub>	R <sub>4</sub>	mp	yield (%)
	-	4-CN-4-COOMe	-	-
	-	Ph	192-5	34
	-	COOMe	136	60
	-	CN	70-73	24
	R <sub>2</sub> = Me	H	oil	67
	R <sub>2</sub> = Me	COMe	112	92
	R <sub>2</sub> = Me	CHO	solid	poor
	R <sub>2</sub> = Me	COOMe	114	74

R<sub>1</sub> = CNNMe<sub>2</sub>

-

-

## 5-MEMBERED RINGS WITH TWO OR MORE HETEROATOMS

R<sub>2</sub> = Me

COOMe

88-89

89

Table 1 cont.

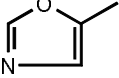
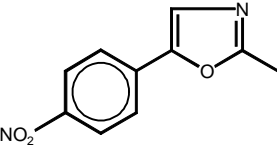
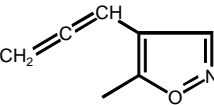
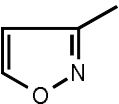
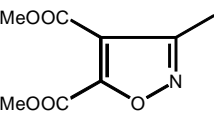
Het	R <sub>1-3</sub>	R <sub>4</sub>	mp	yield (%)
	R <sub>1</sub> = Me -	NMe <sub>2</sub> NMe <sub>2</sub>	bp 87-100 <sup>0.0</sup> 97-100	44 44
	-	Me	157-63	25
	-	H	77-9	94
	2-OAc, 3-Br	H	oil	poor
	-	CN	-	-

Table 1 cont.

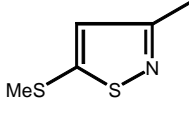
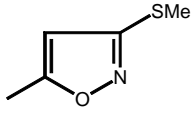
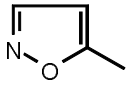
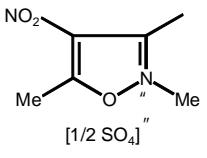
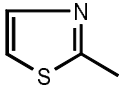
Het	R <sub>1-3</sub>	R <sub>4</sub>	mp	yield (%)	
	-	Ph	102-3	41	H
	-	p-MeO-phenyl	112-3	44	
	-	3,4-diMeO-phenyl	118-9	41	
	-	p-anisyl	102-3	58	
	-	3,4-diMeO-phenyl	108-9	63	
	-	Me	oil	75	
	R <sub>3</sub> =Me	Me	oil	70	
 [1/2 SO <sub>4</sub> ]	-	Ph	175-6	67	
	-	Ph	89-90	poor	

Table 1 cont.

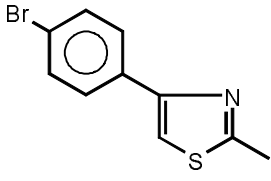
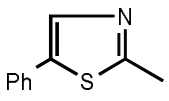
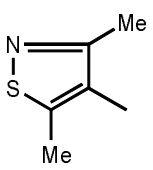
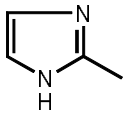
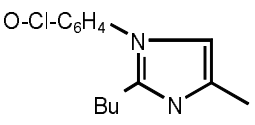
Het	R <sub>1-3</sub>	R <sub>4</sub>	mp	yield (%)
	-	morpholyl	158-9	55
	-	piperidyl	126-8	52
	-	pyrrolidyl	113-5	56
	-	N-Me-piperazyl	129-31	54
<hr/>				
	2-Ph	4,4-bis-SMe	brown liquid	38
<hr/>				
	-	-	oil*	87
<hr/>				
	R <sub>2</sub> = Me	H	oil	63
<hr/>				
	-	COOEt	low melting solid	38
<hr/>				

Table 1 cont.

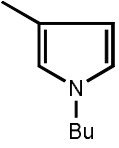
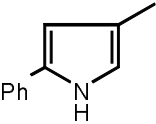
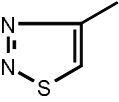
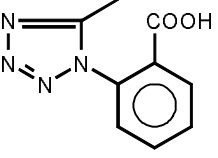
Het	R <sub>1-3</sub>	R <sub>4</sub>	mp	yield (%)
	R <sup>2</sup> =CN	diCN	160	95
	-	H	50	89
	-	Ph	124-6	18
	-	Ph	178	62
	-	H	65	74
	R <sup>1</sup> =Me	-	96	88
	R <sup>2</sup> =Me	-	125	80
	R <sup>3</sup> =Me	-	41	34
	-	Me	65*	74
	-	Ome	164 (1-Z)	38
	-	Ome	97 (1-E)	12

Table 1 cont.

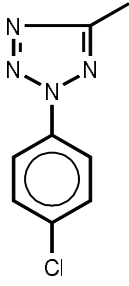
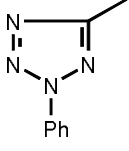
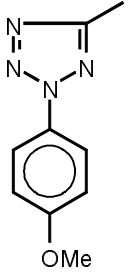
Het	R <sub>1-3</sub>	R <sub>4</sub>	mp	yield (%)
	-	Oet	67 (1-Z)	34
	-	Oet	54 (1-E)	12
	-	Opr <sup>i</sup>	84 (1-Z)	5
	-	Opr <sup>i</sup>	77 (1-E)	75
	-	Obu <sup>t</sup>	106 (1-E)	79
	-	CN	160 (1-Z)	67
	-	CN	142 (1-E)	15
	-	imidazolyl	151 (1-E)	92
	-	benzimidazolyl	198 (1-E)	82
	-	indolyl	164 (1-E)	85
	-	7-Cl-phenothiazinyl	164 (1-E)	38
	-	morpholyl	94 (1-E, 3-Z)	69
	-	morpholyl	161 (1-E, 3-E)	61
-	aziridy 1	79-81*	82	
<hr/>				
	-	morfoly 1	136(1-E,3-E)	56
<hr/>				
	-	morfoly 1	128	53

Table 1 cont.

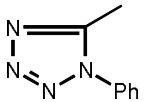
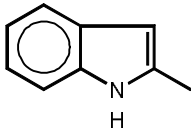
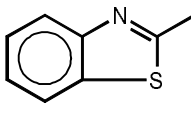
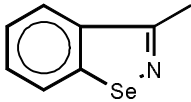
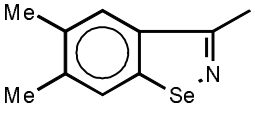
Het	R <sub>1-3</sub>	R <sub>4</sub>	mp	yield (%)
	-	Ph	161-2	74
BENZOLOGUES OF 5 MEMBERED HETEROCYCLES				
	R <sub>2</sub> = Me R <sub>3</sub> = Me	H H	solid 132-3	88 38
	R <sub>1</sub> = CN -	Ph p-Me <sub>2</sub> N-Ph	153 197-9	90 91
	-	CN	140-1	88
	-	CN	102-4	58

Table 1 cont.

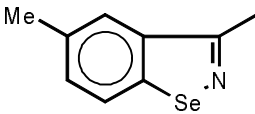
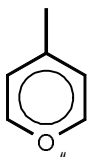
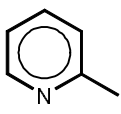
Het	R <sub>1-3</sub>	R <sub>4</sub>	mp	yield (%)
	-	CN	144-54	12
6 MEMBERED RINGS WITH ONE HETEROATOM				
	-	p- NMe <sub>2</sub> -phenyl	145	93
	-	Ph	121-3	44
	-	Ph	121	44
	-	Ph	121-3	68
	-	Ph	121-2	-
	-	Ph	123-4	-
	-	H	152 (picrate)	-
	-	H	bp 70 <sup>1</sup>	-
	-	H	oil	84
	-	H	bp 66 <sup>1.5</sup>	91
	-	Me	bp 48 <sup>0.08</sup>	56
	-	Me	153-5	30
	-	NMe <sub>2</sub>	oil	50



Table 1 cont.

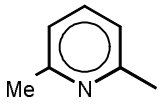
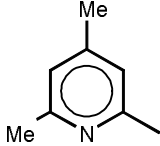
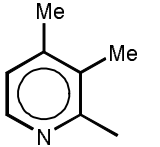
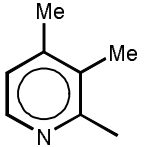
Het	R <sub>1-3</sub>	R <sub>4</sub>	mp	yield (%)
	-	NMe <sub>2</sub>	bp 130-5 <sup>0.3</sup>	-
	-	NH <sub>2</sub>	-	quantitative
	-	Net <sub>2</sub>	-	65
	-	SEt	bp 80 <sup>1</sup>	54
	-	piperidyl	58-60	68
	-	morpholyl	112	56
	R <sub>1</sub> = NH <sub>2</sub> R <sub>2</sub> = Me R <sub>3</sub> = iPr-NH <sub>2</sub>	H H iPrNH	oil oil 171-2	78 92 45
	-	Me	bp 90-91 <sup>1</sup>	30
	-	Ph	108	-
	-	Ph	103-4	-
	-	piperidyl	96	93
	-	Ph	103-4	-
	-	morpholyl	119	55

Table 1 cont.

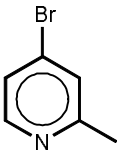
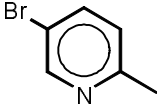
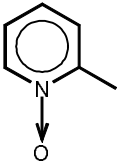
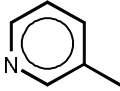
Het	R <sub>1-3</sub>	R <sub>4</sub>	mp	yield (%)
	-	NEt <sub>2</sub>	-	10
	-	Net <sub>2</sub>	-	5
	-	Ph	170-1	76
	-	SEt	bp 90 <sup>1</sup>	63
	-	Ph	104-5	77
	-	NMe <sub>2</sub>	145-7	94
	-	Ph	100-2	59
	-	H	bp 60 <sup>0,2</sup>	72
	R <sub>3</sub> =piperidyl R <sub>2</sub> = Me	H	oil	81
	H	oil	83	

Table 1 cont.

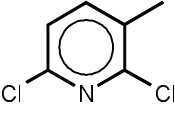
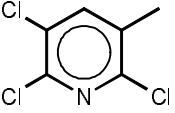
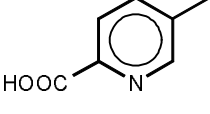
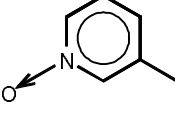
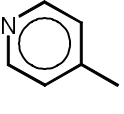
Het	R <sub>1-3</sub>	R <sub>4</sub>	mp	yield (%)
	-	Ph	120-2	63
	-	Ph	133-5	51
	-	H	105-6	-
	-	Ph	196-8	65
	-	Ph	158-60	52
	-	Ph	137-8	-
	-	Ph	159	-
	-	H	bp 71 <sup>1.5</sup>	63
	R <sub>2</sub> = Me	H	oil	91

Table 1 cont.

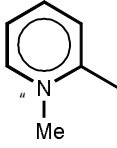
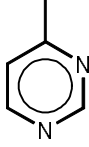
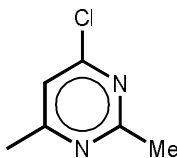
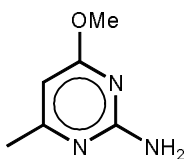
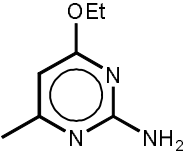
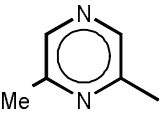
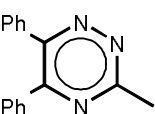
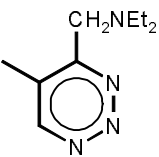
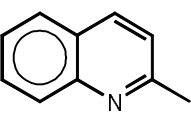
Het	R <sub>1-3</sub>	R <sub>4</sub>	mp	yield (%)
	-	p- NMe <sub>2</sub> -phenyl	224-6	75
	-	Ph	101	8
6-MEMBERED RINGS WITH TWO OR MORE HETEROATOMS				
	-	Me	72-3	42
	-	Ph	121-3	50
	-	Ph	166	62
	-	p-tolyl	201	60
	-	p-anisyl	193	62
	-	3,4-disubst.Ph	186	55
	-	p-anisyl	171	57

Table 1 cont.

Het	R <sub>1-3</sub>	R <sub>4</sub>	mp	yield (%)
	-	Ph	149-50	54
	-	p-tolyl	171	57
-----				
	-	Ph	-	-
	-	-	-	-
-----				
	-	Me	142-4	78
	-	Ph	146-7	62
-----				
	-	H	bp 100 <sup>0.01</sup>	60
	-	-	-	-
-----				
BENZOLOGUES OF 6 MEMBERED HETEROCYCLES				
	-	piperidyl	175-6	quantitative
	-	Ph	57-58	144
	-	Ph	117	13



## II. REACTIONS

This part of the paper covers the transformations of hetaryldienes - except reactions that do not involve the change of the diene moiety - classified according to their nature. To better understand the reactivity of hetaryldienes one has to study the electronic and steric features of these molecules.

### F. Structure and reactivity

Generally a 1,3-diene moiety has a planar arrangement upheld by the conjugation of its  $\pi$ -electrons. The connection of a hetaryl ring to any position of the diene chain would in principle mean spreading out the conjugation on the molecule and coplanarity of the aromatic ring(s) with the diene chain, which suggests that in reactions where the attacking entity approaches the molecule from the top or the bottom (which is the usual pattern) the steric influence directing the incoming reagent originate primarily from other, non-planar substituents. On the other hand the aryl moiety and other conjugating substituents (which by virtue of conjugation have to lie in the plain of the diene chain) do fundamentally determine the electron- and orbital-distribution of the diene chain and thus its reactivity patterns.

Semiempirical calculations using the AM1 Hamiltonian and the MOPAC 6.0 package show (Table 2) that on introduction of a conjugating substituent the energy of the highest occupied molecular orbital (HOMO) increases considerably (cf. entries 1,2,3,5) and the  $\pi$ -contribution (HOMO  $2p_z$  coefficient) of the diene carbon atoms to the HOMO orbital in positions  $\beta$  and  $\delta$  to the substituent is significantly enhanced relative to positions  $\alpha$  and  $\gamma$ . The results also reveal that the change of the geometry of a double bond (cf. entries 3,4 and 5,6) or introduction of a non-conjugating substituent (cf. entries 5,7) have only a minor effect on the HOMO orbital energy and population. Similar considerations lead to the conclusion (also supported by molecular modelling) that the

carbon atoms of higher HOMO coefficient in the diene chain do also accommodate a higher electron density and thus have a larger partial negative charge than the other positions.

Scheme 57

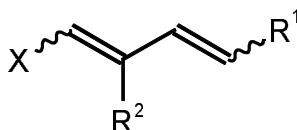


Table 2

Calculated HOMO orbital energies ( $E_{\text{HOMO}}$ , eV) and  $2p_z$  coefficients ( $q_{2p_z}$ , absolute value) of some dienes (AM1, MOPAC 6.0)

Entry	X	R <sup>2</sup>	R <sup>1</sup>	$E_{\text{HOMO}}$	$C^{\alpha}\text{-}q_{2p_z}$	$C^{\beta}\text{-}q_{2p_z}$	$C^{\gamma}\text{-}q_{2p_z}$	$C^{\delta}\text{-}q_{2p_z}$
1	H	H	H	-9,33	0,56	0,43	0,43	0,56
2	<i>E</i> -Ph	H	H	-8,63	0,41	0,44	0,24	0,39
3	<i>E</i> -NMe <sub>2</sub>	H	H	-8,08	0,37	0,53	0,24	0,43
4	<i>Z</i> -NMe <sub>2</sub>	H	H	-8,10	0,35	0,54	0,21	0,34
5	<i>E</i> -NMe <sub>2</sub>	H	<i>E</i> -2-Me-tetrazol-5-yl	-8,02	0,33	0,49	0,26	0,45
6	<i>E</i> -NMe <sub>2</sub>	H	<i>Z</i> -2-Me-tetrazol-5-yl	-8,01	0,34	0,52	0,22	0,43
7	<i>E</i> -NMe <sub>2</sub>	Me	<i>E</i> -2-Me-tetrazol-5-yl	-7,90	0,34	0,51	0,21	0,39

Based on the calculations the following reactivity patterns can be predicted for hetaryldienes: besides the reactions characteristic of olefins (*e.g.* saturation, 2+2 photocycloaddition, rearrangements) hetaryldienes might be expected to undergo regioselective cycloaddition reactions as electron-rich  $2\pi$  or  $4\pi$  components, with the reagent atom of higher LUMO contribution being connected to the diene carbon of higher HOMO contribution, and are susceptible to electrophilic attack at positions  $\beta$  and  $\delta$  relative to the strongest donating substituent. Due to the fairly even orbital and charge



distribution along the diene chain in transformations where only one of the two double bonds takes part the selection will usually be based on steric susceptibility rather than electronic differences.

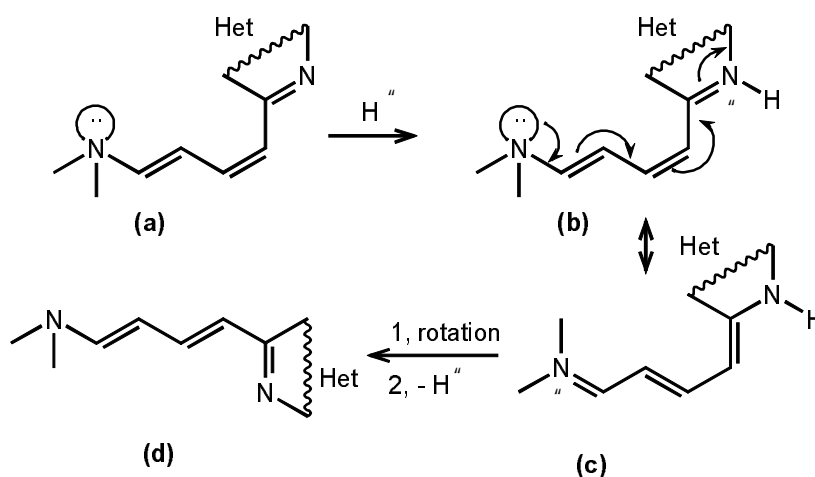
## G. Reactions with electrophiles

This chapter collects the reactions of hetaryldienes with electrophiles. As mentioned previously these attacks are expected to take place at positions  $\beta$  and  $\delta$ . In most cases electrophilic attack on the hetaryl ring might also occur as a competing reaction.

### G.1. Protonation

As olefins are usually sensitive to acids, easily undergoing isomerisation, rearrangement or polymerisation, quantitative protonation reactions have little practical use with hetaryldienes. The use of acid catalysis was found beneficial in certain cases which will be discussed at the appropriate transformations.

Scheme 58



In some cases the hetaryldiene structure can make the proton catalysed isomerisation very facile. In *IZ,3E*-1-hetaryl-4-amino dienes (scheme 58, a) the diene chain bears a lone pair donor atom at one terminus (e.g. nitrogen) and a hetaryl moiety at the other

terminus in a way that it can formally be conjugated to a pyridine type nitrogen. Protonation of the heterocycle gives an iminium ion (**b**) which - if the amine nitrogen is ready to contribute its lone pair - can also be described by a mesomeric form (**c**) where the formally double 1,2-bond becomes single thus allowing rotation around the bond and deprotonation results in the thermodynamically more stable *1E,3E* form (**d**). The process was applied to the synthesis of *E,E* hetaryldienamines [83].

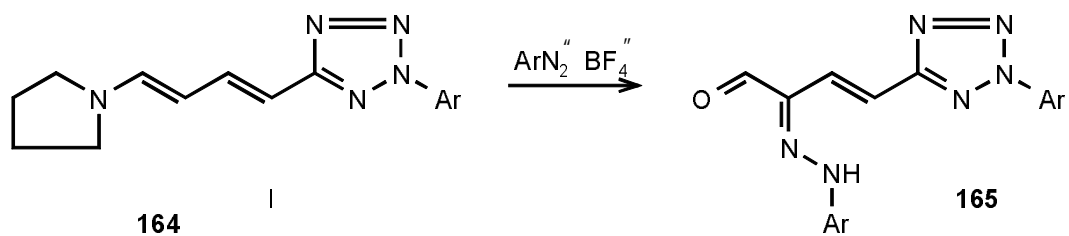
## G.2. Reaction with other electrophiles

Although electrophiles other than proton can also lead to non-desired side-reactions so their use as a reagent with hetaryldienes is fairly limited, interesting comparison can be made between the few published reactions of hetaryldienamines and their carbocyclic analogues.

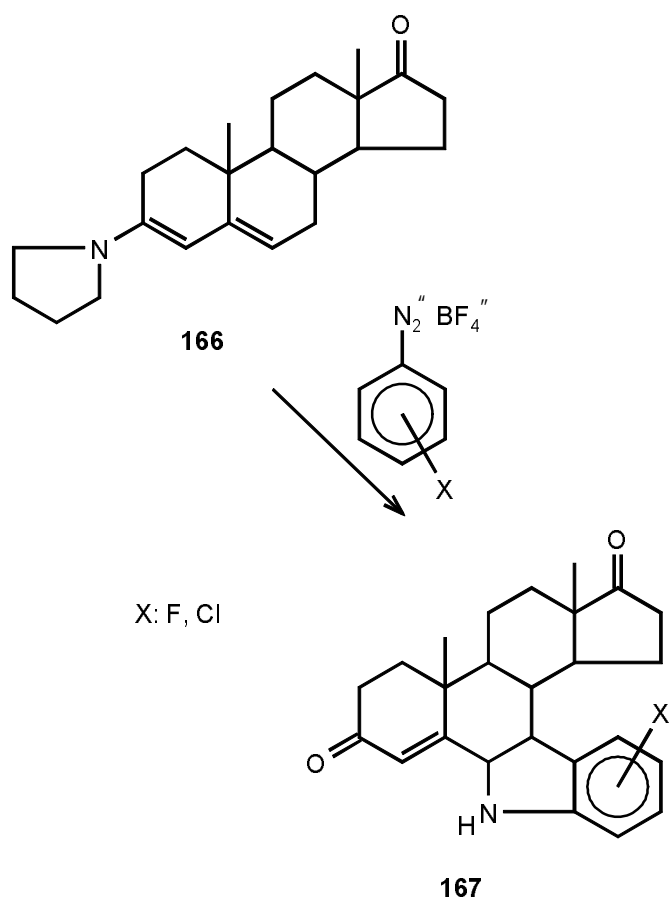
The tetrazolyldienamine **164** was found to react with aryldiazonium salts at the  $\beta$  position and after aqueous work up the  $\alpha$ -hydrazono-aldehyde **165** was isolated in moderate yield (52%) [84]. The analogous dienamine derived from  $\Delta^4$ -androstene-3,17-dione (**166**) was readily attacked by aryldiazonium salts in the  $\delta$  position and was converted after treatment with phosphorous oxychloride and hydrolysis to steroidoindoles (**167**) [85].

Although treatment of **164** with diethyl azodicarboxylate (DEAD) led to the addition of the  $\delta$ -CH bond onto the azo-part and formation of **168** in good yield (60%) - formally an electrophilic attack followed by hydrogen shift - the reaction is believed to follow a cycloaddition-elimination pathway through the dihydro-pyridazine intermediate **169** [84]. A decalin-derived cyclic dienamine with fixed *cisoid* geometry (unable to furnish the cycloaddition intermediate) was attacked at the  $\beta$ -position by DEAD [86] and **170** was formed in moderate yield (42%). The reaction is thought to proceed via the addition of the electron-rich  $\beta$  carbon onto the azo-bond followed by hydrogen shift.

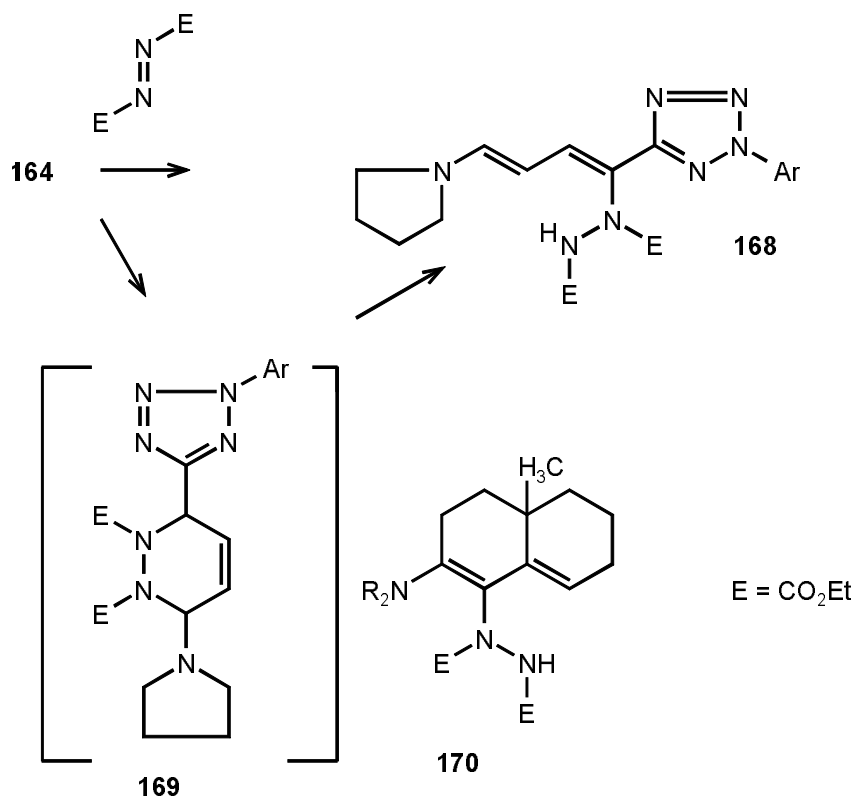
Scheme 59



Ar: 4-Cl-phenyl



Scheme 60



## H. Cycloaddition reactions

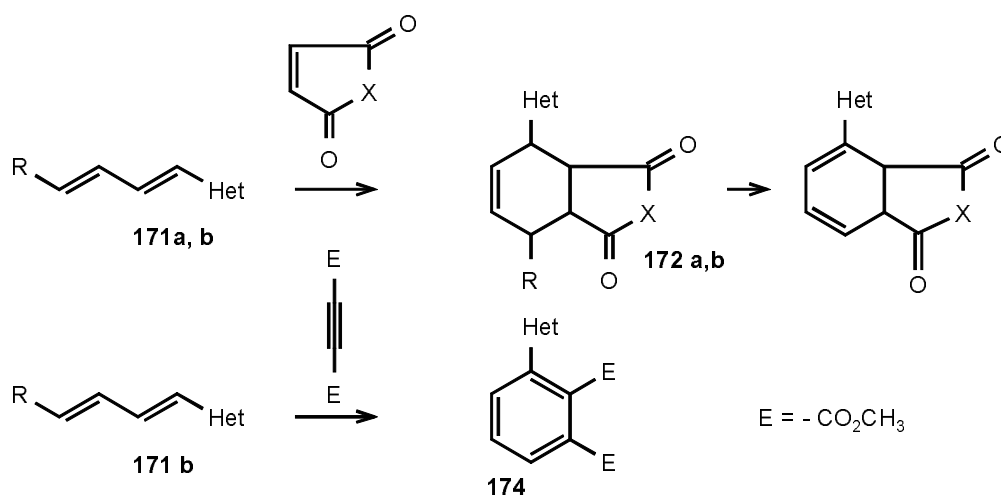
As the frontier orbital analysis of hetaryldienes in chapter F reveals high lying HOMO orbitals one would assume that they are ideally set to participate 4+2 and 4+6 cycloadditions as  $4\pi$  components. As the same HOMO orbital applies if we consider the dienes as ene systems, reactions taking place on electron rich olefins (such as 2+3 dipolar cycloaddition, "inverse electron demand" Diels-Alder reaction or 2+8 cycloaddition) will also find practical use amongst hetaryldienes.

### H.1. Dienes as $4\pi$ components

### H.1.1. Diels-Alder (4+2) cycloadditions

The first report on the Diels-Alder reaction of a hetaryldiene goes back to 1950, when 2'-thienylbutadienes (**171a**) were found to react with maleic anhydride ( $X=O$ ) to give the bicyclic product (**172a**) [87]. A similar reaction was published [86] using hetaryldienamines (**171b**) and N-phenyl-maleinimide ( $X=NPh$ ). Here the primary adduct (**172b**) underwent spontaneous elimination to yield the cyclohexadienofurane (**173b**) in good yield (72%). A similar Diels-Alder reaction - elimination sequence was also used to rationalise the formation of the 3-hetaryl-phthalic acid dimethyl esters (**174**) from the hetaryldienamine (**171b**) and dimethyl acetylenedicarboxylate (DMAD) reported in the same paper.

Scheme 61



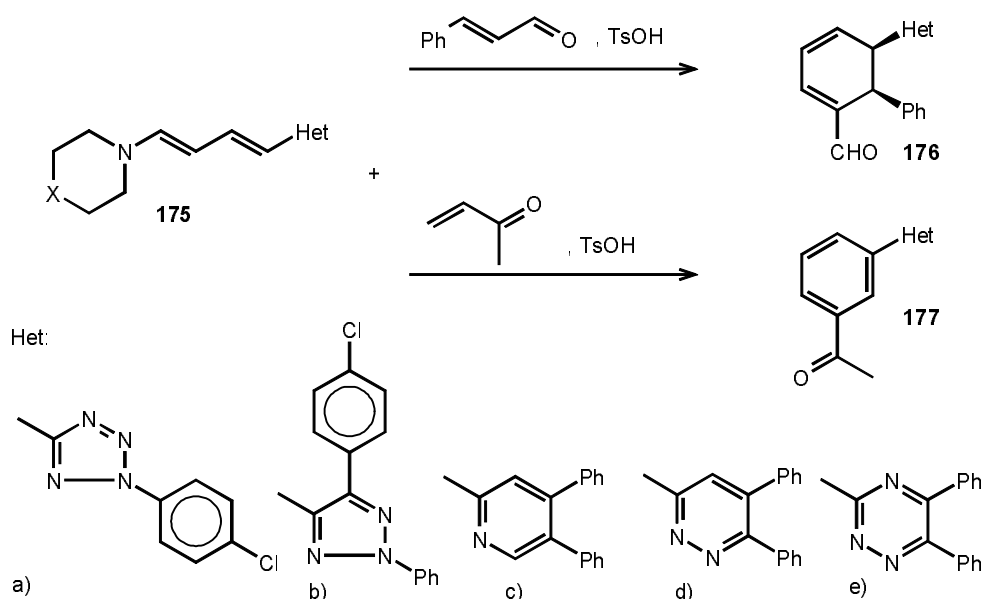
a: Het = 2'-thienyl, R = H, X = O

b: Het = 2(4-chlorophenyl)-tetrazolyl-5, R = morpholino, X = NPh

Although the use of  $\alpha,\beta$ -unsaturated oxo-compounds as dienophiles with electron-rich olefins goes back to 1942 [88] their reaction with hetaryldienes was only reported recently. Cinnamaldehyde and methylvinylketone - activated by a catalytic amount of strong Brønsted acid reacted with a series of hetaryldienamines (**175**) to give cyclohexenes. The intermediates eliminated the amine moiety spontaneously and

cyclohexadienes were formed which were isolated (**176**) or oxidised to benzene derivatives (**177**). The wide range of yields (17-80%) was attributed to the different acid sensitivity of the starting dienes and products [89].

Scheme 62

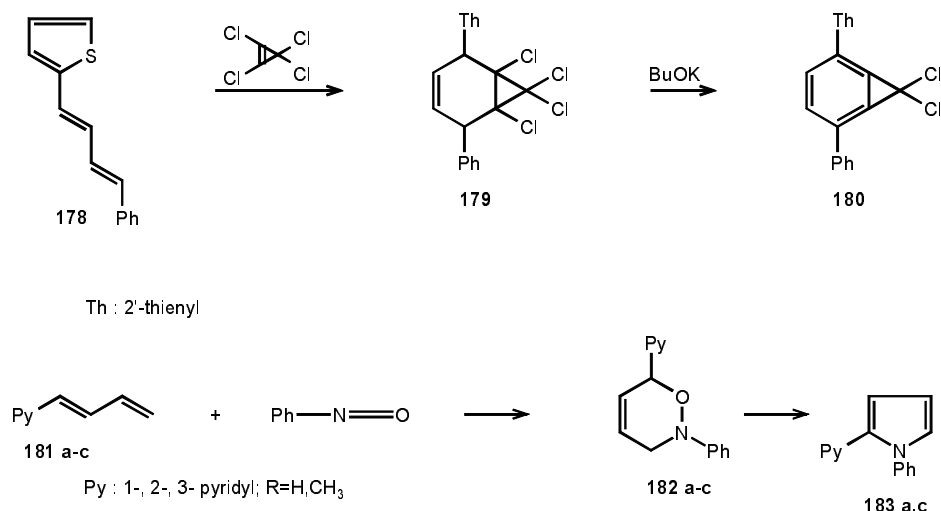


The highly reactive 1,2,3,3-tetrachlorocyclopropene system was used in the synthesis of cyclopropenobenzene (**180**) starting from a 2'-thienyl-diene (**178**). The first step of the procedure is the Diels-Alder reaction of **178** yielding the fused cyclohexene (**179**) in 33% yield, which was converted to the end product **180** in 28% yield by potassium *tert*-butoxide [90].

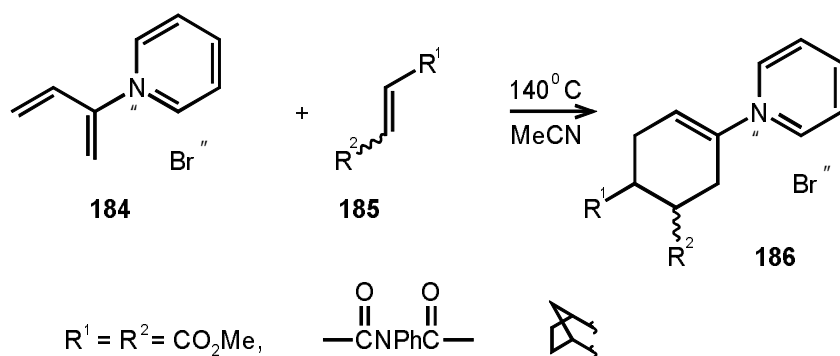
Nitrosobenzene was found to react as a hetero-dienophile when treated with pyridyl-dienes (**181a-c**) to yield dihydrooxazine derivatives (**182a-c**). The intermediates containing 2'-pyridyl or 4'-pyridyl substituents (**182a,c**) were transformed into the pyrrol derivatives **183a,c** on treatment with base, while their 3'-pyridyl analogues remained intact under the applied conditions [91].

An unusual diene, the cationic N-(2-butadienyl)-pyridinium salt (**184**) was reacted with electron deficient or strained olefins (**185**) in acetonitrile at 140 °C in a sealed vessel to give the cyclohexene cationic derivatives (**186**) in good yield (79-92%) [92].

Scheme 63

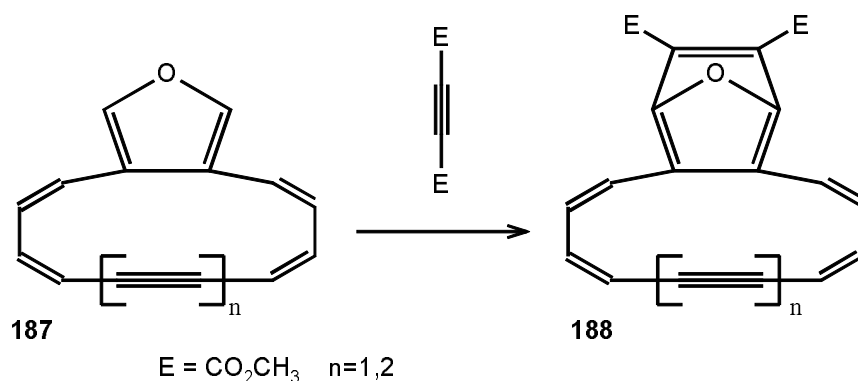


Scheme 64

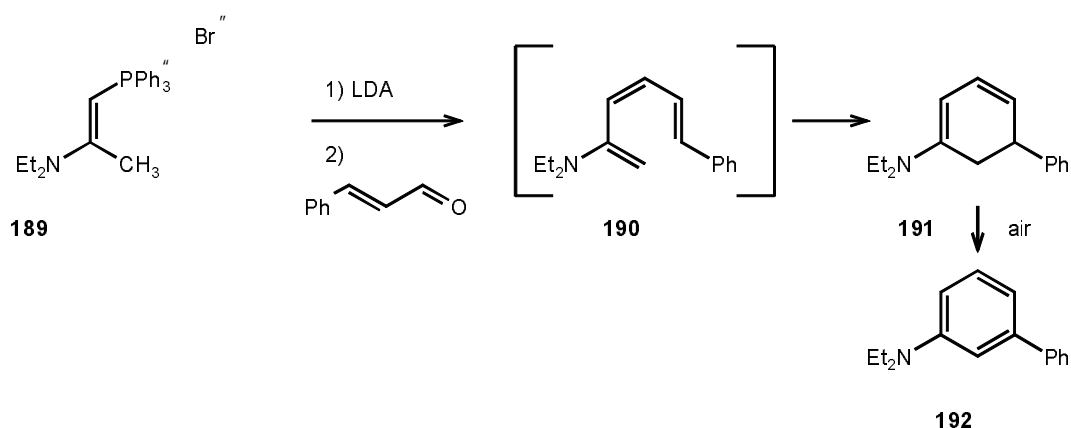


The "irregular" Diels-Alder behaviour of the cyclic polyene **187** - it reacts with DMAD on its furan moiety if  $n=1$  to yield **188** in 90%, but doesn't react with DMAD if  $n=2$  [93] - was attributed to the anti-aromatic character of **188** ( $n=2$ ) and **187** ( $n=1$ ) and the aromatic stabilisation in **188** ( $n=1$ ) and **187** ( $n=2$ ).

Scheme 65



Scheme 66



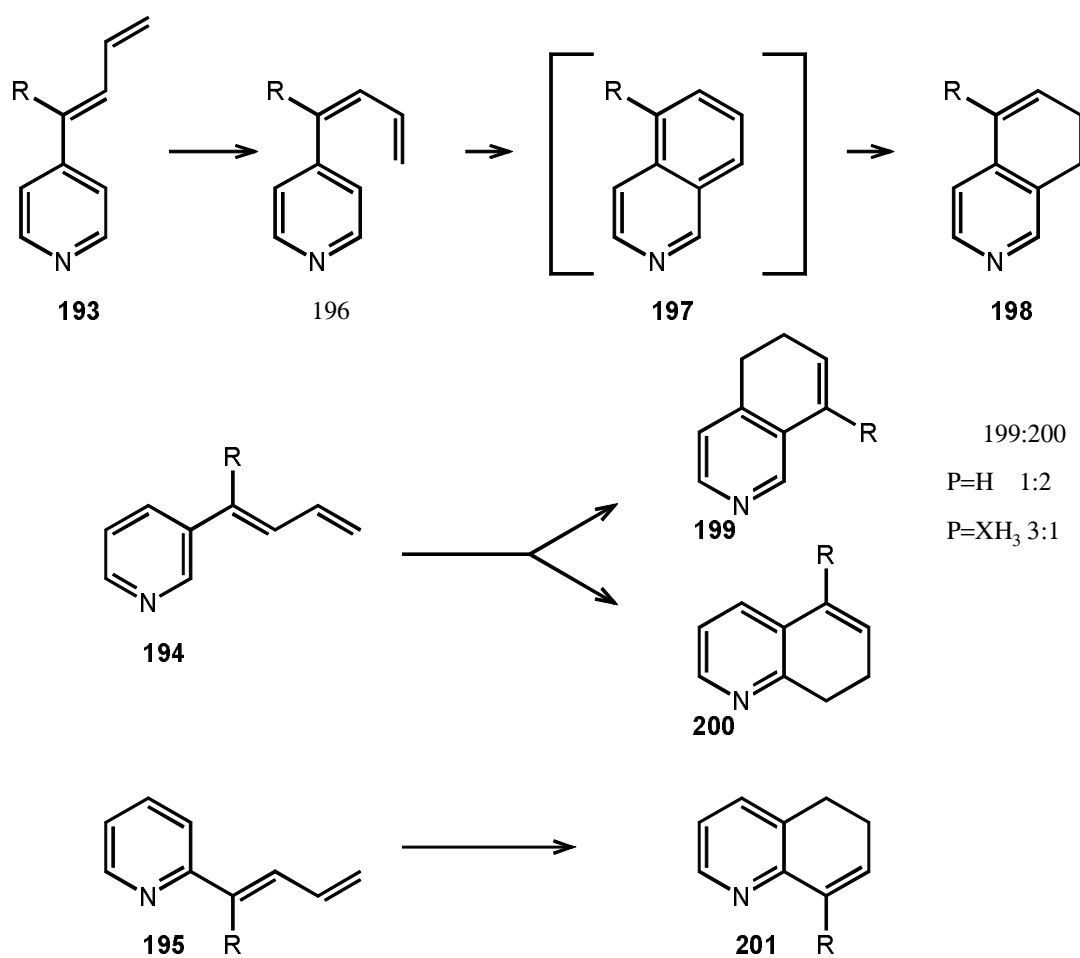
The intramolecular Diels-Alder reaction is frequently used in the synthesis of polycyclic systems. The ring construction step might utilise a stable starting material and forcing reaction conditions or the facile transformation of an *in situ* formed intermediate. This latter case is represented in the formation of the biphenyl-derivative **192**. The enaminophosphonium salt (**189**) was converted to the hexatriene intermediate (**190**) which cyclised to the cyclohexadiene (**191**). Oxidation of **191** afforded the aromatic product **192** [4].

The cyclisation of pyridyldienes (**193-195**) to quinolines and isoquinolines under mild conditions is prohibited by the *E* geometry of the 1,2-double bond. Under forcing conditions, however a side chain isomerisation may occur and the formed isomers (**196** and its analogues) undergo intramolecular Diels-Alder reaction to give dihydroquinolines

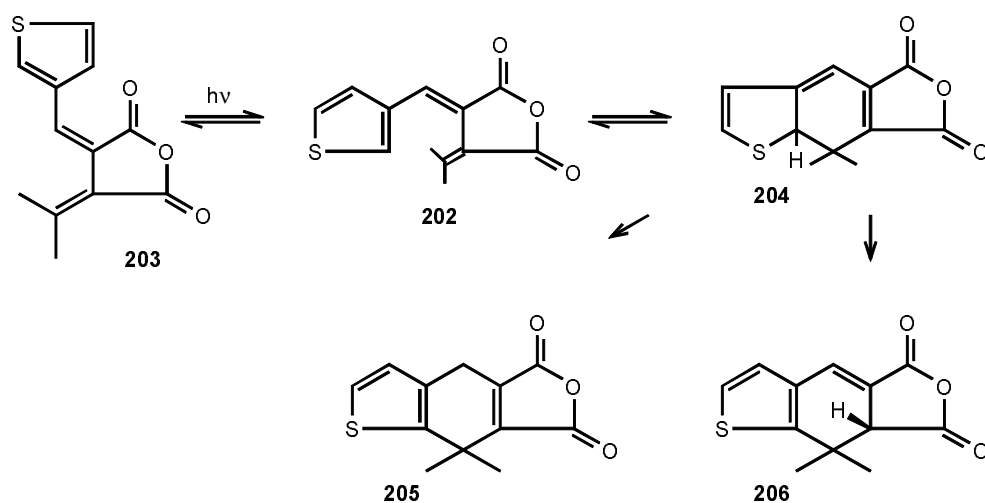


and dihydroisoquinolines (**198-201**). The regioselectivity of the process was shown to be dependent on the substitution pattern of the diene chain [94].

Scheme 67



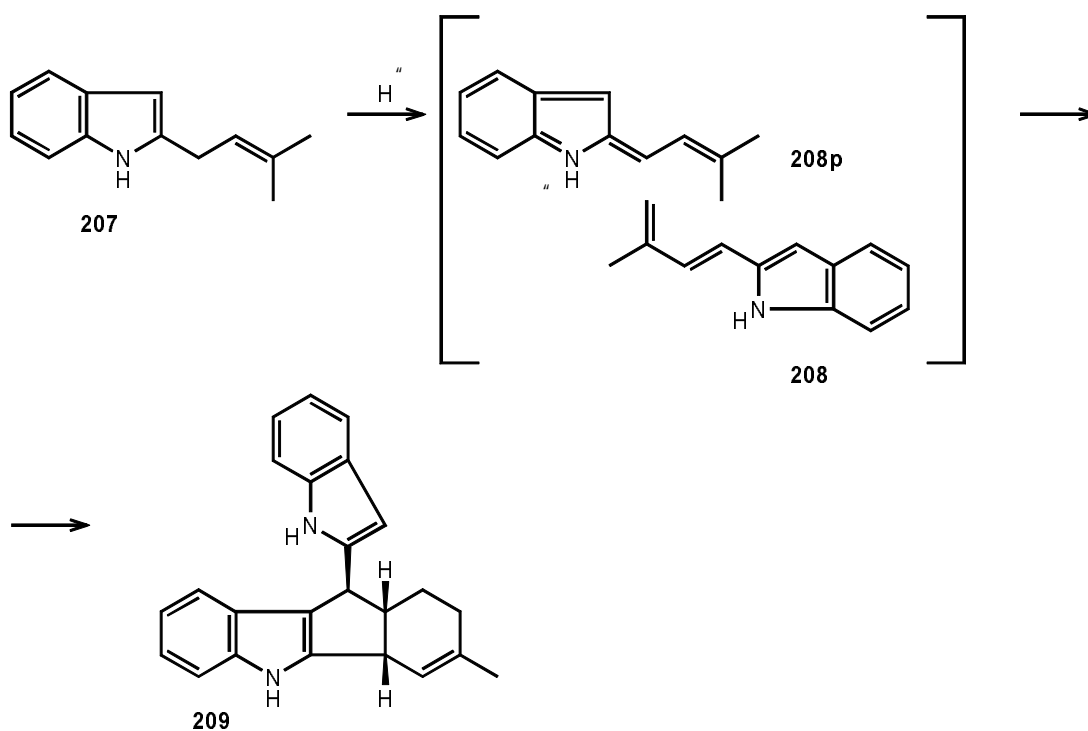
Scheme 68



The *E*-thienyldiene (**202**) was converted selectively into a series of intramolecular reaction products (**203-206**). On prolonged irradiation at 366 nm a *ca.* 7:3 equilibrium mixture of the *E-Z* fulgides (**202**) and (**203**) was formed. When **202** was heated to 140 °C it cyclised to **204** which on irradiation with white light regenerated **202**. Carrying out the same reaction in the presence of a catalytic amount of trifluoroacetic acid **202** was converted quantitatively into **205**, the reaction proceeding probably through **204**. Heating of **202** in 1,2-dichlorobenzene in a sealed tube at 180 °C led to the quantitative formation of **206** in an hour. Attempts to achieve the acid catalysed transformation of **206** into **205** were unsuccessful.

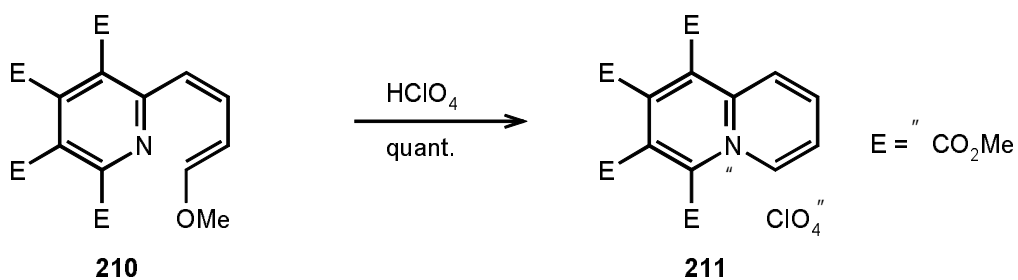
The acid catalysed Diels-Alder dimerisation of the dehydroprenylindole (**208**) is thought to be the key step in the biosynthesis of yuehchukene (**209**). The process starts by the oxidation of prenylindole (**207**) to dehydroprenylindole (**208**) which in the presence of acid gives its protonated form **208p**. Diels-Alder reaction of **208** with **208p** followed by cyclisation leads to the natural product **209** [74].

Scheme 69

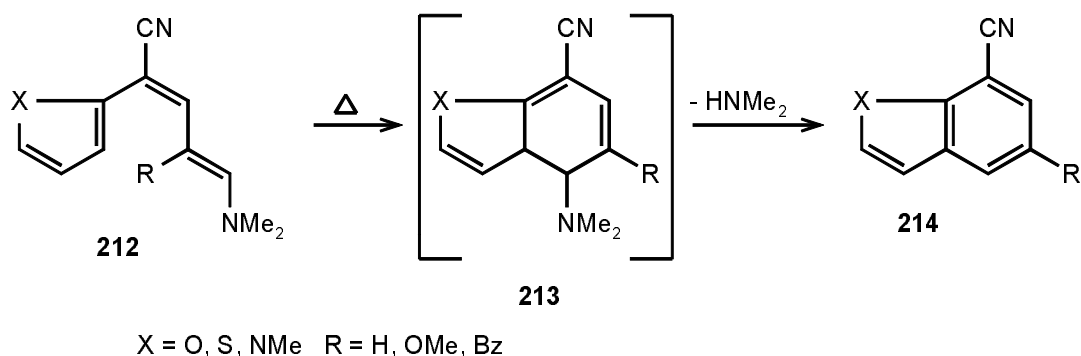


A strong Brønsted acid was used to achieve the ring closure of the pyridyl-dienylether **210** to the quinolizinium derivative **211** in quantitative yield [58]. It is interesting to note that this ring closure procedure represents the reversal of the commonly employed ring opening technique of bridgehead nitrogen containing condensed salts with nucleophiles.

Scheme 70



Scheme 71

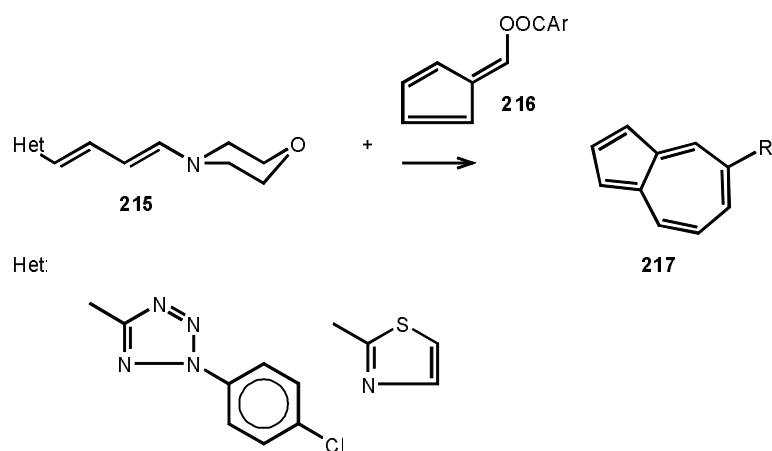


The previous examples demonstrated clearly that intramolecular cycloadditions proceeding with the destruction of an aromatic system require forced conditions. The same applies to the intramolecular Diels-Alder reaction of hetaryldienes (**212**) which yielded benzo[b]furans, -thiophenes and indoles (**214**) through the **213** intermediates [23].

### H.1.2. 4+6 cycloadditions

Another class of "Woodward-Hoffmann allowed" thermal cycloadditions is of the less frequently exploited 4+6 cycloadditions. Acyloxyfulvenes (**216**) reacted with hetaryldienamines (**215**) as  $6\pi$  systems and after the elimination of the amine moiety azulenes (**217**) were formed in moderate yield (46-65%) [86].

Scheme 72

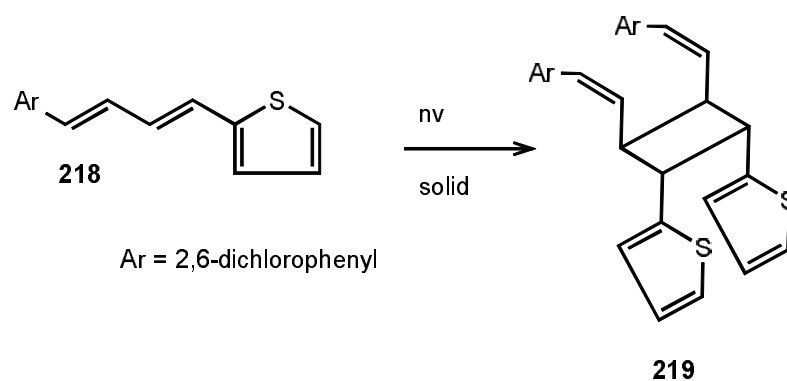


## H.2. Dienes as $2\pi$ components

### H.2.1. 2+2 cycloadditions

Although the photochemical 2+2 cycloaddition of olefins is frequently used in organic synthesis its extension to hetaryldienes is limited. The only report on this subject discusses the solid phase photochemical transformation of the 2'-thienyldiene (**218**) into its dimer (**219**) on irradiation [96].

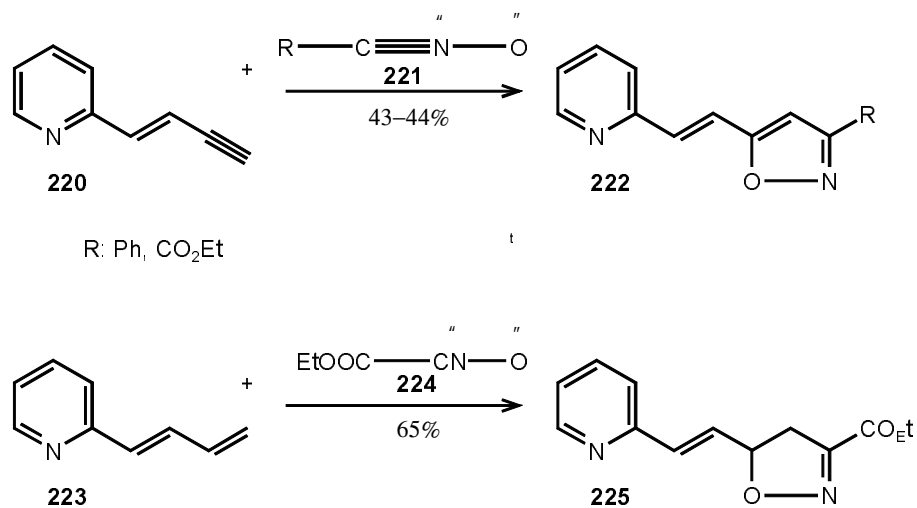
Scheme 73



### H.2.2. 2+3 cycloadditions

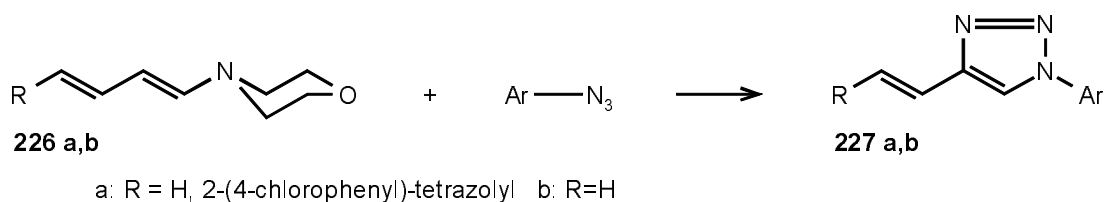
Hetaryldienes having an electron-rich diene system react readily with 1,3-dipoles; the site of attack mostly determined by the steric hindrance of the double bonds and regioselectivity governed by electronic factors. The pyridyl-ene-yne (**220**) reacted with its terminal acetylene bond when treated with the nitrileoxides (**221**) and gave pyridylvinylisoxazoles (**222**) in moderate yield [97]. The analogous reaction of the pyridylbutadiene (**223**) gave the isoxazoline derivative (**225**) in good yield. No other isomers were detected in the reaction mixtures.

Scheme 74



The tetrazolyldienamine (**226a**) gave tetrazolylylvinyltriazole (**227a**) on treatment with arylazides [84] *via* a dipolar cycloaddition followed by morpholine elimination. The analogous product (**227b**) formed in the transformation of morpholinobutadiene (**226b**) suggests that the amine moiety takes part in the stabilisation of the transition state (cf. chapter H.2.4.).

Scheme 75



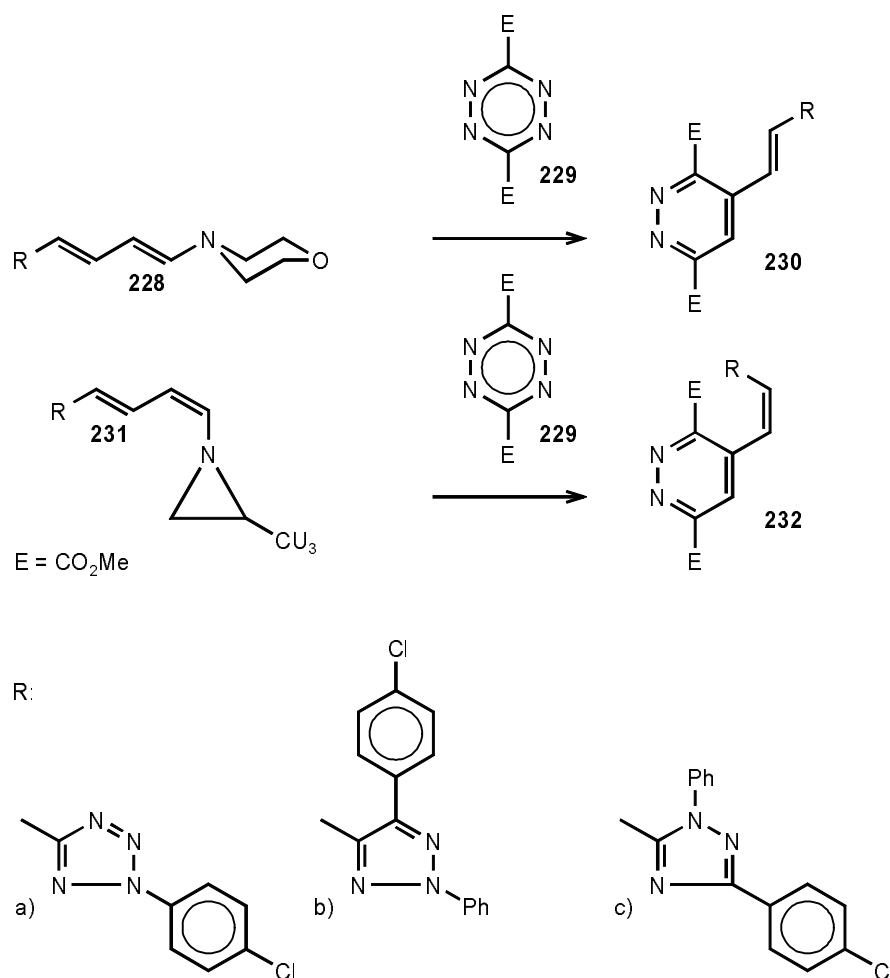
### H.2.3. "Inverse electron-demand" Diels-Alder (2+4) cycloadditions

Hetaryldienes having an additional p-donating substituent, especially dienamines have high lying HOMO orbital which makes them suitable dienophiles in the "inverse electron-demand" Diels-Alder reaction. A series of *E,E*-hetaryldienamines (**228**) were reacted with 3,6-dimethyl 1,2,4,5-tetrazine dicarboxylate (**229**) and *E*-azolylylvinylpyridazines

(**230**) were isolated in moderate to good yield [83, 98]. In each case the tetrazine reacted with the enamine part retaining the geometry of the 1,2 double bond. A series of the analogous *Z,E*-azolyldienamines (**231**) gave the corresponding *Z*-azolylvinyldiazines (**232**) [98].

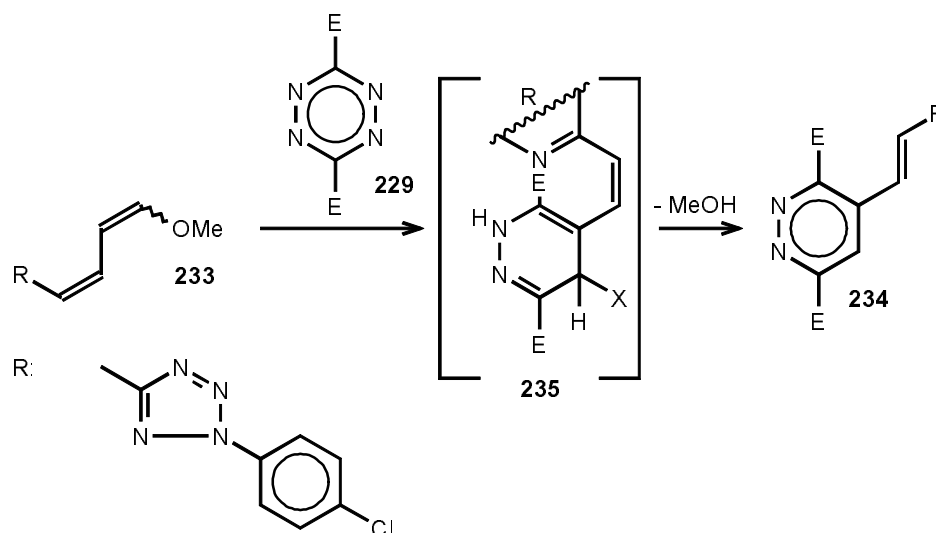
Tetrazolyl-methoxy-butadiene (**233**) which consists as a mixture of the *Z,Z* and *Z,E* isomers was expected to give a product with a *Z*-side chain geometry but reaction of **233** with **229** in boiling toluene resulted in the formation of the *E*-azolylvinyldiazine (**234**). As neither the starting material nor the product isomerised under the applied conditions the surprising behaviour was attributed to the reaction intermediate (**235**) [98] which was isolated and shown to possess an azolyl-dienamine substructure capable of isomerisation (cf. chapter G.1.)

Scheme 76

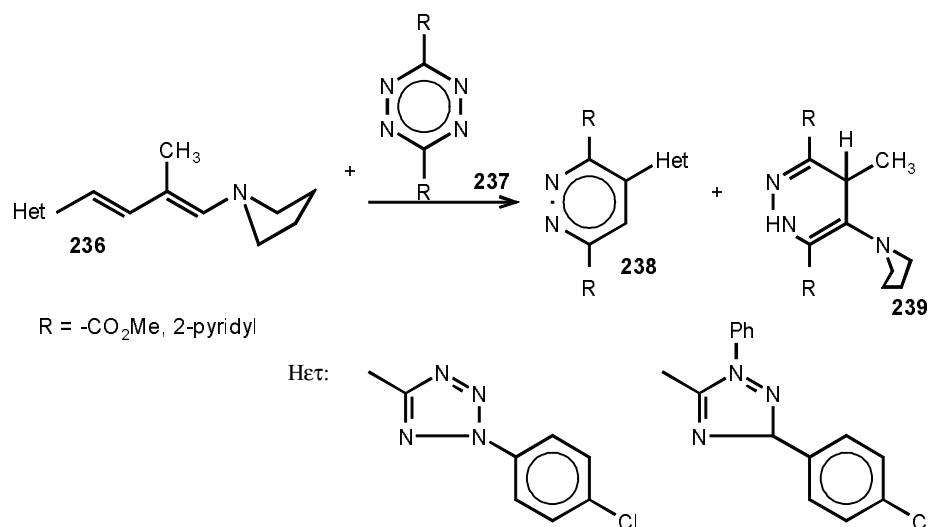


Attempts directed at the capturing of the primarily formed dihydropyridazine intermediate by introduction of a methyl group into the appropriate position of the hetaryldiene diene and thus disabling amine elimination failed as the reaction took a different course. The dienamine (**236**) took up two equivalents of the tetrazine (**237**) and a 1:1 mixture of hetarylpyridazine (**238**) and amino-dihydropyridazine (**239**) was formed in each case. Experimental evidence suggests that the reaction proceeds via a double "inverse electron demand" Diels-Alder addition-disproportionation pathway [99].

Scheme 77



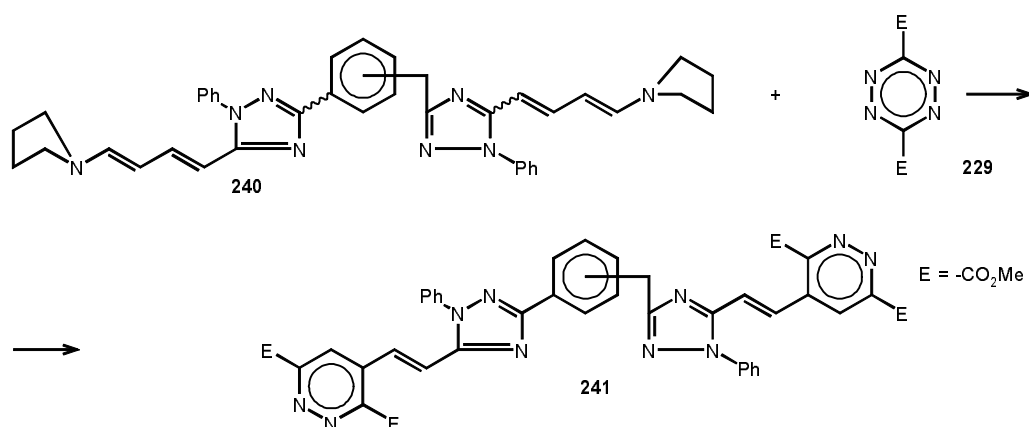
Scheme 78





The application of the "inverse electron demand" Diels-Alder reaction in polymer synthesis is a topic of current interest. The synthesis of hetaryldienamines was extended to their bis-analogues (**240**) which in a model experiment also reacted smoothly with the tetrazine **229** and the bis-adduct **241** was formed in good yield [100].

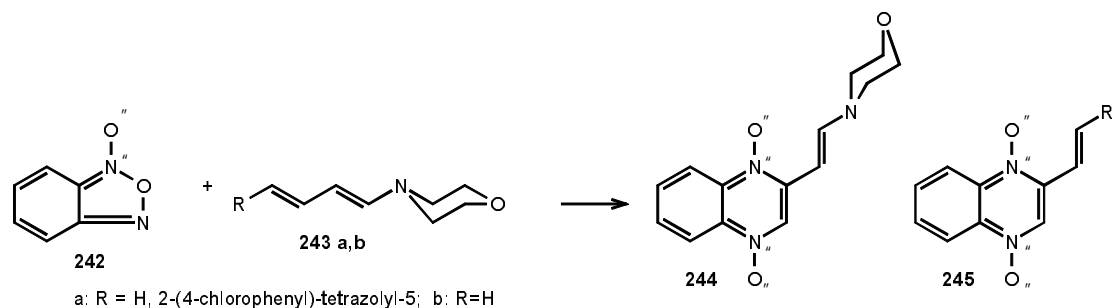
Scheme 79



#### H.2.4. 2+8 cycloadditions

The 2+8 cycloaddition of electron-rich olefins with electron deficient conjugated tetraenes is an analogue of the inverse Diels-Alder reaction. A representative of this class is the reaction of the tetrazolyldienamine **243a** with benzofuroxane which yielded the tetrazolylylvinylquinoxaline dioxide **245** in poor yield (23%) [84]. The analogous transformation of morpholino-butadiene (**243b**) resulted in the formation of the enamino-quinoxaline-bis-oxide **244** in 75% yield [101]. Unlike in the case of arylazides (chapter H.2.2.) the site of attack in these reactions seems to be determined by steric factors.

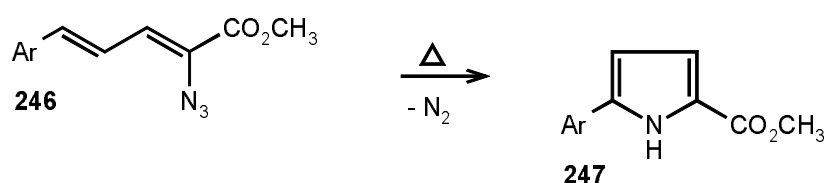
Scheme 80



## I. Rearrangements

The rearrangement of hetaryldienes requires the incorporation of sensitive or reactive functionalities which can be activated in the course of the process. Azido-hetaryldienes (**246**) for example eliminate nitrogen on heating to give nitrenes which ring close spontaneously to pyrrol derivatives (**247**) [24, 25].

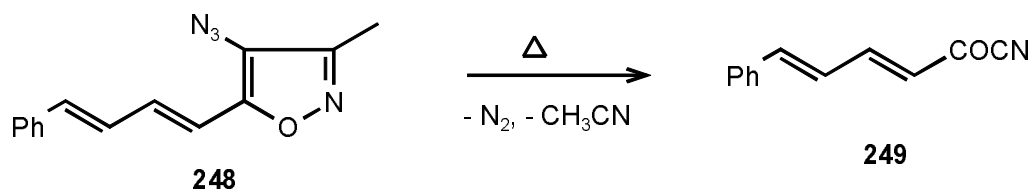
Scheme 81



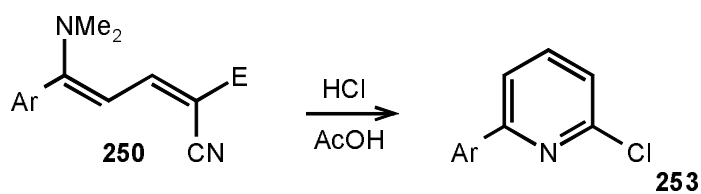
Ar: Phenyl, 2'-Thienyl, 3'-Thienyl, 2'-Furyl, 3'-Furyl, 2'-Pyrrolyl

Interestingly, the placement of the azide onto the heterocycle instead of the diene chain led to a different reaction. Although the nitrene formed from **248** could have ring closed onto the diene, the isoxazolyldiene **248** lost nitrogen and acetonitrile on heating to give the acylnitrile **249**.

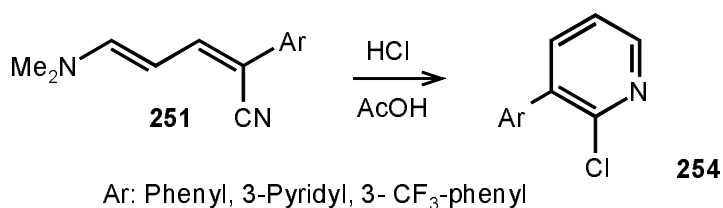
Scheme 82



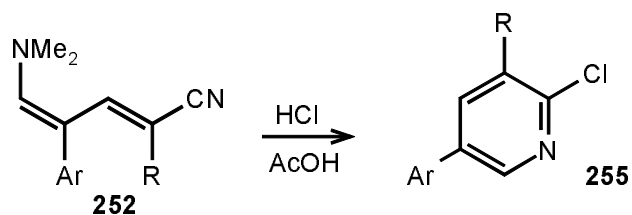
Scheme 83



Ar: Phenyl, 3-Pyridyl, 3- $\text{CF}_3$ -phenyl; E:  $\text{CO}_2 + \text{Bu}$



Ar: Phenyl, 3-Pyridyl, 3- $\text{CF}_3$ -phenyl



Ar: 3-pyridyl, 3- $\text{CF}_3$ -phenyl, 4-Cl-phenyl,  
2-Me-phenyl, 3,4- $(\text{CH}_3\text{O})_2$ -phenyl

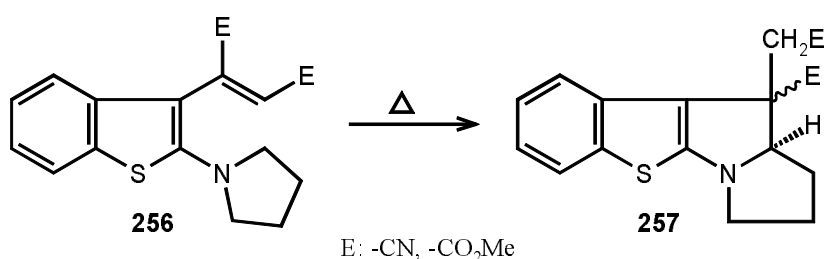
R: H,  $\text{CO}_2\text{CH}_3$ ,  $\text{SO}_2\text{Ph}$ , CN

The 1-cyano-4-dimethylaminobutadiene part provides the means for the transformation in the hydrogen chloride mediated rearrangement of the hetaryldienes **250-252** to the hetarylpiperidine derivatives **253-255**. Yields are strongly substituent and substitution

pattern dependent and vary in the range of 30-95% [79]. Using methanolic ammonia to promote ring closure instead of hydrogen chloride-acetic acid the chlorine is replaced by an amine function in the products.

Appropriately substituted benzo[b]thiophenes (**256**) were shown to undergo stereoselective thermal rearrangement to benzothieno[3,2-b]pyrrolizine derivatives (**257**) [102] the stereochemical outcome of the process strongly dependent on the polarity of the applied solvent. Toluene as a reaction medium favoured the formation of the ( $\beta$ -E)-isomer (86% isolated yield), while the use of acetic acid led to the ( $\alpha$ -E)-isomer in 73% yield.

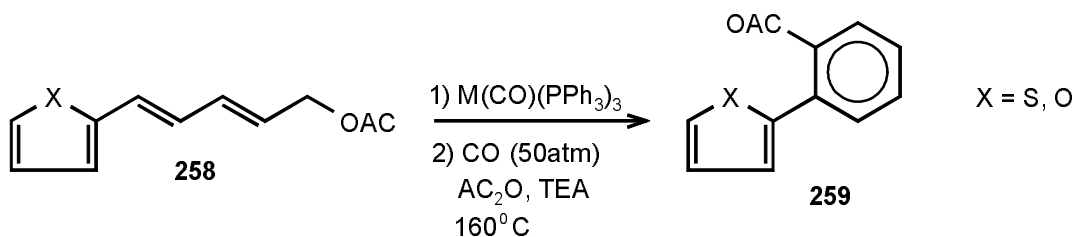
Scheme 84



### J. Miscellaneous transformations

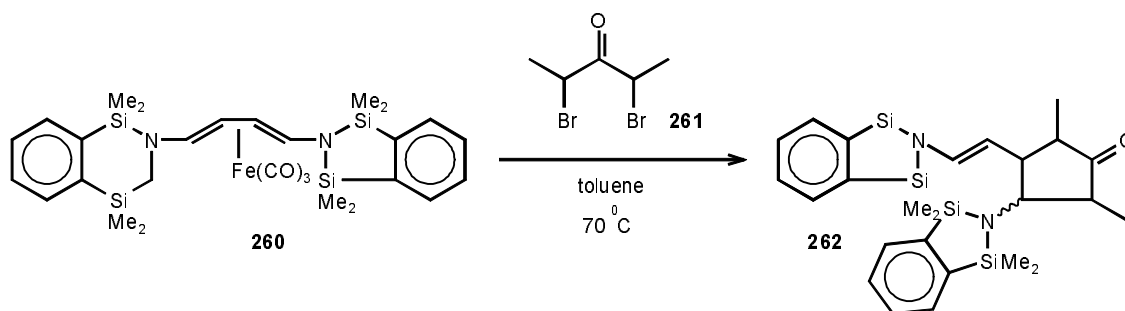
The palladium catalysed transformation of allylic acetates was extended to furyl- and thienyl-vinyls. Allylic carbonylation of **258** followed by rearrangement and acetylation under the applied conditions led to the *o*-hetaryl-phenol derivatives (**259**) in moderate yield [95].

Scheme 85



The iron carbonyl complex of the bis-benzodisilazinyl-diene (**260**) reacted with 2,4-dibromo-pentan-3-one (**261**) and a cyclopentanone moiety was formed in the reaction onto one of its double bonds (**262**). The low yield of the transformation (20%) makes this reaction more a sign to show new fields to explore than a practical application [104].

Scheme 86



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