CYCLOADDITION REACTIONS OF PYRIDINIUM YLIDES AND OXIDOPYRIDINIUMS

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Abstract - Inter- and intramolecular cycloaddition reactions of pyridinium ylides and of oxidopyridiniums are presented, along with such reactions of related azaaromatics.

I. INTRODUCTION

Since cyclization reactions of *N*-substituted pyridinium salts are a convenient approach to fused heterocycles, they are the topic of numerous publications. [1-9] Among these processes cycloaddition reactions, so inter- as intramolecular, play an important role.

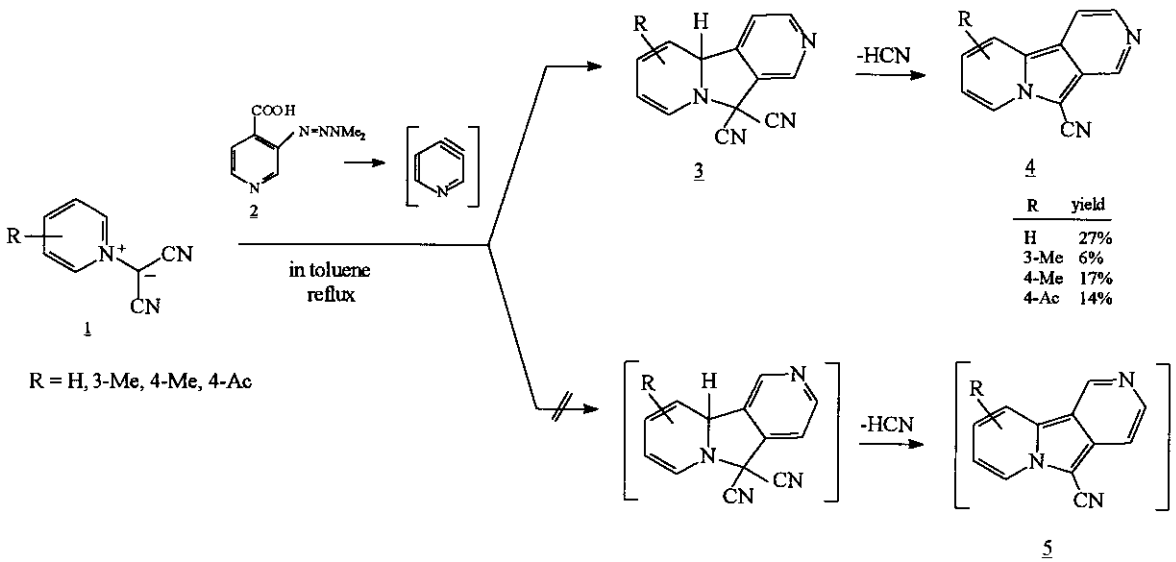
In the continuation of our research concerning the reactivity of *N*-substituted benzonaphthyridinium salts [10-12] we describe here inter- and intramolecular cycloaddition reactions of pyridinium ylides , and of oxidopyridiniums, and such reactions of related compounds.

II. CYCLOADDITION REACTIONS OF PYRIDINIUM YLIDES

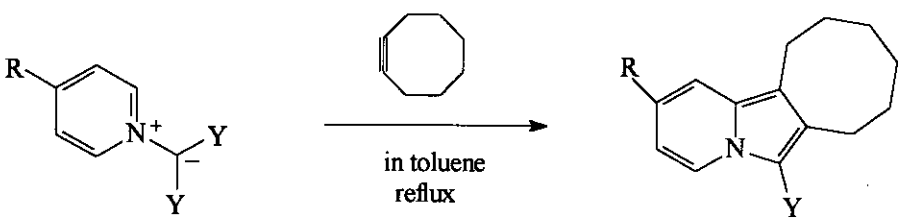
a. Intermolecular cycloaddition reactions

Intermolecular cycloadditions comprise 1,3-dipolar cycloaddition reactions, many examples of these processes are known .[13] The reaction of dicyanomethylides (1) with pyridinecarboxylic acid (2), the precursor of 3,4-didehydropyridine, was studied. The initially formed products (3) undergo the hydrogen cyanide elimination, leading to pyrido[4,3-*a*]indolizines (4).[14] It is interesting that no formation of products (5), regioisomers of 4 was observed in spite of theoretical predictions and in contrast to

analogous reactions with benzyne. [15] This result involves a zwitterionic character of the 3,4-dide-hydropyridine precursor.



1,3-Dipolar cycloaddition reaction of ylides (6) with cyclooctyne affords smoothly indolizines (7). [16]



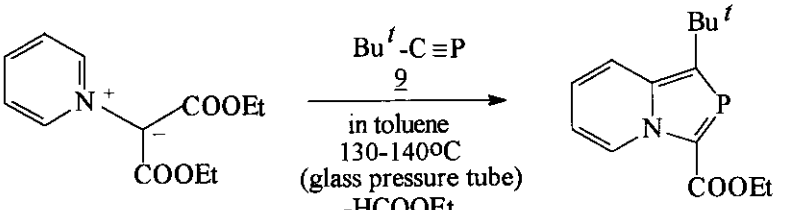
R = H, Me, COMe
Y = CN, COOMe

7

R	Y	time	yield
H	CN	1.5 h	62%
Me	CN	5 h	41%
COMe	CN	1 h	64%
H	COOMe	9 h	62%
Me	COOMe	1 h	41%
COMe	COOMe	2 h	66%

When the electron withdrawing substituents are present in the 4-position of pyridinium ylides, the yields are higher, what suggests that the reactions are controlled by dipole-(LUMO)-cyclooctyne (HOMO). This observation is in agreement with molecular orbital calculations with PM 3, AM 1 and MNDO methods.[16]

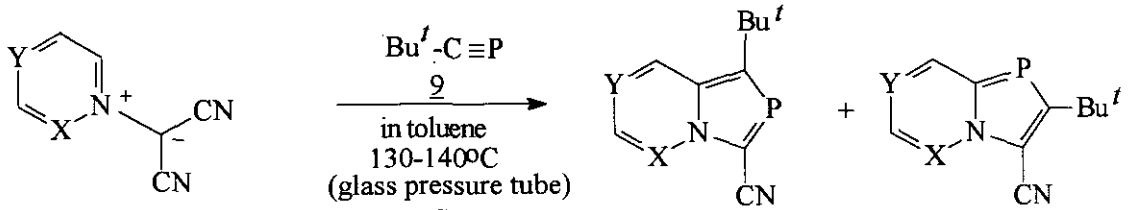
In the study of the reactivity of pyridinium ylide (8) towards phosphaalkynes, this species was treated with 9. The reaction proceeding *via* a regiospecific 1,3-dipolar cycloaddition and the subsequent elimination of ethyl formate leads to phosphaindolizine (11).[17]



8 11

30% yield

However, ylides (12) react with 9 in an unspecific way to give the regioisomers (13) and (14).[17]



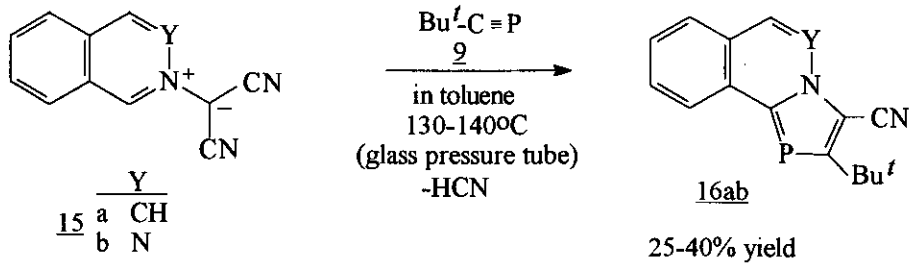
12	X	Y
a	CH	CH
b	N	CH
c	CH	N

13 14

1 : 1

40-60 % yield

Reactions of isoquinolinium and phthalazinium ylides (15a,b) with 9 proceed in a similar manner as in the case of 8, giving rise, under elimination of hydrogen cyanide, to fused 1,3-azaphospholes (16a,b); the elimination of hydrogen cyanide is here promoted by the addition of triethylamine. These processes are regiospecific, although here the dipole orientation is reverse of that in the case of 8.[17] Analogous reactions with Et_2MeC-C≡P have been performed.[17]

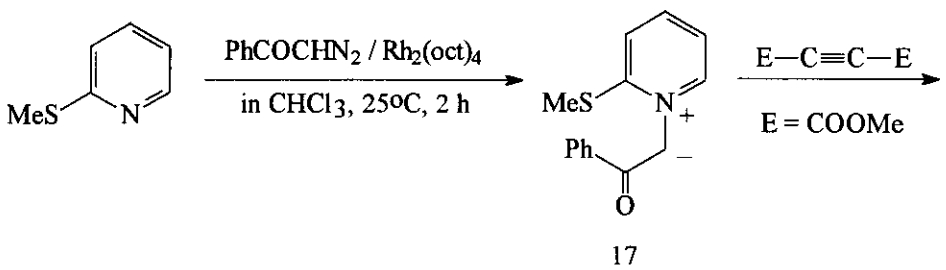


15 a CH
b N

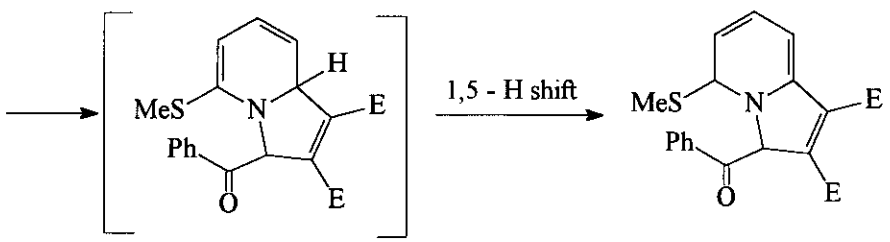
16ab

25-40% yield

The treatment of 2-methylthiopyridine with α-diazoacetophenone in the presence of rhodium (II) octanoate as catalyst leads to the ylide (17) which in the reaction with DMAD undergoes 1,3-dipolar cycloaddition resulting in 18, converted into the final product (19) by a 1,5-sigmatropic hydrogen shift. [18]



17



18

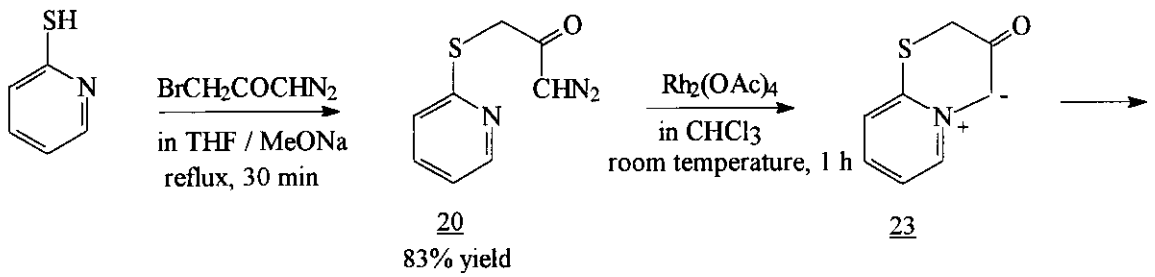
19

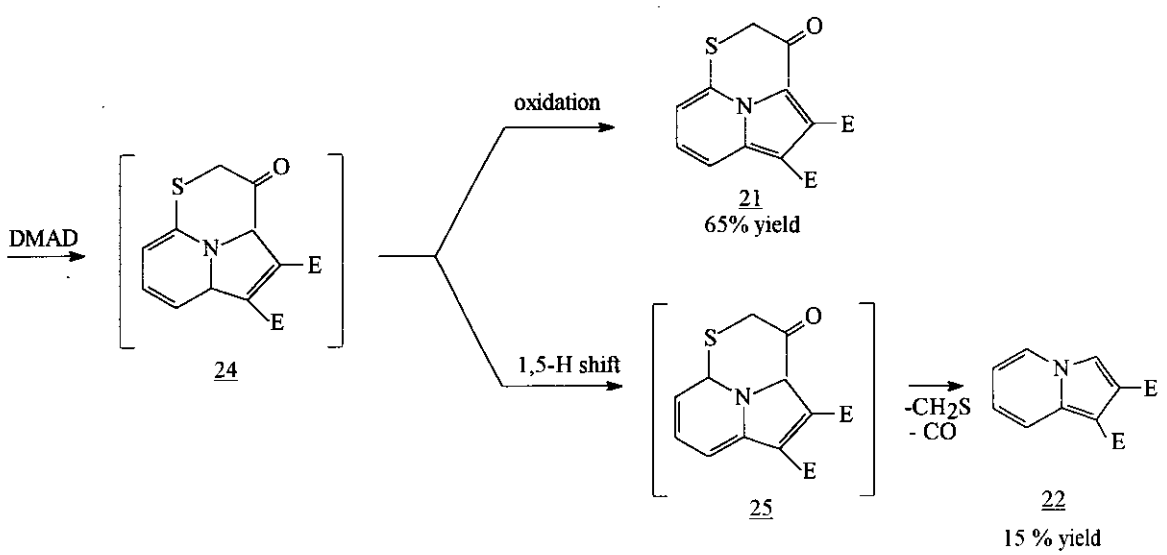
60% yield

2-Mercaptopyridine reacts with 1-bromo-3-diazo-2-propanone to give the α-diazo ketone (20). The reaction of 20 with DMAD, catalyzed by rhodium (II) acetate, affords a mixture (21) and (22) of indolizines.

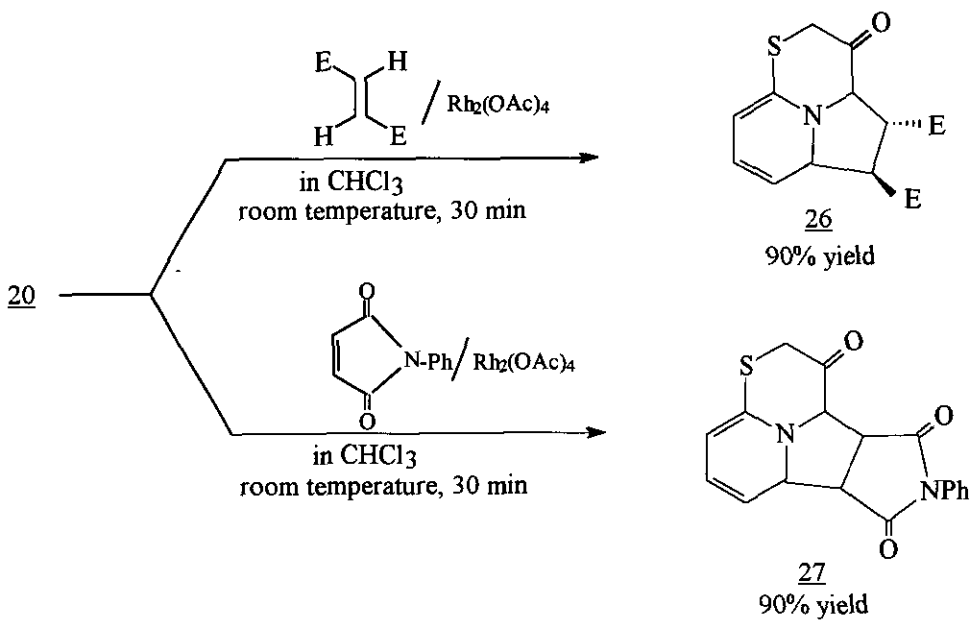
The process involves the 1,3-dipolar cycloaddition of the generated pyridinium ylide (23) with DMAD, leading to the cycloadduct (24), which is readily oxidized to 21. The 1,5-hydrogen shift of 24 results in

the formation of the intermediate (25), converted by fragmentation analogous to that of *N*-acyl-2-(1-diazaacetyl)pyrrolidines [19] into indolizine (22). [18]

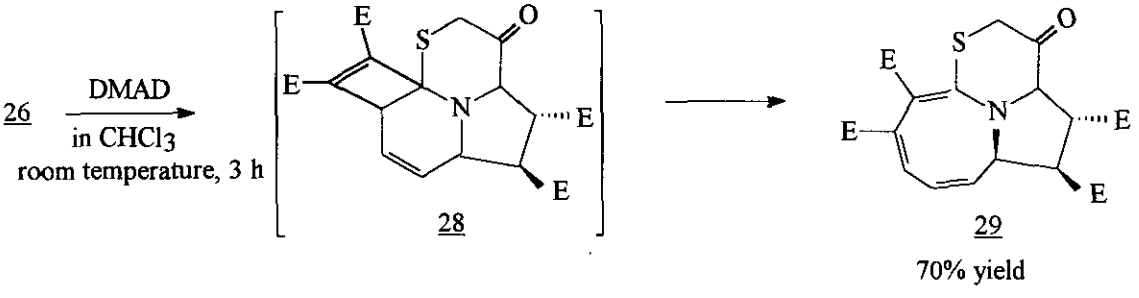




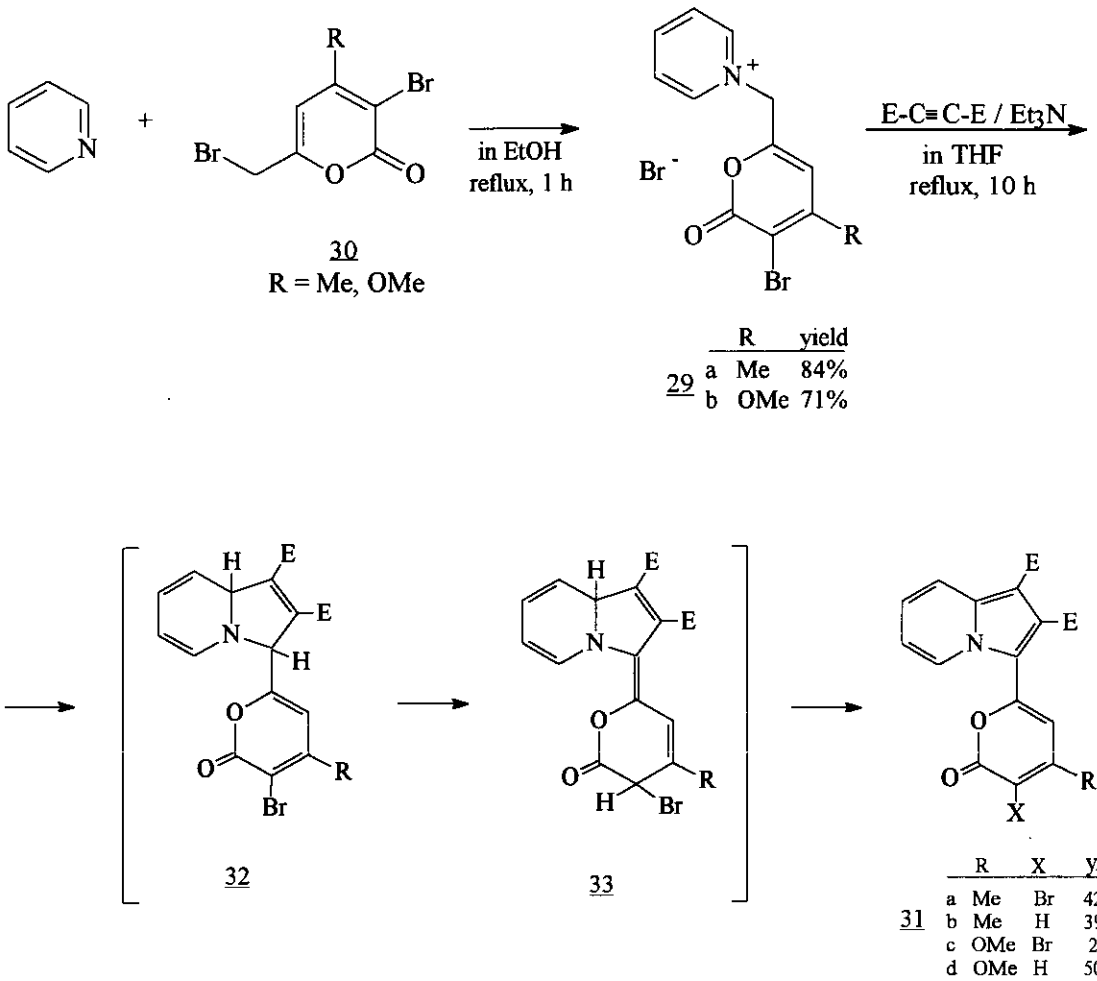
Cycloaddition reactions of 20 with dimethyl fumarate and *N*-phenylmaleimide resulting in (26) and (27) respectively, have also been performed.



When the cycloadduct (26) was submitted to the reaction with DMAD, the initial [2 + 2] cycloaddition gave rise to the intermediate (28) undergoing an electrocyclic ring opening to azocin-3-one (29). [18]



The quaternary salts obtained from pyridine and 2-pyrones (30) undergo a 1,3-dipolar cycloaddition with DMAD, resulting in indolizines (31a-d). The reaction proceeds *via* intermediates (32) and (33) ; the dehydrogenation leads to products (31a,c) and the dehydrobromination, *via* 1,5-sigmatropic reaction, to products (31b,d). [20]



30
R = Me, OMe

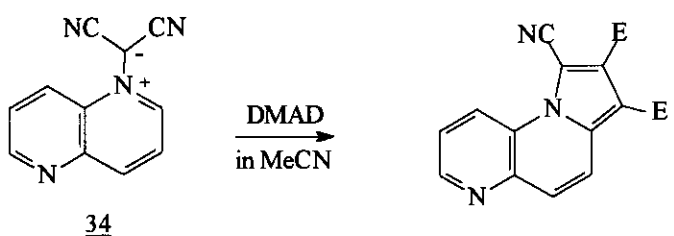
29

	R	yield
a	Me	84%
b	OMe	71%

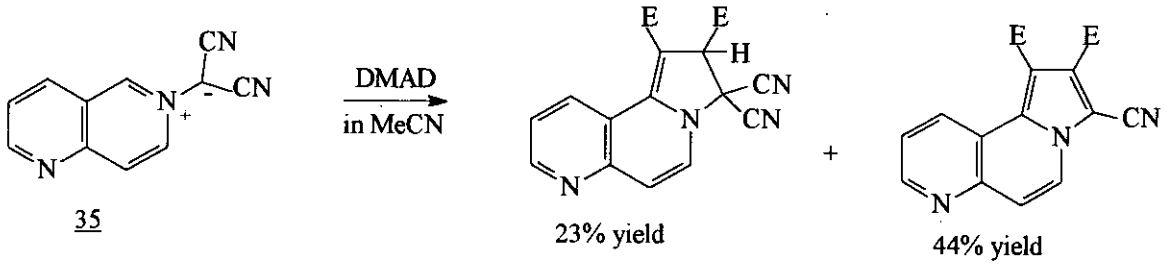
31

	R	X	yield
a	Me	Br	42 %
b	Me	H	39 %
c	OMe	Br	2 %
d	OMe	H	50 %

1,3-Dipolar cycloaddition reactions of naphthyridinium ylides (34-37) with DMAD shown below have been investigated. [21]



34



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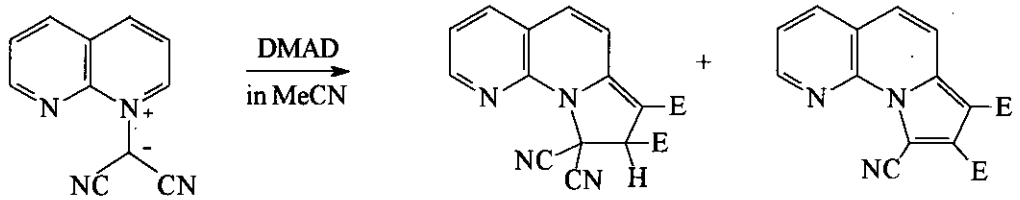

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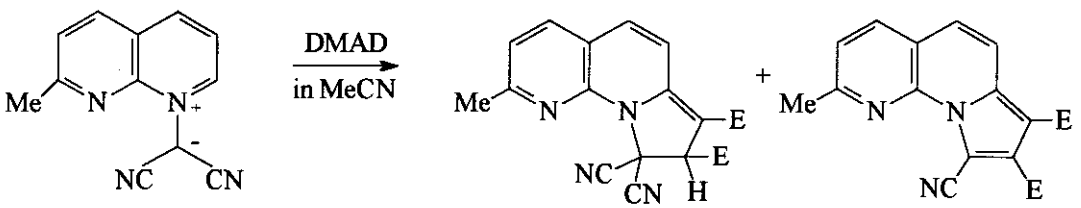
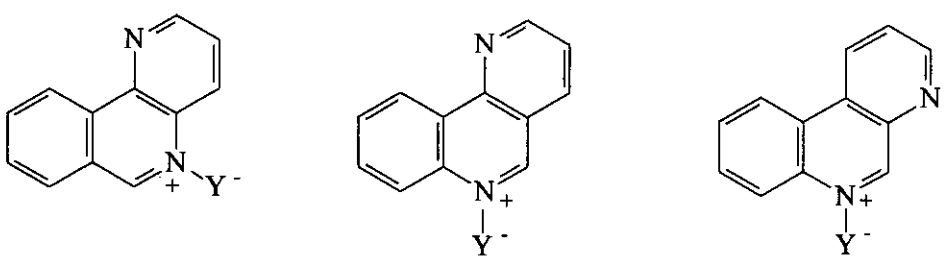


37

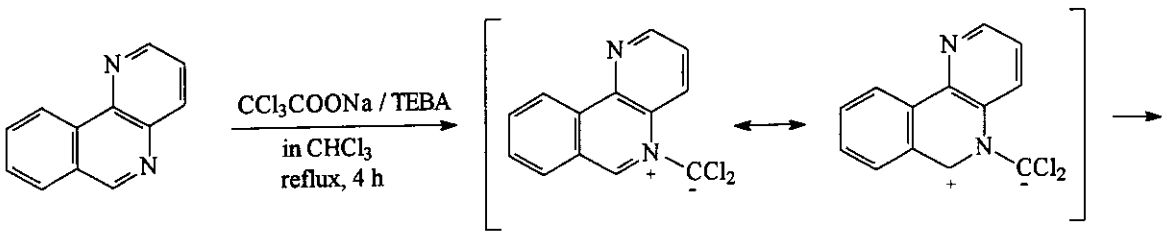
Ylides have been formed by treatment of appropriate naphthyridines with TCNEO; in the case of 37, the ylide is formed at N 8, and not at N 1 atom. [21]

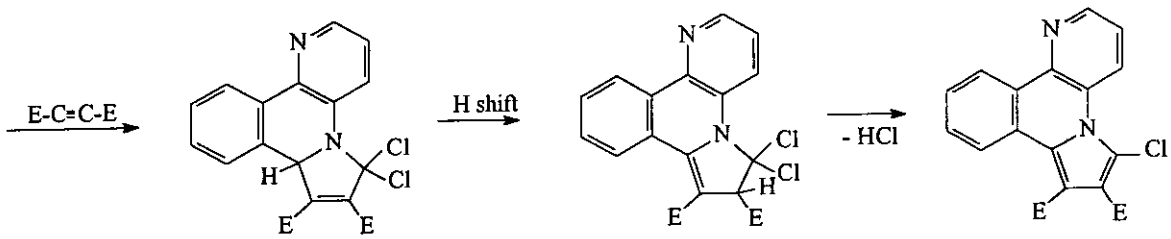
In the study of ylides derived from quaternary salts of diazaphenanthrenes, cycloaddition reactions of the following ylides have been performed with a series of dipolarophiles, such as acrylonitrile, ethyl acrylate, diethyl maleate, DMAD and others.[10]



Y = CCl_2, CHCOPh, CHCOOEt

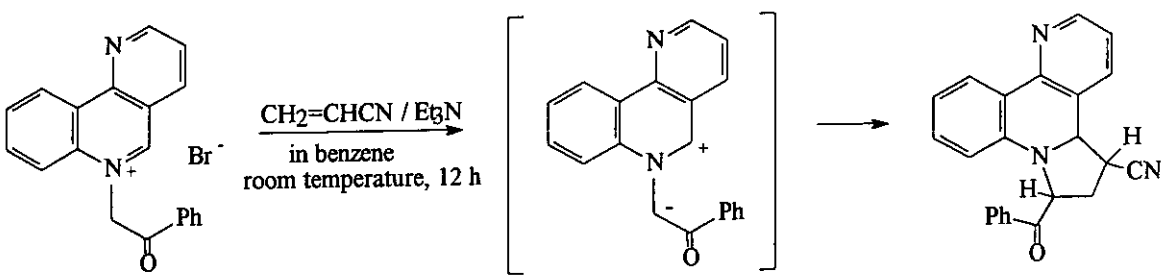
For example:





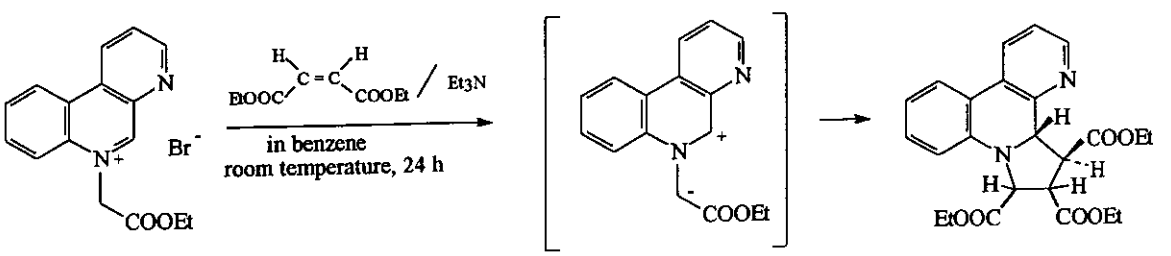
5.3% yield

Ref.10



37% yield

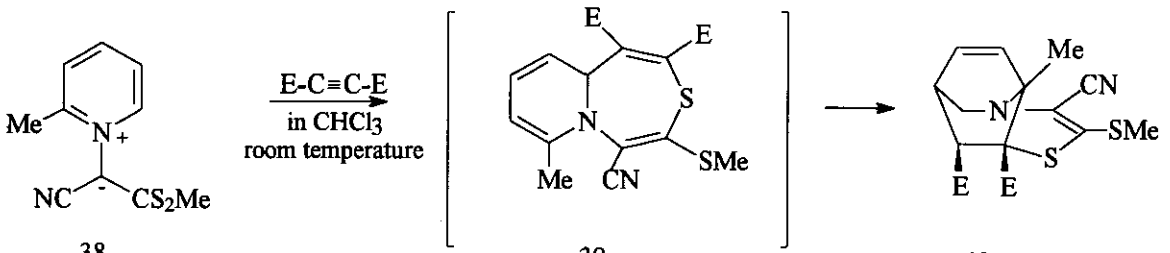
Refs. 11, 22-24



19.8 % yield

Refs. 12, 25

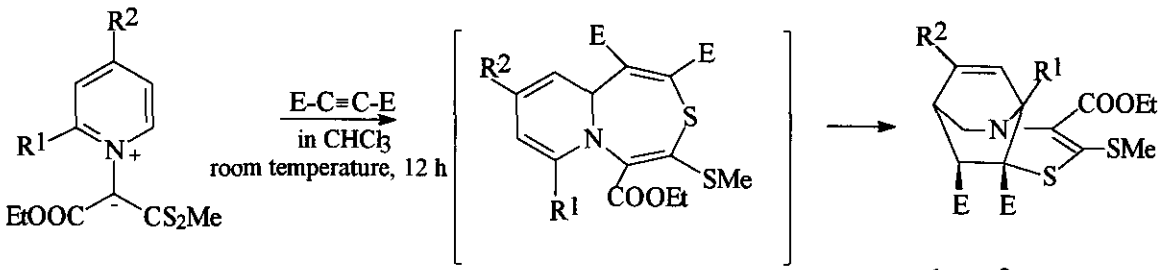
An example of the 1,5-dipolar cycloaddition is the reaction of the ylide (38) with DMAD, leading to the intermediate pyridothiazepine (39), which undergoes an intramolecular Diels-Alder reaction resulting in the tetracyclic product (40). [26,27]



38 39 40

28 % yield

Reactions of ylides (41) with DMAD proceed in an analogous manner. [26]



	R1	R2
a	H	H
b	Me	H
c	H	Me

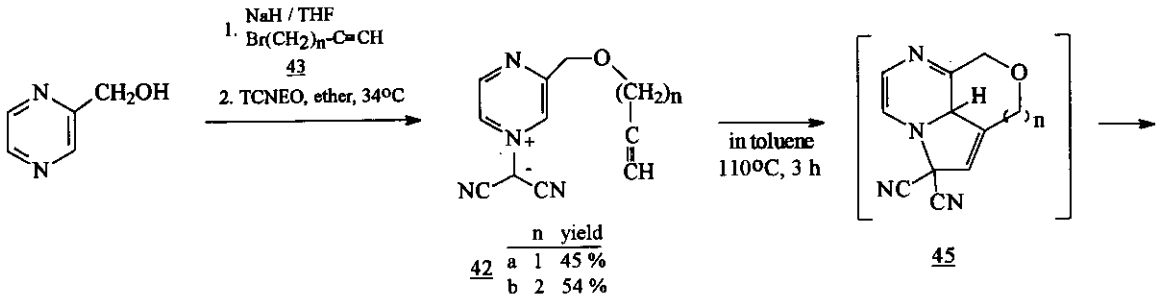
41

R1	R2	yield
H	H	51 %
Me	H	46 %
H	Me	38 %

b. Intramolecular cycloaddition reactions

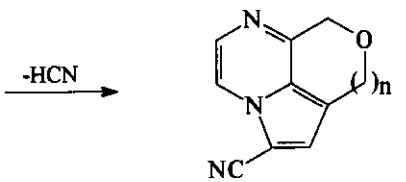
Many intramolecular cycloaddition reactions have been studied. [28,29] Describing [3+2] intramolecular cycloadditions, it should be mentioned the thermally induced transformation of pyrazinium ylides (42a,b). [17,30] Ylides have been obtained from 2-hydroxymethylpyrazine by treatment with alkynyl bromide (43) and TCNEO.

Ylides (42a,b) refluxed in toluene afforded fused 7-azaindolizines (44a,b); this reaction proceeds *via* primary intramolecular 1,3-dipolar cycloadduct (45) undergoing the hydrogen cyanide elimination. In the case of 42a also a minor product (46) is formed *via* 47 intermediate. [30]

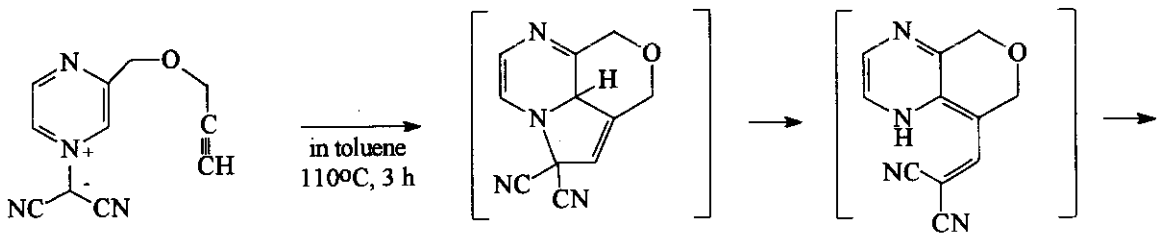


	n	yield
42 a	1	45 %
b	2	54 %

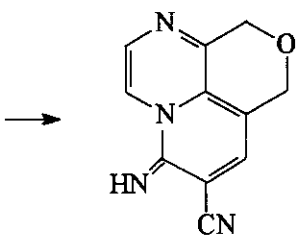
45



	n	yield
44 a	1	52 %
b	2	79 %



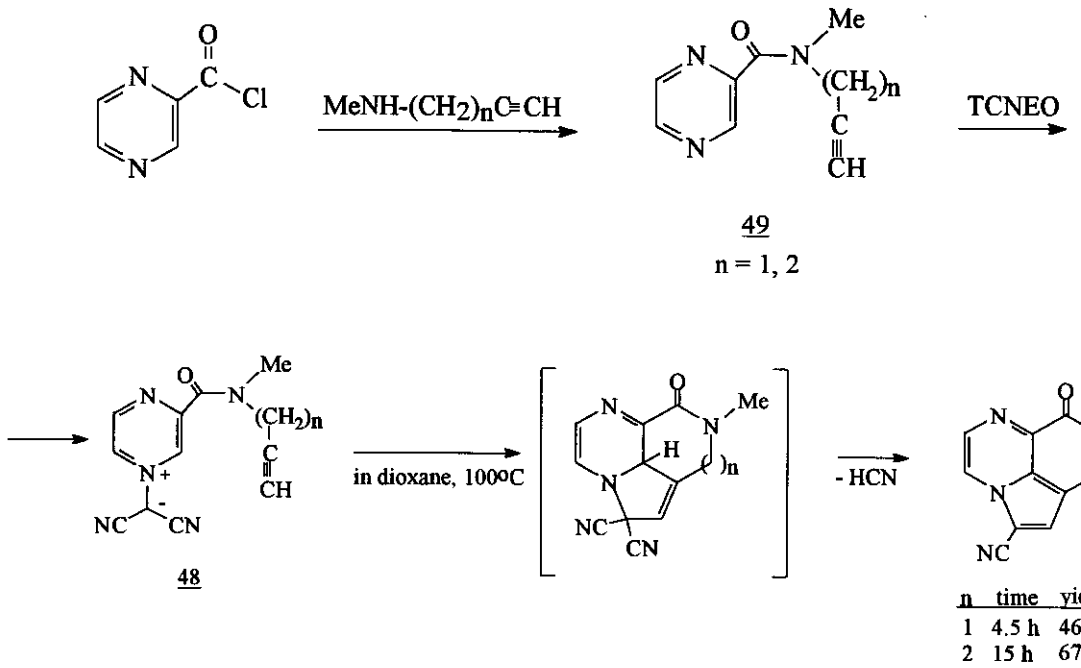
42a 45a 47



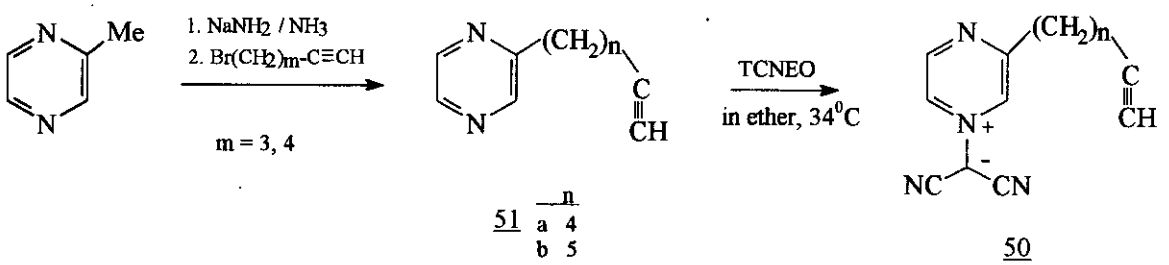
46

8% yield

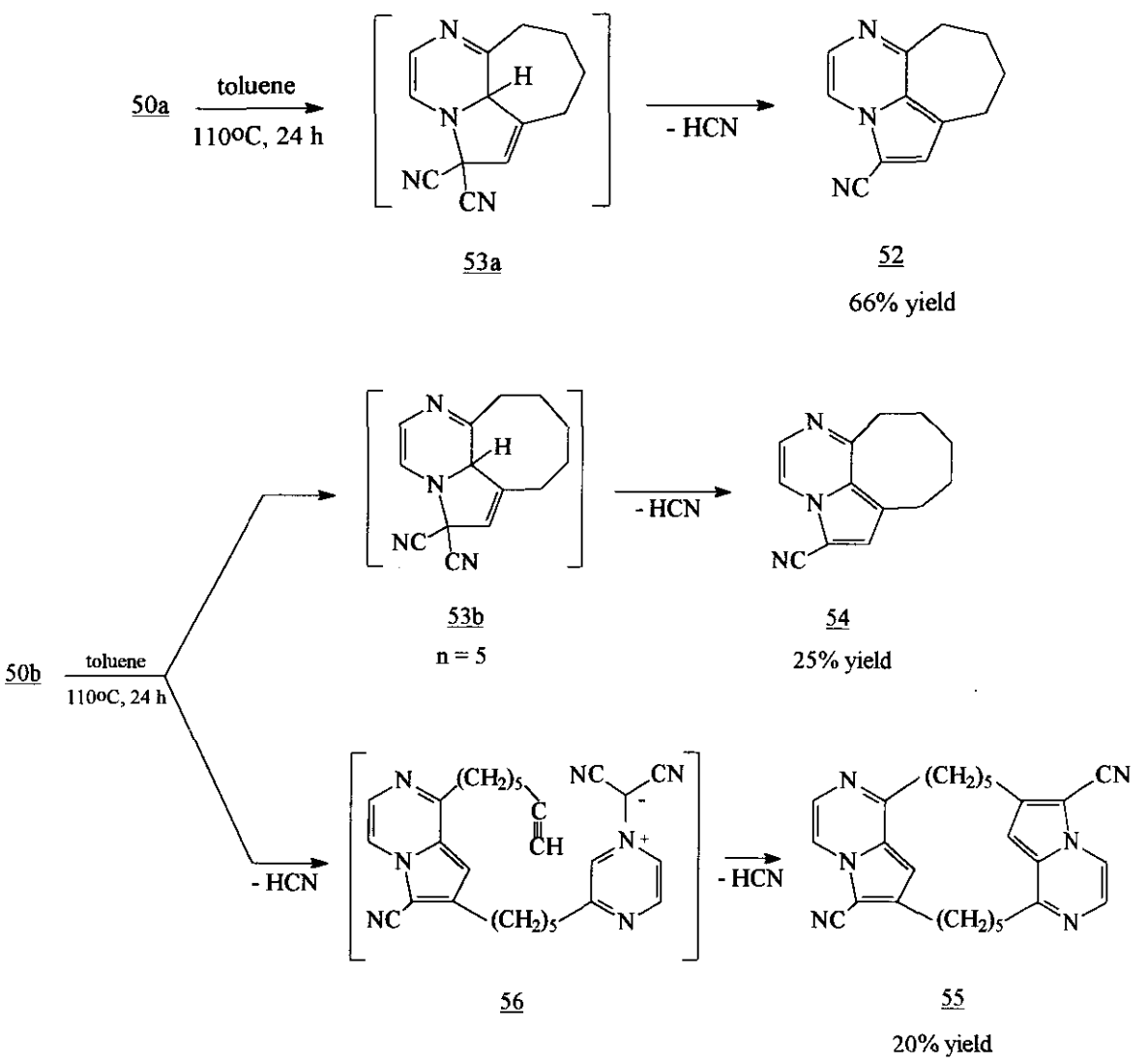
The cycloaddition of the ylide (48), prepared from pyrazine-2-carboxylic acid chloride *via* 49 proceeds in a similar way.[30]



The reaction of the ylide (50) obtained from 2-methylpyrazine *via* 51 leads to intra- or intermolecular cycloadducts, depending on the length of the aliphatic chain.

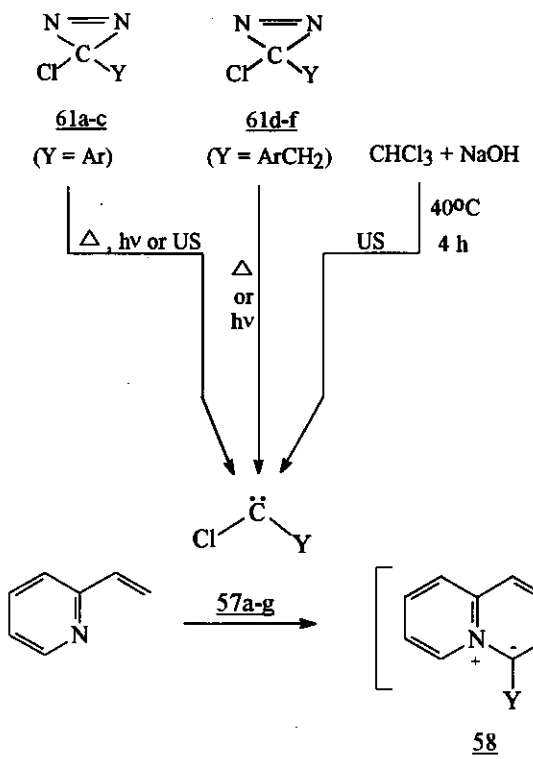


In the case of 50a intramolecular cycloadduct (52) is formed *via* the intermediate (53a), while in the case of 50b along with the analogous intramolecular cycloadduct (54), *via* 53b, also the product of intermolecular cycloaddition , *i.e.* 55 is obtained *via* the intermediate (56).[30]



The treatment of 2-vinylpyridine with chlorocarbenes (57) results in the formation of pyridinium ylides (58) undergoing a smooth intramolecular 1,5-dipolar cycloaddition reaction to give dihydroindolizines (59); the subsequent hydrogen chloride elimination from 59 affords indolizines (60). [31-34]

Arylchlorocarbenes were generated from corresponding arylchloroazirines (61a-c) by thermolysis, photolysis or ultrasound (US) irradiation, benzylchlorocarbenes however only by thermolysis or photolysis of benzylchloroazirines (61d-f), as they are stable to US. Dichlorocarbene (61g) has been generated from NaOH-$CHCl_3$ solid-liquid system by the action of US.[31]



60

	Y		yield
a	Ph	hν	10 %
		△	52 %
		US	40 %
b	4-MeC_6H_4	hν	12 %
		△	52 %
		US	54 %
c	4-ClC_6H_4	hν	11 %
		△	52 %
		US	47 %
d	$PhCH_2$	△	27 %
e	4-$MeC_6H_4CH_2$	△	21 %
f	4-$ClC_6H_4CH_2$	△	21 %
g	Cl	US	13 %

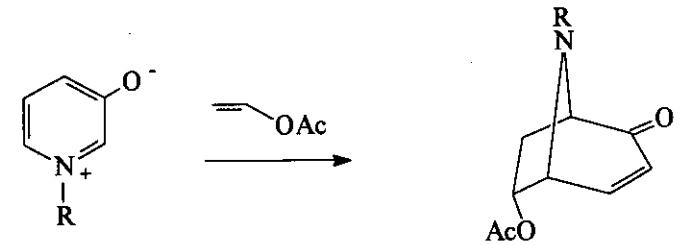
photolysis : λ = 350 nm, in hexane, 25 °C,24 h
thermolysis: in dry benzene, reflux, 16 h
US: in hexane, irradiation for 48 h

III. CYCLOADDITION REACTIONS OF OXIDOPYRIDINIUMS

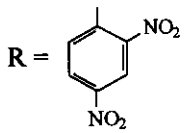
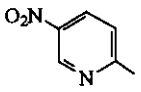
Numerous works deal with inter- and intramolecular cycloaddition reactions of 3-oxidopyridiniums providing in a facile way interesting bicyclo compounds; some examples will be presented here.

a. Intermolecular cycloaddition reactions

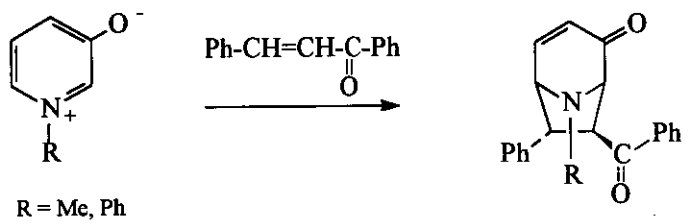
Describing intermolecular processes of oxidopyridiniums,[35-38] it should be mentioned the 1,3-dipolar cycloaddition of the oxidopyridinium (62) with vinyl acetate leading to the cycloadduct (63), bridged across 2,6-positions .[39]



62 63

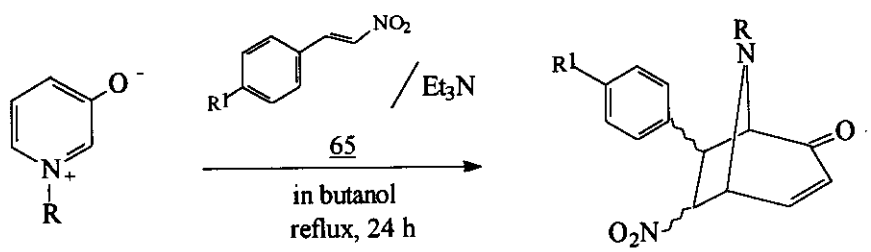
R =  , 

Another example of intermolecular cycloaddition of 3-oxidopyridiniums is the following reaction .[40]



R = Me, Ph

It was observed that the 1,3-dipolar cycloaddition of 3-oxidopyridiniums (64) with β-nitrostyrenes (65) resulting in 66 is highly regiospecific and not stereospecific; this fact may be explained in view of the effect of nitro group on HOMO and LUMO levels of the β-nitrostyrene olefinic bond.[41]



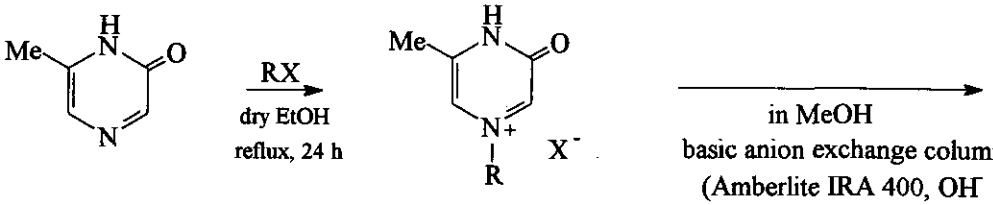
64 65 66

R = Me, Ph R^1 = H, OMe 50-55% yield

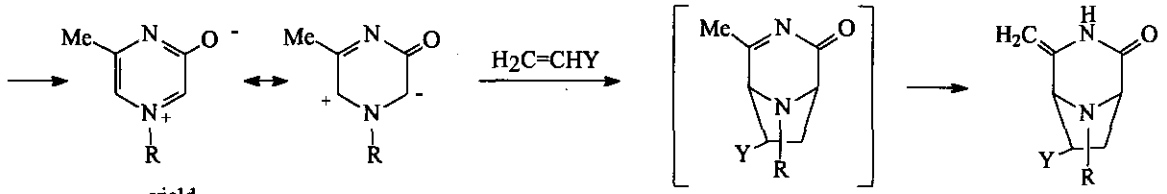
The 1,3-dipolar cycloaddition reaction of oxidopyraziniums (67a,b) with a series of dipolarophiles leads to products (68). Oxidopyraziniums (67a,b) have been prepared by quaternization of 6-methylpyrazin-2-one

and the subsequent deprotonation of the formed salts (69) under basic conditions.[42] The reaction proceeds *via* the initial, not isolable cycloadduct (70).

It should be pointed out that 67b is more soluble than 67a therefore the reaction times of 67b are shorter, and the excess of dipolarophile is not necessary.[42]



		R	X	yield
69	a	Me	I	80 %
	b	$PhCH_2$	Br	80 %

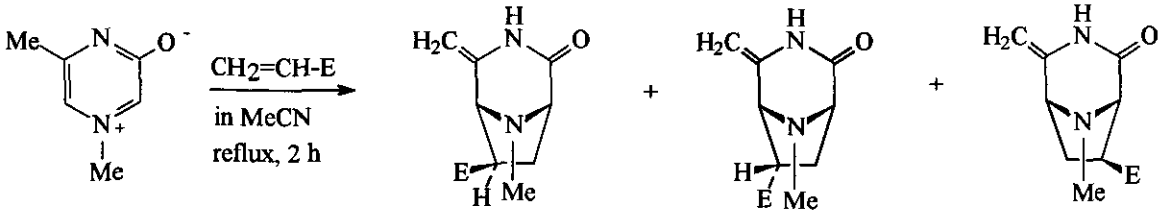


		yield
67	a	96 %
	b	97 %

70 68

The stereochemistry of the above cycloadditions of CH_2=CHY for various Y is given below.

The reaction of 67a with methyl acrylate affords the mixture of exo- and endo-isomers (68a) and (68b), along with a small amount of the regio isomer (71).



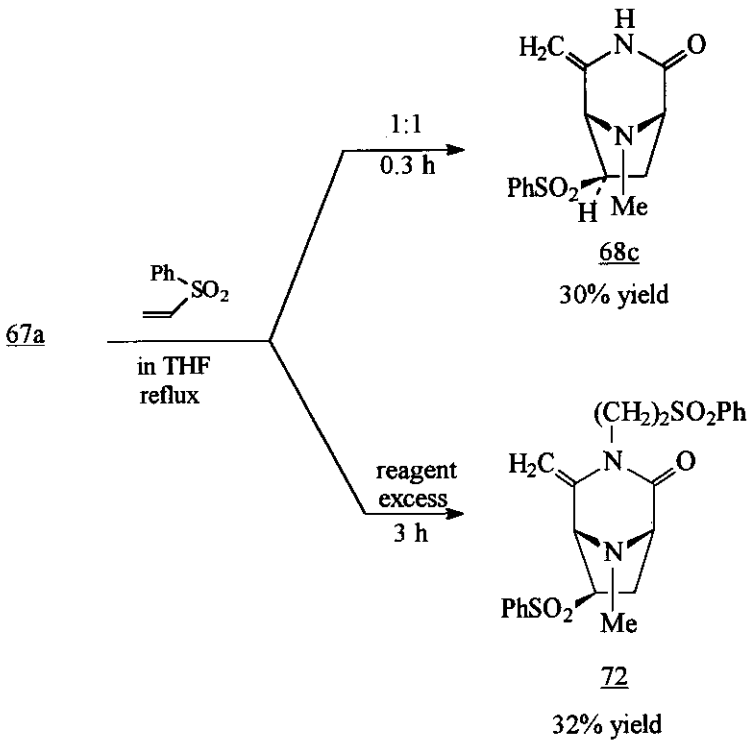
67a

68a 42% yield

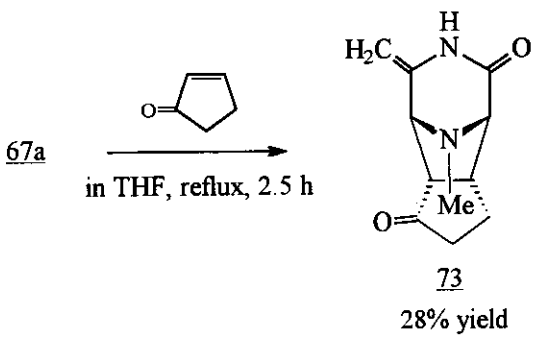
68b 13% yield

71 1% yield

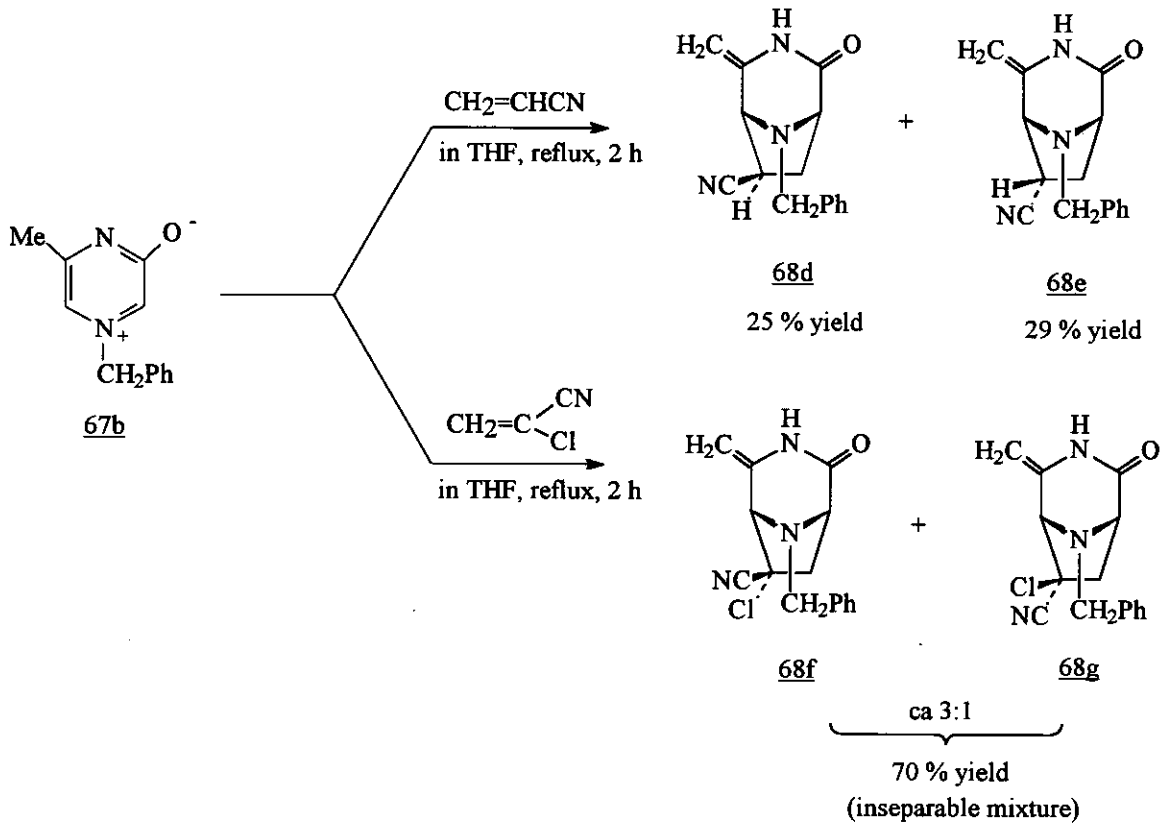
The treatment of 67a with phenyl vinyl sulfone leads to the expected cycloadduct (68c), while with the excess of this reagent the *N*-substituted product (72) of 68c is obtained.



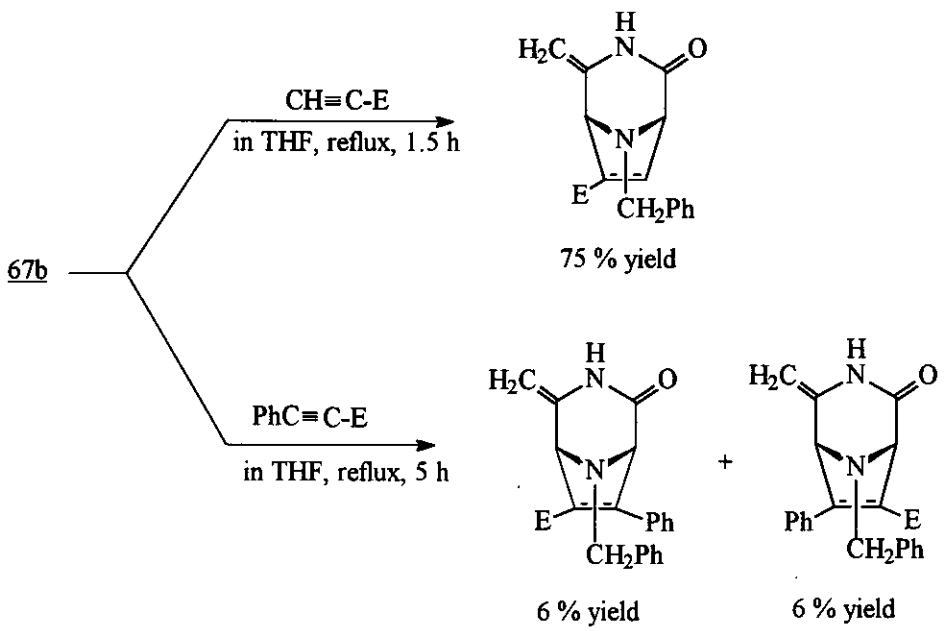
The reaction of 67a with 2-cyclopentenone provides the endo adduct (73).



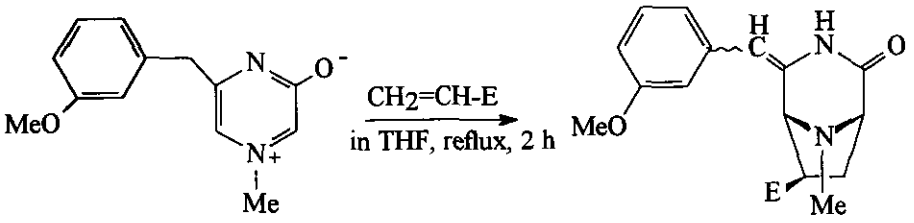
The oxidopyrazinium (67b) reacts with acrylonitrile to give exo- and endo-isomers (68d) and (68e), and with chloroacrylonitrile a mixture of isomers (68f) and (68g) was produced.



Using methyl propiolate or methyl phenylpropiolate as alkyne dipolarophiles, following reactions of (67b) have been performed.



It is worth noting that the reaction of the oxidopyrazinium (74) with methyl acrylate, leading to the exo-cycloadduct (75) is useful in the synthesis of quinocarcin .[42]

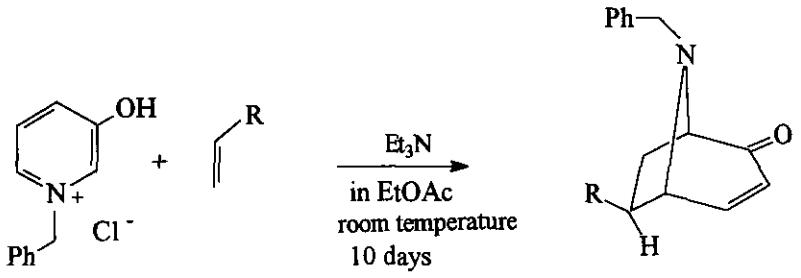


74 75

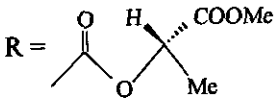
50 % yield

An example of the asymmetric 1,3-dipolar cycloaddition of 3-oxidopyridiniums, generated from 3-hydroxypyridinium quaternary salts is the reaction of *N*-methyl-3-oxidopyridinium with (R)-(+)-*p*-tolyl vinyl sulfoxide serving as a chiral dipolarophile. [43]

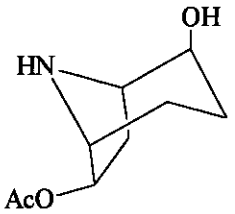
Similar reaction of the oxidopyridinium formed from *N*-benzyl-3-hydroxypyridinium chloride with the acrylate of methyl (S)-lactate (76) occurs preferentially at the re face of 76 giving rise to 6-exo-cycloadduct (77).[44]



76 77

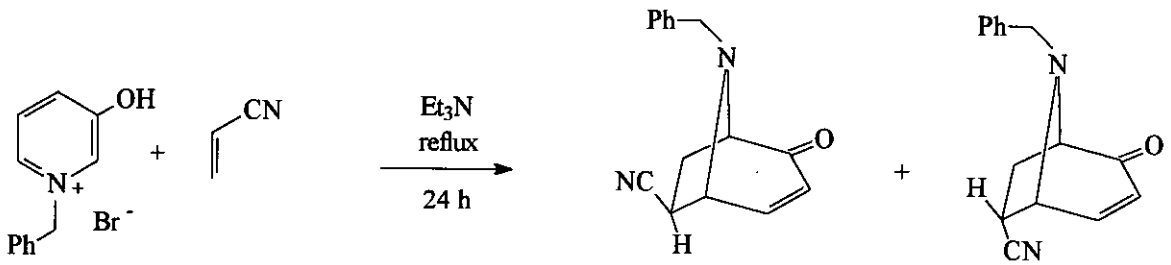


This process is the first step of the asymmetric synthesis of an optically active alkaloid Bao Gong Teng A , (–)- 78 showing strong antiglaucoma properties.[45]



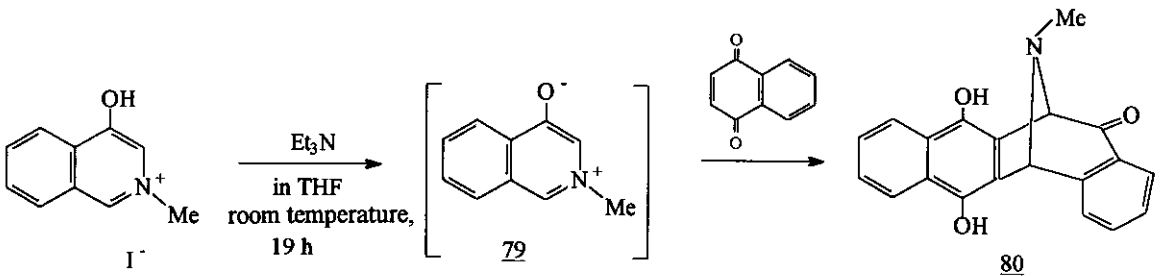
(–) -78

It should be noted that the first step of the total synthesis of racemic (78) is the following process .[45]



54 % yield 36 % yield

It was observed that oxidoisoquinolinium (79) formed from 4-hydroxy-*N*-methylisoquinolinium iodide by treatment with triethylamine in THF reacts with 1,4-naphthoquinone used as dipolarophile to give product (80) , bridged by 1,3-positions. [46]



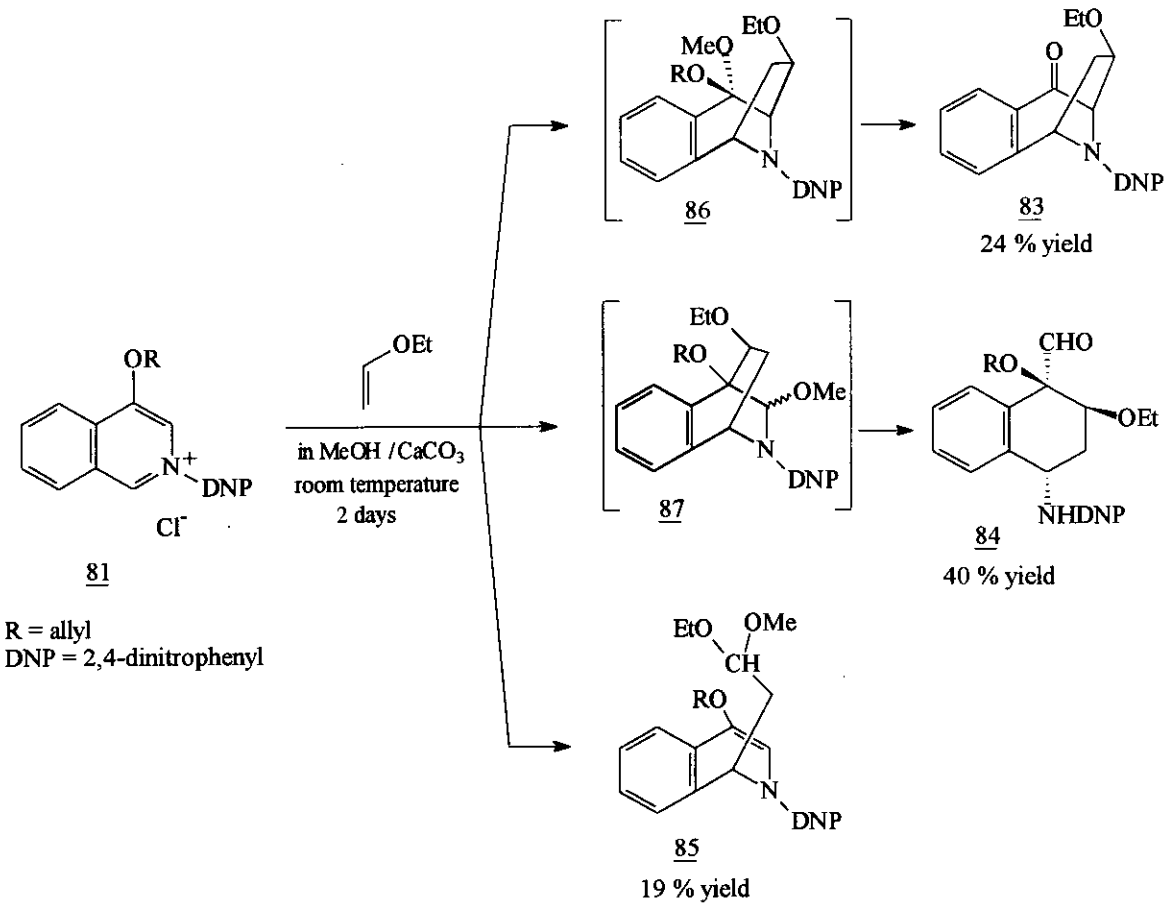
80

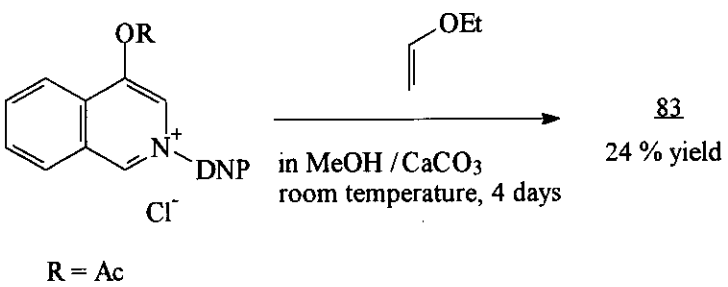
92 % yield

In the study of the Bradsher cycloaddition [47,48] the reaction of 4-hydroxyl-protected isoquinolinium salts (81) and (82) with ethyl vinyl ether has been performed.

The salts (81) and (82) treated with ethyl vinyl ether give cycloadducts bridged by 2,6-positions, i.e. the ketone (83).. The salt (81) produces besides 83 also the aldehyde (84) and the adduct (85). The ketone

(83) is formed *via* the intermediate ketal (86), and the aldehyde (84) *via* the tricyclic aminal (87). In the case of 82 the only product is 83. [49]

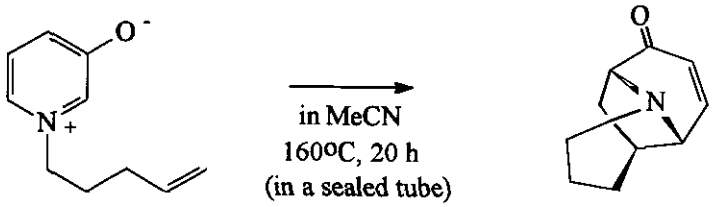




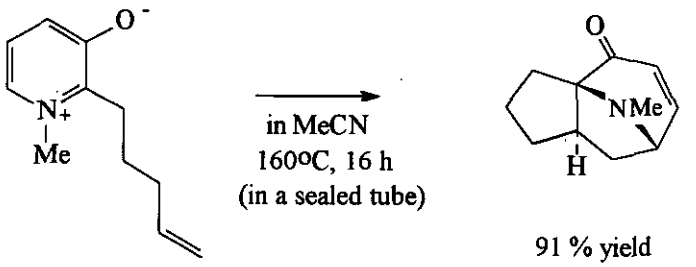
These reactions are useful in the synthesis of the sakyomycin class of the angucycline antibiotics.[49]

b. Intramolecular cycloaddition reactions

Examples of intramolecular cycloaddition of 3-oxidopyridiniums are following reactions.[50]

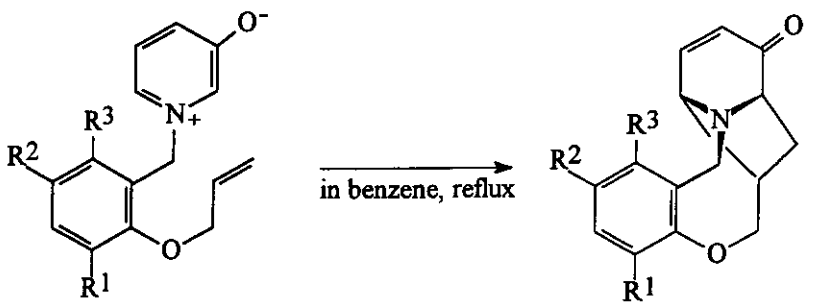


70 % yield



91 % yield

In order to investigate the influence of steric buttresses, the presence of the bulky substituent ortho to the allyloxy group on the reactivity of oxidopyridiniums (88a-d), their intramolecular cycloaddition has been studied .[51,52] It was established that in the case of 88a and 88b the reaction does not proceed. Oxidopyridiniums (88c) and (88d) afford cycloadducts (89c) and (89d), respectively; the higher yield of the reaction of 88d resulting in 89d is explained by the presence of two methyl groups in para position, forcing dipole and dipolarophile into a closer proximity. [51]



88
a $R^1 = R^2 = R^3 = H$
b $R^1 = Me$, $R^2 = R^3 = H$
c $R^1 = R^2 = Bu^t$, $R^3 = H$
d $R^1 = R^3 = Me$, $R^2 = H$

		time	yield
89c	$R^1 = R^2 = Bu^t$, $R^3 = H$	5 days	15 %
89d	$R^1 = R^3 = Me$, $R^2 = H$	12 h	80 %

IV. CONCLUSION

Cycloaddition reactions of pyridinium ylides and of oxidopyridiniums are a convenient approach to fused heterocycles, often not so readily obtained by other routes. It should be pointed out that these reactions, so inter- as intramolecular proceed smoothly, mostly under mild conditions. They are a method of the synthesis, in one step, of complex polycyclic compounds with a high degree of stereocontrol and are often used in the chemistry of natural products.

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