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REACTIONS OF PYRIDINIUM *N*-YLIDES AND THEIR RELATED PYRIDINIUM SALTS

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Abstract – This review describes some reactions of pyridinium *N*-ylides and their closely related pyridinium salts and the formation of various nitrogen-containing heterocycles which are not easily obtainable by other methods and are of high synthetical and pharmaceutical interest.

1. INTRODUCTION

Various reactions of pyridinium *N*-ylides and related pyridinium salts have been documented by many researchers since the first formation of pyridinium phenacylides by Dr. F. Kröhnke,[1] and some reviews of these compounds have also been provided.[2] From the mutual structural relations between the corresponding pyridinium methylides and aminides (**I**) and pyridinium salts (**II**) shown in Figure 1, four major reactions for pyridinium *N*-ylides (**I**), 1) the dipolar cycloaddition and cyclization of **Ib** or **Id**, 2) the nucleophilic addition of the ylidic anion of **Ia**, 3) the electrophilic addition of a positive carbon at the 2- (**Ib**), 4- (**Ic**), or 6-position (**Id**) on the pyridine ring, and 4) the ylidic bond fission, can be expected, while two major ones for pyridinium salts (**II**), 1) the electrophilic addition of a positive carbon at the 2- (**IIb**), 4- (**IIc**) or 6-position (**IId**) on the pyridine ring and 2) the nucleophilic addition of the carbanion or amide of **IIIa** or **IVa** generated by the deprotonation of the acidic methylene or amino group at the 2-, 4-, or 6-position, can be anticipated. This review covers the theoretically and synthetically important reactions of pyridinium *N*-ylides (**I**) and their related pyridinium salts (**II** and others) as of early 2012.

2. SYNTHESIS OF PYRIDINIUM YLIDES AND THEIR RELATED SALTS

Synthetic routes to pyridinium methylides **3**−**7**, 3-(1-pyridinio)thiophene-2-thiolates **8**−**10** and pyridinium aminides **12**−**17** are shown for compounds which will be used in this review as their representatives in Scheme 1. These routes consist of the formation of simple types of pyridinium methylides (**3**) and aminides (**12**) via the alkaline treatment of the pyridinium salts **2** and **11** which are easily obtainable by

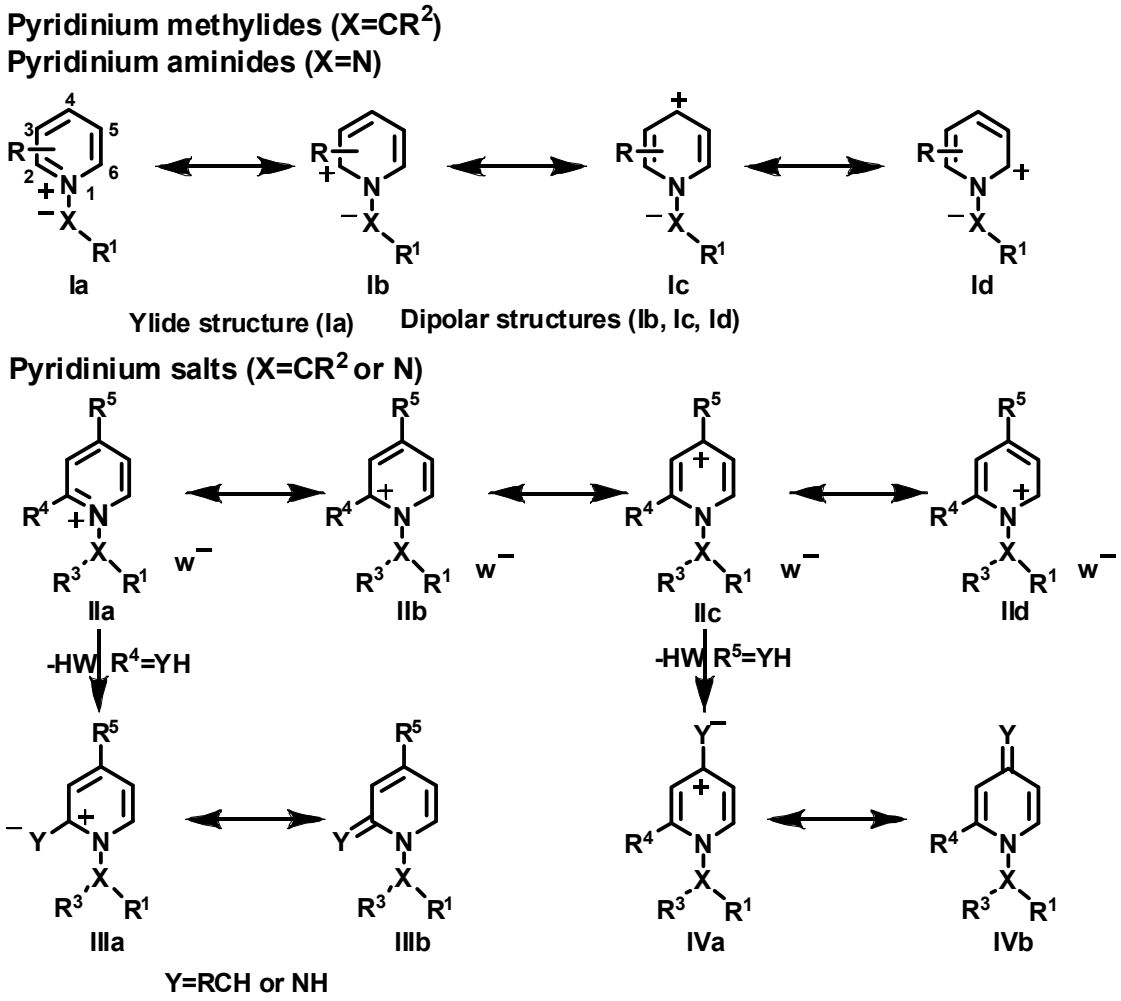
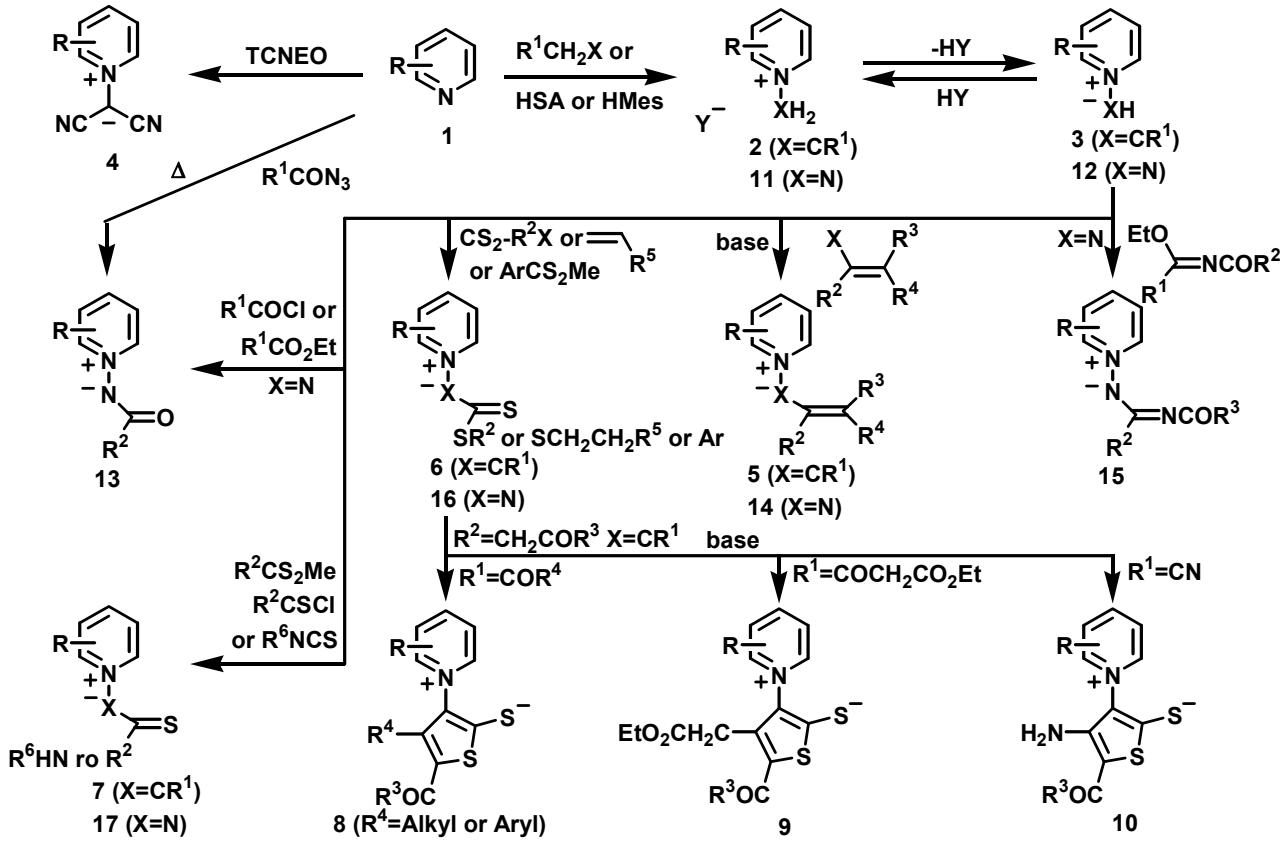


Figure 1

the reactions of pyridine derivatives (**1**) with various electrophiles such as alkyl halides, hydroxylamine *O*-sulfonic acid (HAS)[3] or hydroxylamine *O*-mesitylenesulfonate (HMes),[4] followed by their functionalization. For example, pyridinium *N*-ylides **4**−**7** and **13**−**17** can be easily synthesized by the introduction reactions of an acyl,[5] vinyl,[6] imidoyl,[7] or thiocarbonyl group[8] onto the ylidic anion atom of ylides **3** and **12**, and the intramolecular dehydration or nucleophilic addition of the functionalized pyridinium methylides such as **6** obtained thus provide the corresponding 3-(1-pyridinio)thiophene-2-thiolates (**8**−**10**).[9] The nucleophilicity of the ylidic anion atom (nitrogen) in pyridinium aminides **12** in these reactions is higher to some extent than that in pyridinium methylides **3**, because methylides **3** did not attack an ester carbonyl[10] and an imidate carbon atom[7] but aminides **12** reacted with them. On the other hand, pyridinium dicyanomethylides (**4**) have been generally prepared by the reactions of tetracyanoethylene oxide (TCNEO) with pyridine derivatives (**1**).[11] Though the direct formation of pyridinium acylaminides (**13**) from the thermolysis of acyl azides in the presence of pyridine derivatives (**1**) are also known,[12] such methods are not usually used except for a few examples because of their handling difficulty and their narrow scope of application.



Scheme 1

It is important to notice that pyridinium ylides such as **3**, **4**, and **13** have planar or near planar structures (dipole like) but other ylides **5**−**10** and **14**−**17** have non-planar structures owing to the cation-anion and cation-π interactions (Figure 2). The cation-anion interaction of pyridinium ylides **3** and **13** having an acyl group on the ylidic anion atom as shown in its betaine structures **3'** and **13'** is negligible, but that of pyridinium ylides **6**, **7**, **16**, and **17** possessing a thiocarbonyl group at the same position is not so and has significant influence on the structures, since the carbon-sulfur bond is considerably longer than the carbon-oxygen bond and this situation is favorable for the intramolecular cation-anion interaction. In addition pyridinium ylides **5** and **14** which have an aryl group on the anionic terminal of the 1,5-dipoles should have nearly perpendicular structures (allyl anion like) due to the strong cation-π interactions between the pyridinium ring and the aryl ring.[13]

Pyridinium salts related to pyridinium methylides and aminides can be formed by their reactions with various alkyl halides, α-haloacetates, and α-haloketones. Pyridinium ylides **3**, **12**, and **13** are alkylated at the anion atom of the 1,3-dipolar structure and ylides **5**−**10** and **14**−**17** at that of the 1,5-dipolar structure.

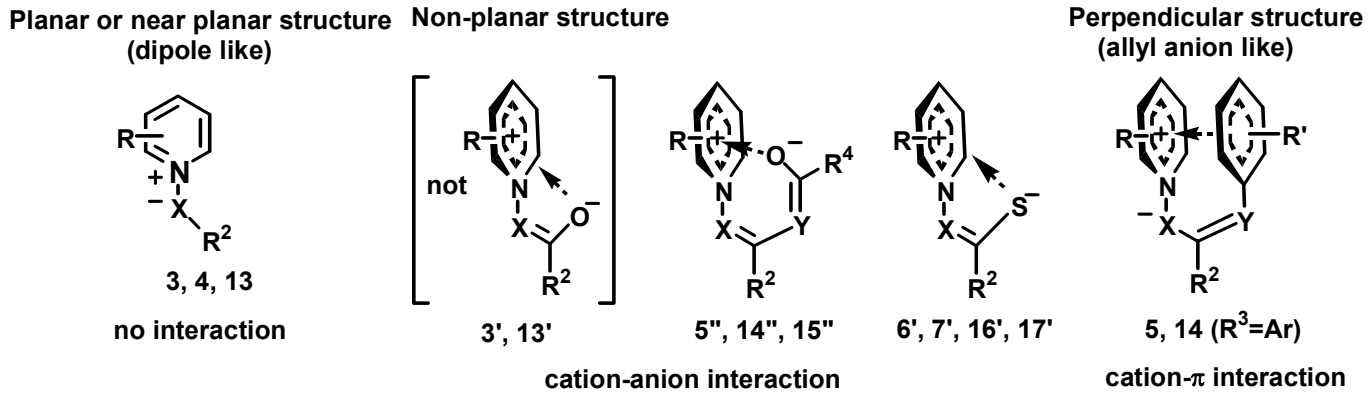
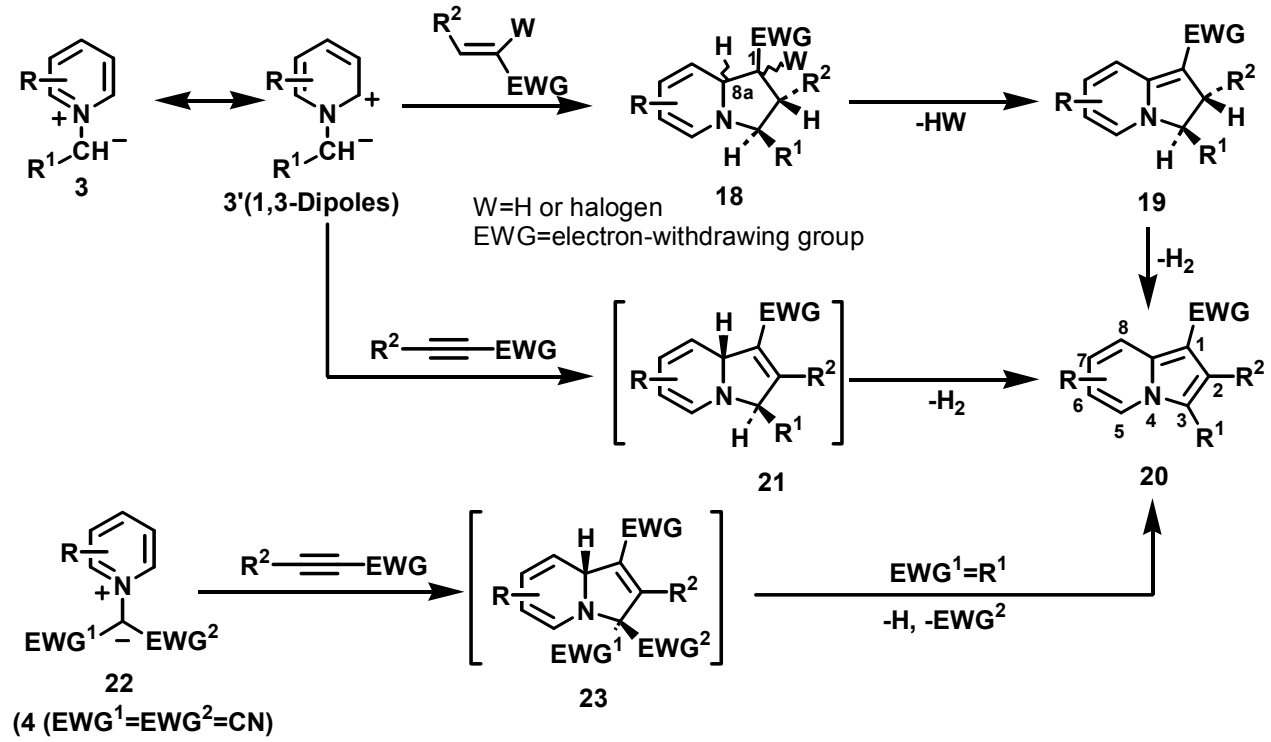


Figure 2

3. REACTIONS OF PYRIDINIUM YLIDES

3.1. REACTIONS AS DIPOLES

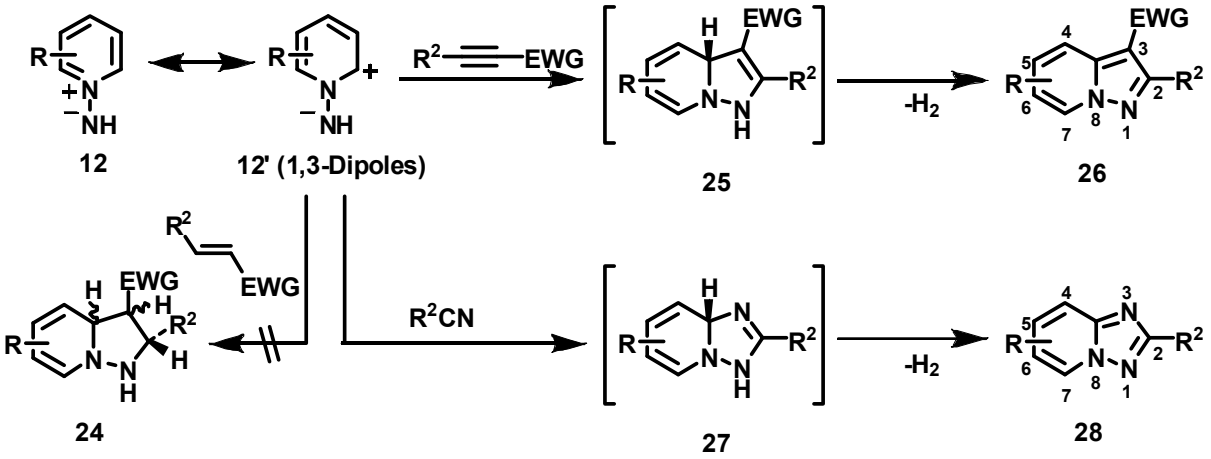
Thermal 1,3-dipolar cycloadditions (π4s+π2s) of pyridinium (monosubstituted)methylides (**3**) and (*N*-monosubstituted)aminides (**12**) with various electron-poor alkenes, alkynes, and nitriles are well known routes for obtaining indolizines, pyrazolo[1,5-*a*]pyridines, and 1,2,4-triazolo[1,5-*a*]pyridines. For example, the 1,3-dipolar form (**3'**) of methylides **3** reacted with acrylates, acrylonitriles, and maleimides to form the corresponding 1,2,3,8a-tetrahydroindolizine derivatives **18** which then underwent stepwise elimination to afford indolizines **20** (Scheme 2).[14] The isolation of some non-aromatic compounds **18**[14b,c] and **19**[14a] has been also described. Similarly, the reactions of **3** with electron poor alkynes such as dialkyl



Scheme 2

acetylenedicarboxylates and methyl phenylpropiolates, and with benzyne provided the corresponding indolizine and benzo[*a*]indolizine derivatives **20** via the smooth dehydrogenation of the primary 3,8a-dihydroindolizines **21**.[15] Pyridinium (1,1-disubstituted)methylides **22** can be also used in such cycloadditions and their reactions with the same dipolarophiles provided the corresponding indolizine derivatives **20** with the elimination of one electron-withdrawing group at the 3-position.[16] Pyridinium dicyanomethylides (**4**) have been often employed as useful substrates for the synthesis of indolizine-3-carbonitriles (**20** (R^1=CN)) because of smooth elimination of a hydrogen cyanide from primary bicycloadducts **23** (EGW^1=EGW^2=CN).[11,17]

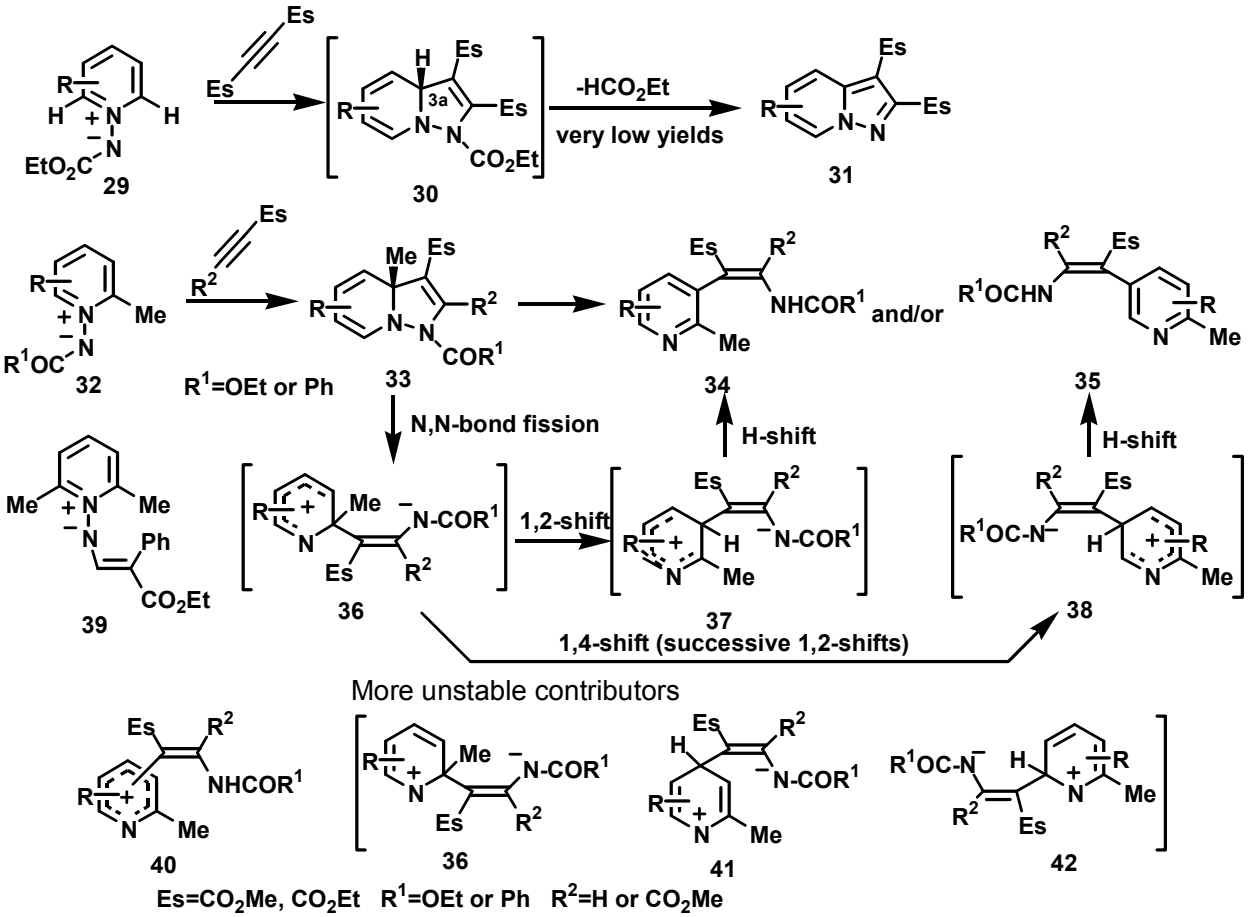
In contrast with pyridinium methylides **3** and **22**, the 1,3-dipolar cycloadditions of aminides **12** and **13** with olefinic compounds were scarcely reported due to the high nucleophilicity of the anionic nitrogen atom which will be described later. However, the reactions of **12** with acetylenic compounds such as acetylenedicarboxylates and propiolates[18] or with nitriles[19] proceeded smoothly to give the corresponding pyrazolo[1,5-*a*]pyridines **26** or 1,2,4-triazolo[1,5-*a*]pyridines **28** via the aromatization of the resulting 1,3a-dihydro-adducts **25** or **27** respectively (Scheme 3).



Scheme 3

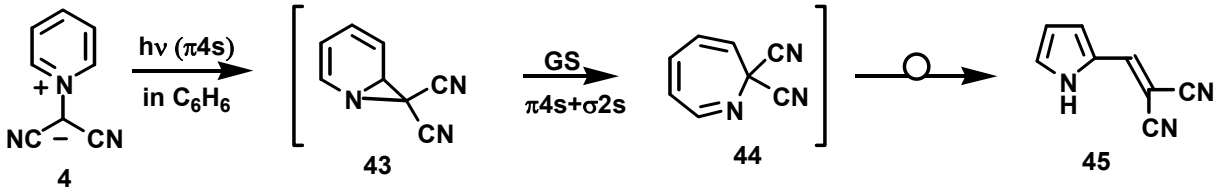
As in the case of pyridinium (1,1-disubstituted)methylides **22**, 1,3-dipolar cycloadditions of (2-unsubstituted)pyridinium (ethoxycarbonyl)aminides **29** with DMAD afforded the corresponding dimethyl pyrazolo[1,5-*a*]pyridine-2,3-dicarboxylates (**31**), but their yields were very low due to the difficulty in eliminating the *N*-ethoxycarbonyl group from adducts **30** (see Scheme 4). On the other hand, the reactions of 2-methylpyridinium acylaminides (**32**) with the same reagent gave some unstable primary adducts, 3a-methyl-1,3a-dihydropyrazolo[1,5-*a*]pyridine derivatives (**33**), which were smoothly converted to 3-vinylpyridines **34** and/or 5-vinylpyridines **35**.[20] Similar rearrangement was also observed in the reaction of 2,6-dimethylpyridinium vinylaminides such as **39** with ethyl propiolate.[21] The proposed mechanism for this rearrangement was first N−N bond fission of adducts **33**, the 1,2- and 1,4-shifts of the

aza-allyl anion moiety onto the aza-arenium ring to give **37** and **38** respectively, and the 1,4-shift (σ2s + π4s) of a hydrogen at the 3- or 5-position of the pyridine ring to the nitrogen anion atom. Since this cationic 1,2-shift (ω0s + σ2s) is a symmetry allowed process in ground state (GS) but the 1,4-shift (π2s + σ2s) is not so, the latter process should be three sequences of such 1,2-shifts. However, the driving force and the preferred 3- and 5-positions on the pyridine ring in this rearrangement could not be well realized at that time. The molecular calculation (MOPAC-PM3) using model **40** made the following stability order (**38**>**37**>>**41**≃**42**>>**36**) clear, that is, the contributors such as **36**, **41**, and **42** in which the positive charge is localized on the electronegative hetero atom (nitrogen) are unstabilized.[22]



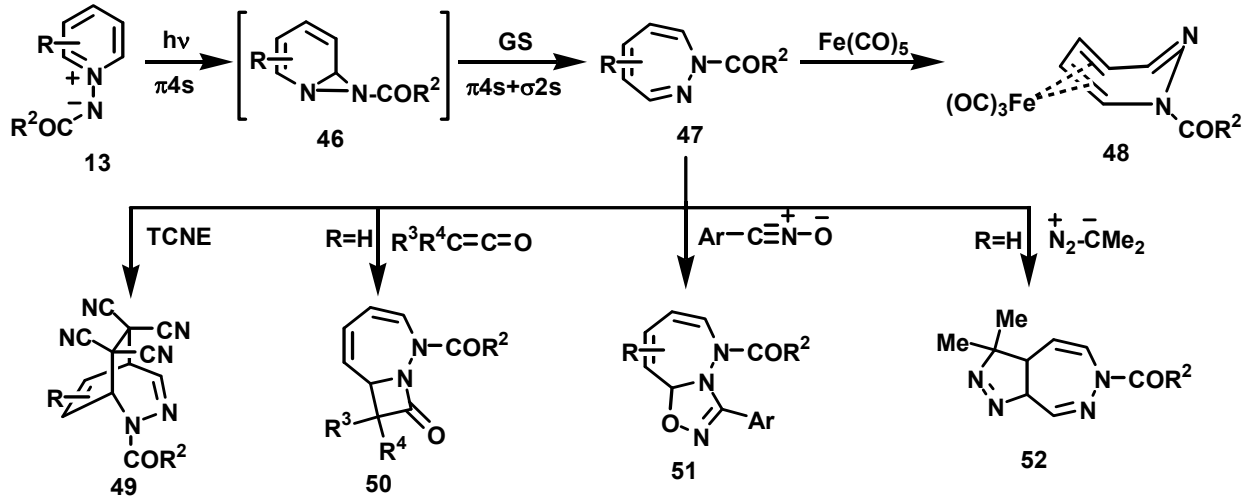
Scheme 4

Photochemical 1,3-dipolar cyclization of pyridinium ylides were first found by Streith *et al.*[23] They reported the formation of 2-(2,2-dicyanovinyl)pyrrole (**45**) in low yield from the irradiation of parent pyridinium dicyanomethylide (**4**) in benzene and proposed a reaction sequence in which the photochemical disrotatory cyclization (π4s) of **4**, the disrotatory ring enlargement (π4s + s2s) of the resulting 1-azanorcaradiene **43** in the ground state, and the ring contraction-rearrangement of 2,2-dicyano-2*H*-azepine (**44**) was involved.



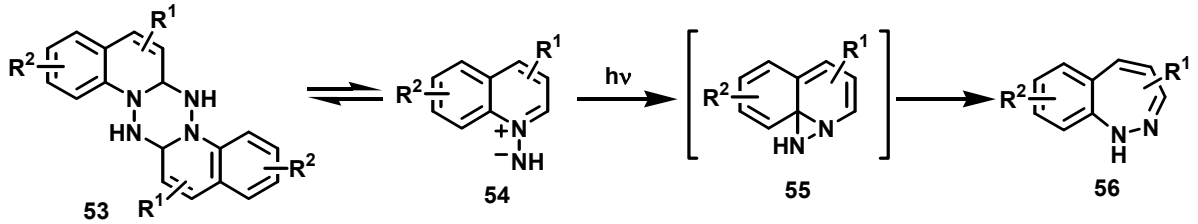
Scheme 5

J. Streith *et al*. extended this photolysis to some pyridinium acylaminides (**13**) and found their simpler and more effective transformation to 1(1*H*),2-diazepine derivatives.[24] By the ensuing research of Sasaki[25] and Snieckus groups[26] the wide scope of this photolysis was established and various reactions of 1(1*H*),2-diazepines obtained thus with iron pentacabonyl,[24] tetracyanoethylene,[25] ketenes,[27] nitrile oxides,[28] and diazoisopropane[29] to give compounds **48**–**52** were also investigated (Scheme 6).



Scheme 6

Interestingly, Tsuchiya *et al*. reported the formation of *N*-unsubstituted 1(1*H*),2-benzodiazepine derivatives **56** by the irradiation of quinolinium (unsubstituted)aminides (**54**) generated in situ from the dimer **53**[30] (Scheme 7).



Scheme 7

The 1,3-dipoles conjugated with an unsaturated double or triple bond are defined as 1,5-dipoles.[31] The 1,5-dipolar cyclization of such molecules are useful methods for synthesizing various five-membered

heterocycles because of the smooth and symmetry allowed process (π6s) in ground state. Theoretically there are two types of pyridinium ylides which can act as a 1,5-dipole: a) pyridinium ylides **IV** having a double bond conjugated with the ylidic carbanion atom and b) pyridinium ylides **V** or **V'** having a double or triple bond at the 2-position on the pyridine ring (Figure 3).

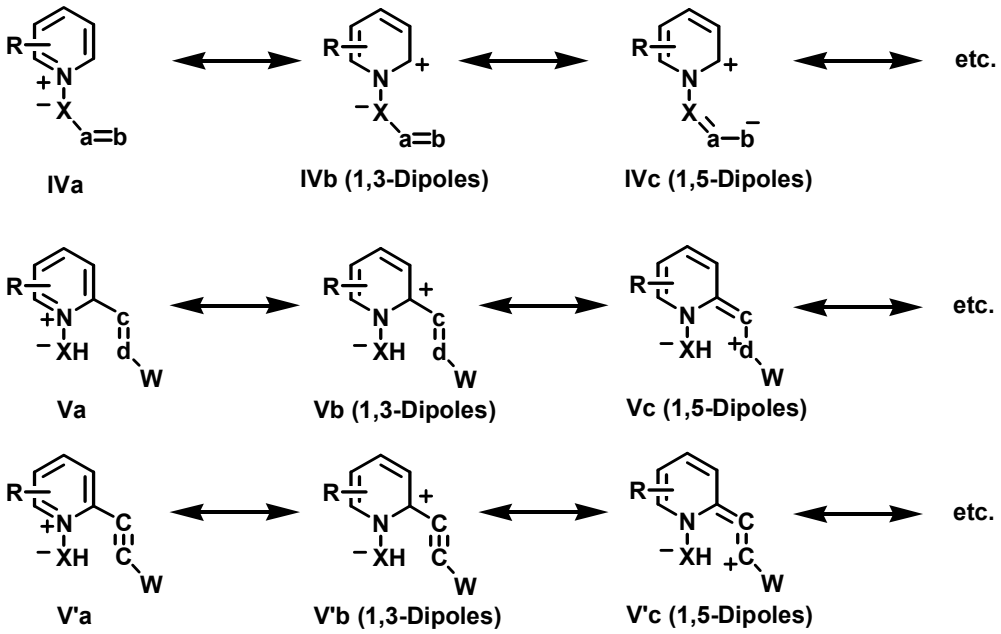
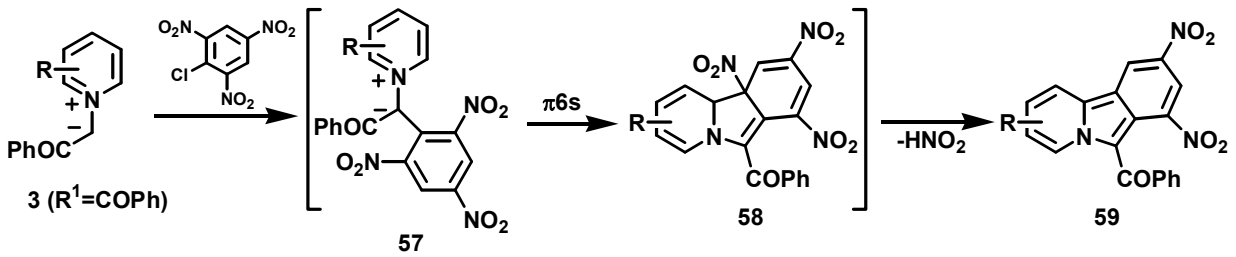


Figure 3

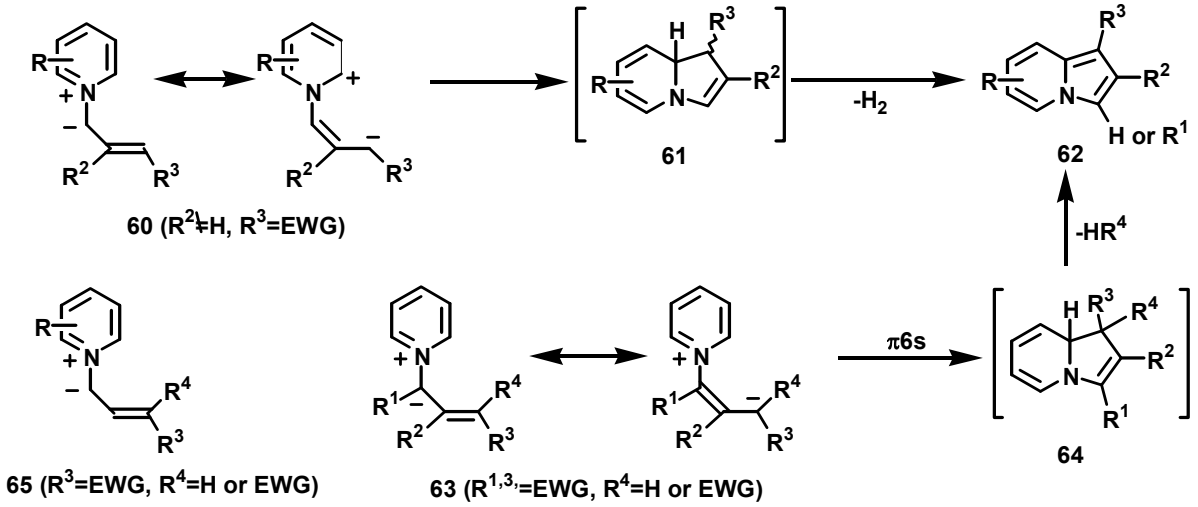
Both types of pyridinium ylides have been synthesized and their reactivity has also been investigated. The first example for the 1,5-dipolar cyclization of type **IV** pyridinium ylides was reported by Kröhnke *et al.*[32] in 1966. They examined the reactions of pyridinium phenacylides (**3**) with picryl chloride in the presence of a base and demonstrated the formation of benz[*a*]indolizine derivatives **59** by way of the cyclization of **57** in this mode and the subsequent elimination of nitrous acid from the tricycloadducts **58** (Scheme 8).



Scheme 8

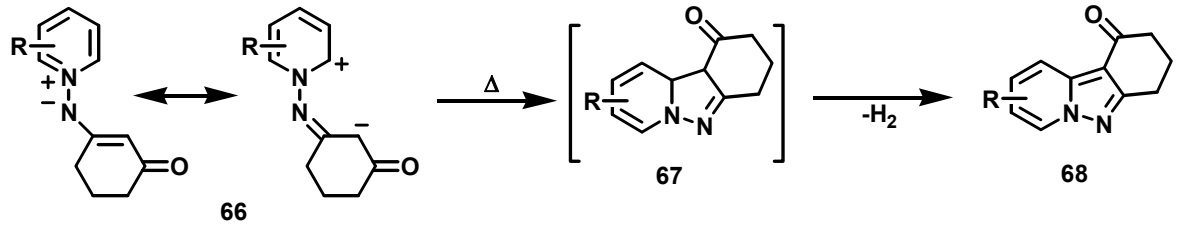
Pyridinium (2,3-disubstituted) allylides (**60**), readily available from the alkaline treatment of the corresponding pyridinium salts **2** (R^1=vinyl group), underwent the expected 1,5-cyclization, followed by the dehydrogenation of primary 1,8a-dihydroadducts **61** at comparative low temperatures to yield the

corresponding 3-unsubstituted indolizine derivatives **62** (See Scheme 9).[33] Stabilized pyridinium (1,2,3- or 1,3,3-trisubstituted)allylides (**63**) also underwent such cyclization under more severe reaction conditions.[6e] In contrast, pyridinium (3-substituted)- and (3,3-disubstituted)allylides (**65**) did not form the intramolecular mode of adducts, but they intermolecularly reacted with the carbon-carbon double bond in another molecule or with other dipolarophiles to afford 3-vinylindolizine derivatives.[33c,34]



Scheme 9

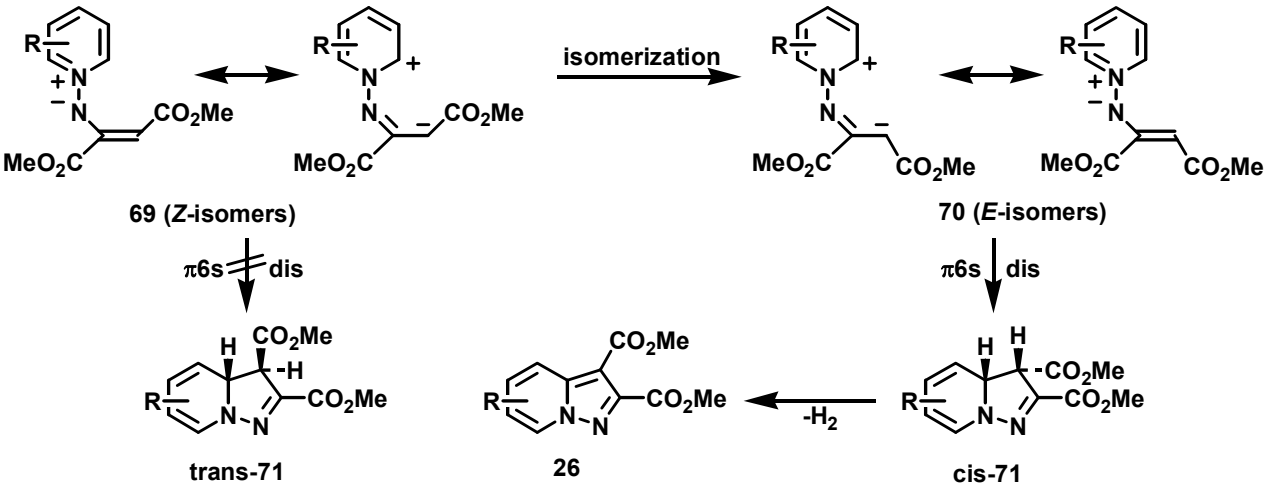
Similar 1,5-dipolar cyclizations for pyridinium vinylaminides have been reported by some investigators. For example, Tamura *et al*. examined the reactions of pyridinium (1-oxo-2-cyclohexen-3-yl)aminides (**66**) in toluene at the reflux temperature and found the formation of the expected pyrido[1,2-*b*]indazoles (Scheme 10).[6a,33a]



Scheme 10

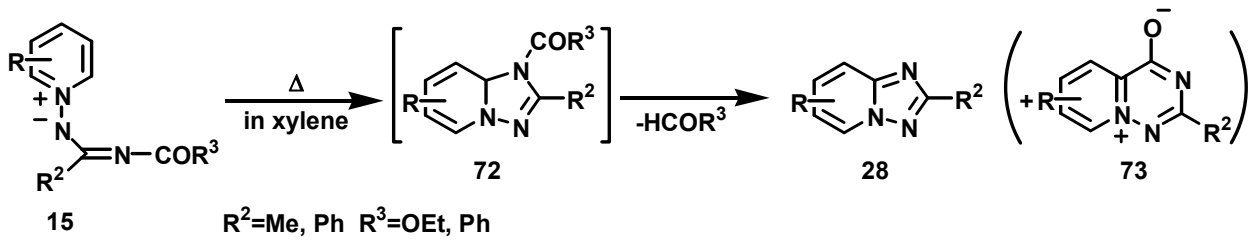
Sasaki *et al*. also studied the 1,5-dipolar cyclization of the *Z*-isomers **69** of pyridinium [1,2-bis(methoxycarbonyl)vinyl)]aminides in chloroform at room temperature and obtained the primary adducts, 3,3a-dihydropyrazolo[1,5-*a*]pyridines (*cis*-**71**) which were very unstable and readily oxidized to pyrazolo[1,5-*a*]pyridines **26** upon exposure to air (Scheme 11).[6b] From the facts that the precursors of pyrazolo[1,5-*a*]pyridines **26** were *cis*-**71** but not *trans*-**71** and the mode in a 1,5-dipolar cyclization in the ground state is disrotatory (dis), they presumed the reaction mechanisms to be as follows: 1) the *cis*-*trans*

isomerization of the vinyl group of the aminides **69**, 2) the smooth cyclization of the resulting *E*-isomers **70**, and 3) the dehydrogenation of the cycloadducts cis-**71** to aromatic pyrazolo[1,5-*a*]pyridines **26**.



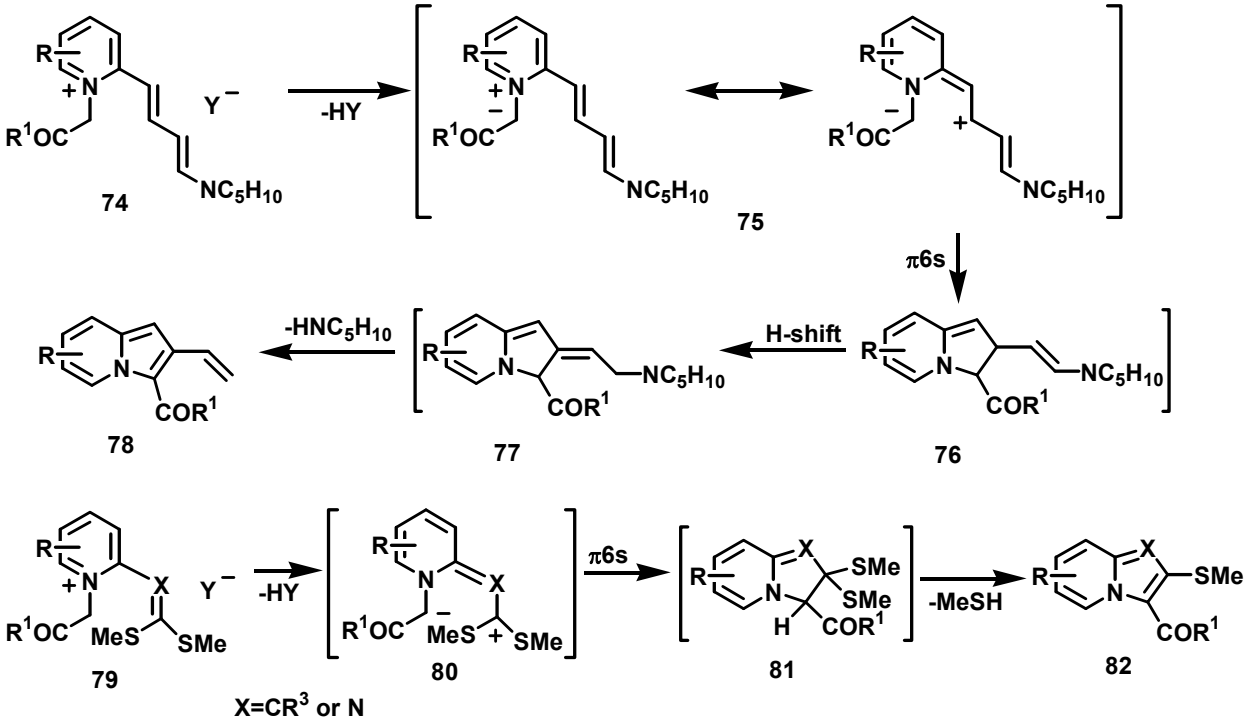
Scheme 11

We examined the thermolyses of pyridinium (*N*-acylimidoyl)aminides (**15**) in xylene at the reflux conditions to obtain 1,2,4-triazolo[1,5-*a*]pyridines (**28**) which were derived from their 1,5-dipolar cyclization, though other products, pyrido[6,1-*f*]-*as*-triazinium-4-olates **73**, were also given (Scheme 12).[7]



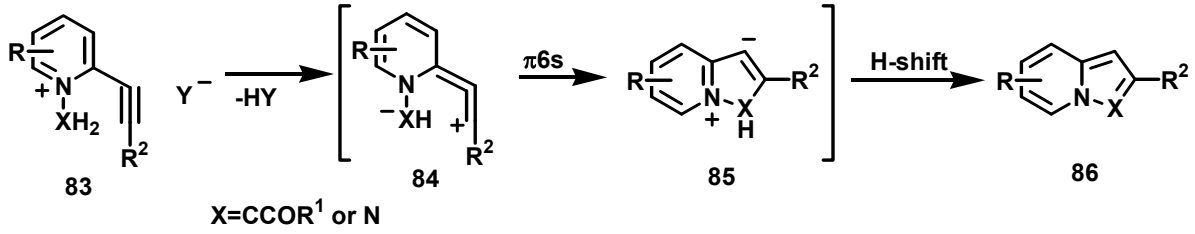
Scheme 12

On the other hand, a 1,5-dipolar cyclization of type **V** pyridinium ylides was reported first by Mörler and Kröhnke.[35] They investigated the alkaline treatment of 1-(acylmethyl)pyridinium salts **74** having a 4-piperidino-1,3-butadien-1-yl group at the 2-position to obtain 3-acyl-2-vinylindolizine derivatives **78** via the generation of pyridinium methylides **75**, their 1,5-dipolar cyclization to 2,3-dihydroindolizines **76**, the 1,3-shift of the 2-proton onto the vinyl group, and the 1,4-elimination of a molecule of piperidine from **77**. (See Scheme 13) Similarly, Kobayashi *et al*. reported the syntheses of 2-methylthio-3-acylindolizines or imidazo[1,5-*a*]pyridines **82** by way of the 1,5-dipolar cyclization-aromatization route of pyridinium methylides **80**, which were generated in situ from the alkaline treatment of pyridinium salts **79** possessing a 2,2-bis(methylthio)vinyl or bis(methylthio)methyleneamino group at the 2-position.[36]



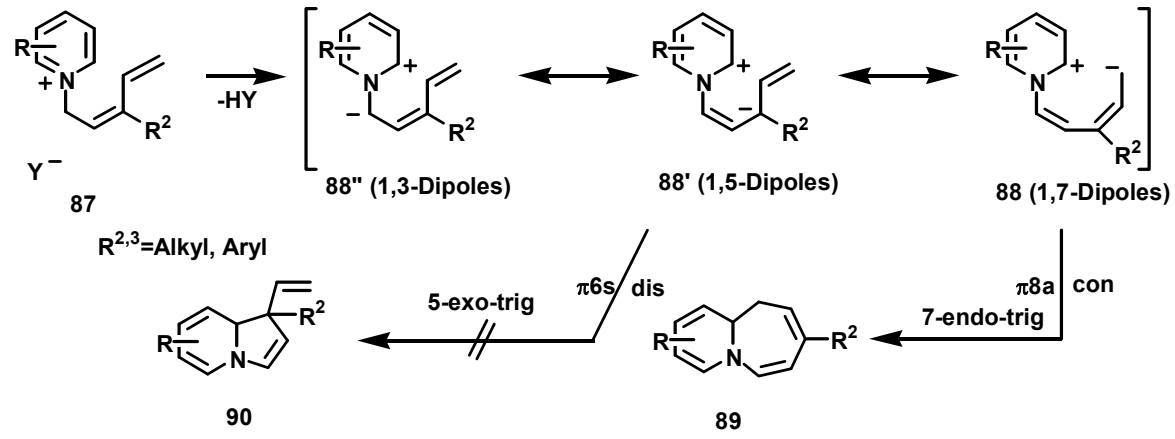
Scheme 13

Tsuchiya *et al*. examined a cyclization of type **V'** pyridinium ylides and found the smooth transformations of 2-alkynylpyridinium methylides or aminides **84**, generated in situ from the alkaline treatment of the corresponding pyridinium salts **83**, to 1-unsubstituted indolizines or 3-unsubstituted pyrazolo[1,5-*a*]pyridines such as **86** via the 1,5-dipolar cyclization-proton shift (Scheme 14).[37]



Scheme 14

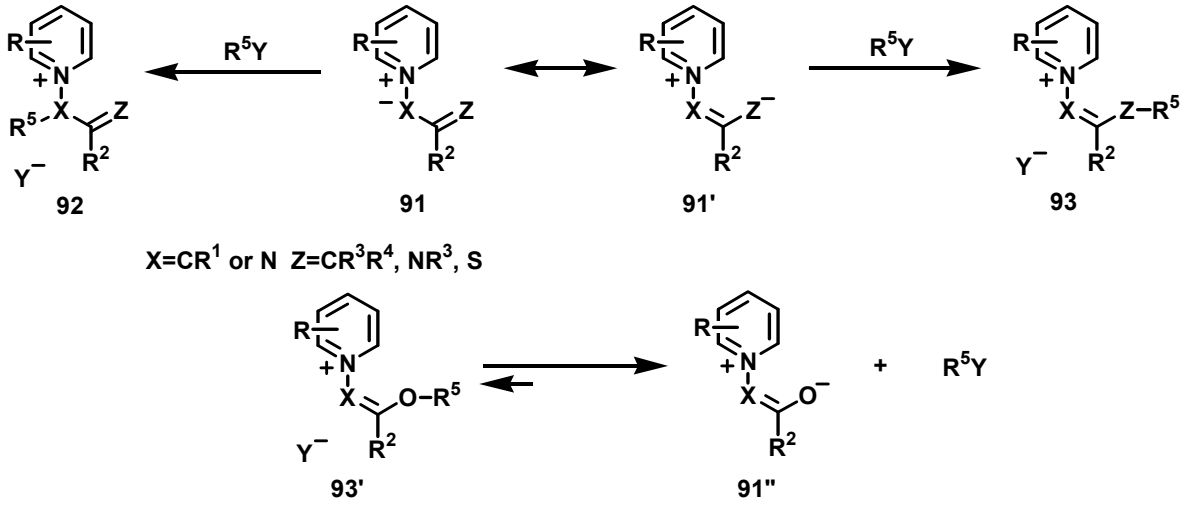
An electrocyclic reaction of more extended dipoles has also been known. Marx and Eberbach described a thermal and exclusive 1,7-dipolar cyclization (π8a) of pyridinium 1,3-pentadien-1-yl-5-ides (**88**) to provide the corresponding 5,5a-dihydropyrido[1,2-*a*]azepines (**89**) (Scheme 15).[38] This procedure is very interesting from the standpoint of the synthesis of medium-sized nitrogen-containing heterocycles, since, in systems in which the different types of reactions by the other contributors are also possible, the 1,5-dipolar cyclization (5-exo-trig) of contributors **88'** is usually more favorable than the 1,7-dipolar one (7-endo-trig) as shown in the cyclization from **75** to **76** in Scheme 13. The cation-anion interaction may work effectively in this 1,7-dipole system.



Scheme 15

3.2. REACTIONS AS NUCLEOPHILES

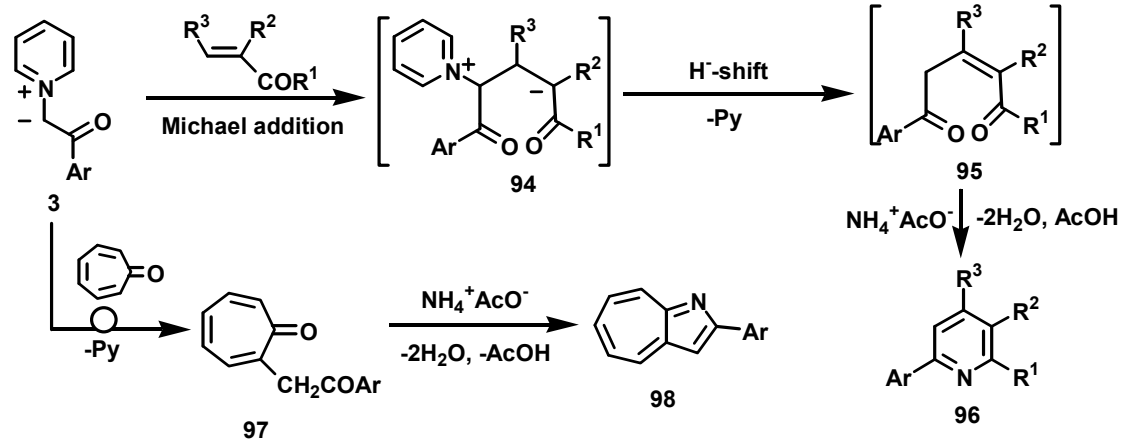
It has been known that the anionic atom of pyridinium ylides acts as a nucleophilc center. One of the title compounds, pyridinium salts, can be readily obtained by this method. For example, 1,3-dipoles **91** was alkylated by various alkyl halides and dialkyl sulfates to give the corresponding salts **92,** while similar alkylations of 1,5-dipoles **91'** afforded pyridinium salts **93** having a vinyl or methyleneamino group at the 1-position (See Scheme 16). However, attempts for the *O*-alkylations in the 1,5-dipole forms of pyridinium 1,1-diacylmethylides or acylaminides by the same reagents were usually unsuccessful because of the presence of its faster dealkylation process.[39]



Scheme 16

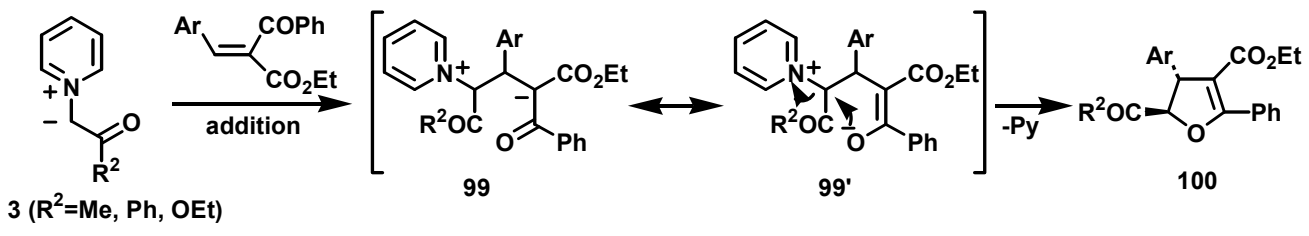
Beside their dipolar cycloadditions and cyclizations, the nucleophilic reactions between pyridinium methylides or aminides and electron poor alkenes, which afford the alkyl- and amino-substituted alkenes, cyclopropanes, enamines, and aziridines with the elimination of pyridine, have also been described. These are of practical and preparative importance, since usual synthetic routes for such compounds consist of

the addition of elctrophilic species such as alkyl halides, carbenes, and nitrenes to electron-rich alkenes and their species can not usually react to electron-poor alkenes and alkynes. In 1961 Zecher and Kröhnke developed a new preparative method of tri- and tetra-substituted pyridine derivatives **96** from the reactions of pyridinium phenacylides **3** with certain α,β-unsaturated ketones in the presence of ammonium aetate[40] (See Scheme 17). They suggested the reaction mechanisms which proceeded by way of first Michael addition of the carbanion of methylide **3** to the β-position of the α,β-unsaturated ketone, the 1,2-hydride shift of the resulting adduct **94** with the elimination of pyridine and the regeneration of the double bond, and final condensation between enedione **95** and ammonium acetate with the loss of water and acetic acid. The formation of 2-aryl-1-azaazulenes **98** from similar condensations of **3** with tropones and ammonium acetate was also reported.[41] Some of the initially formed monoalkylated products such as **95** in these reactions have been isolated.[41,42]



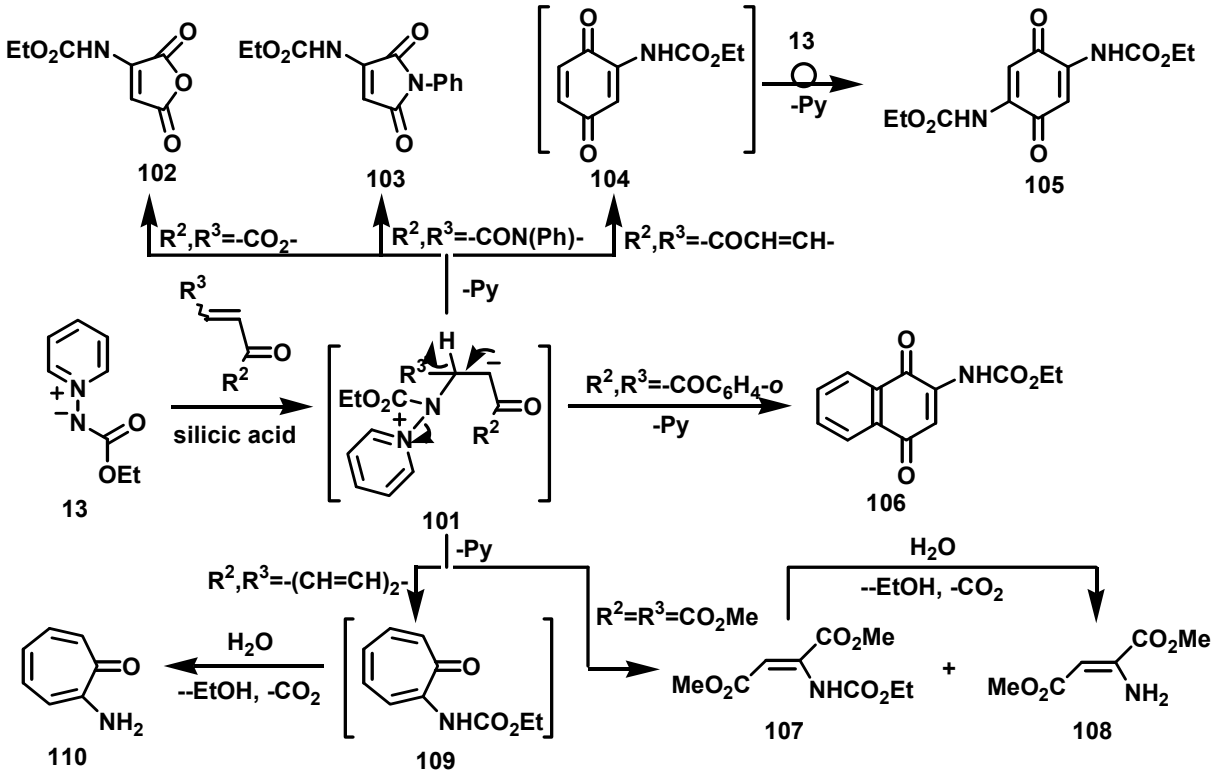
Scheme 17

On the other hand, the use of (benzylidene)benzoylacetates in place of α,β-unsaturated ketone in this reaction afforded different type of products. Chuang and Tsai reported an effective and stereoselective synthesis of 2,3-dihydrofuran derivatives **100**, which were obtained from the reactions of pyridinium methylides **3** with ethyl (benzylidene)benzoylacetates via the formation of the primary adducts **99**, followed by the intramolecular nucleophilic addition of the anionic oxygen atom to the carbon atom having the pyridinio group in the same molecule **99'** with the loss of pyridine (Scheme 18).[43]



Scheme 18

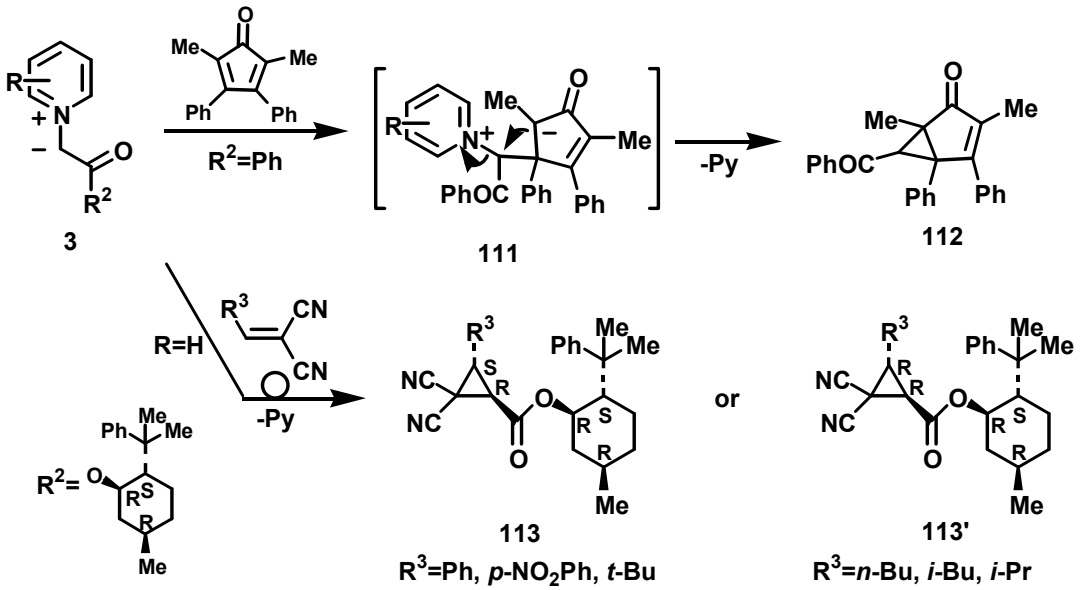
Though an enamine synthesis from the nucleophilic reactions of pyridinium aminides and electron-poor olefins did not usually afford good results, it was indicated that the activation of such olefins by an acidic catalyst promoted the formation. For example, Sasaki *et al*. reported facile formation of the corresponding enamine derivatives **102**, **103**, **105**, **106** from the reactions of pyridinium (ethoxycarbonyl)aminide (**13**) with maleic anhydride, *N*-phenylmaleimide, *p*-benzoquinone, and 1,4-naphthoquinone in the presence of silicic acid (silica gel) at room temperature (Scheme 19).[44] Similar reactions of **13** with dimethyl maleate or fumarate under more severe conditions gave a mixture of dimethyl 2-(ethoxycarbonylamino)fumarate carbamate (**107**) and dimethyl 2-aminofumarate (**108**), while that with tropone yielded only 2-aminotropone **110**. The primary amino compound **108** and **110** must be formed by the hydrolysis of the initially prepared carbamates **107** and **109** respectively under the reaction conditions employed here.



Scheme 19

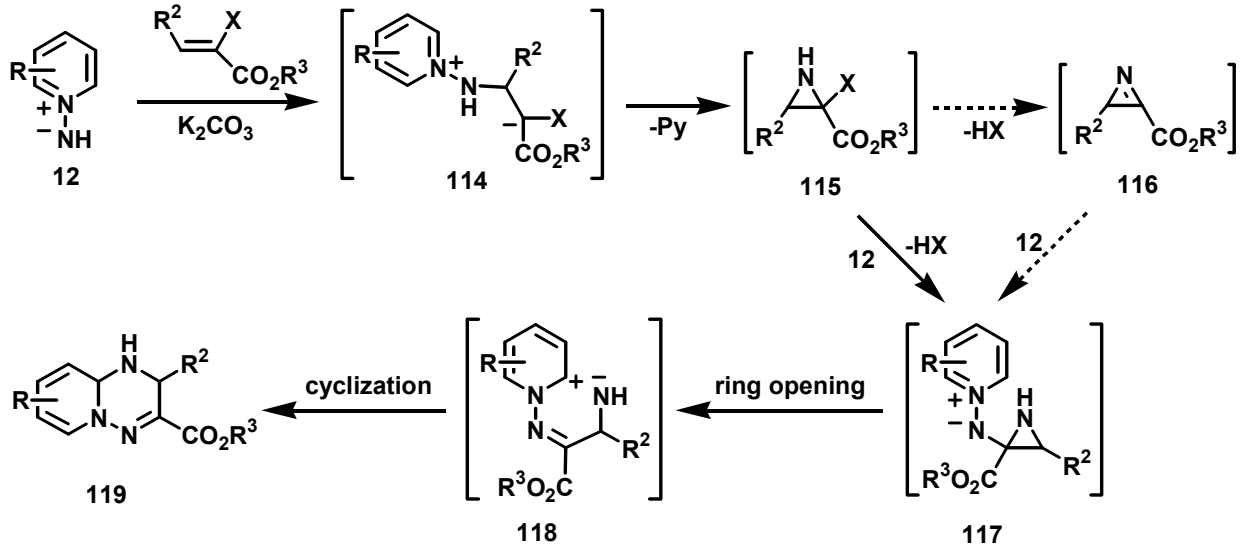
The formation of cyclopropane derivatives from the reactions of *S*-ylides with Michael acceptors have been well known.[45] Useful and enantioselective cyclopropanation reactions of pyridinium methylides (**3**) and electron-poor alkenes have also been observed by some investigators.[46] Two examples of them are shown in Scheme 20.

In general, it is well known that aziridine is considerably unstable and easily undergoes the ring opening reaction or the decomposition under thermal and acidic reaction conditions. Hence, the formation of aziridine derivatives from the nucleophilic reactions between pyridinium aminides and electron-poor



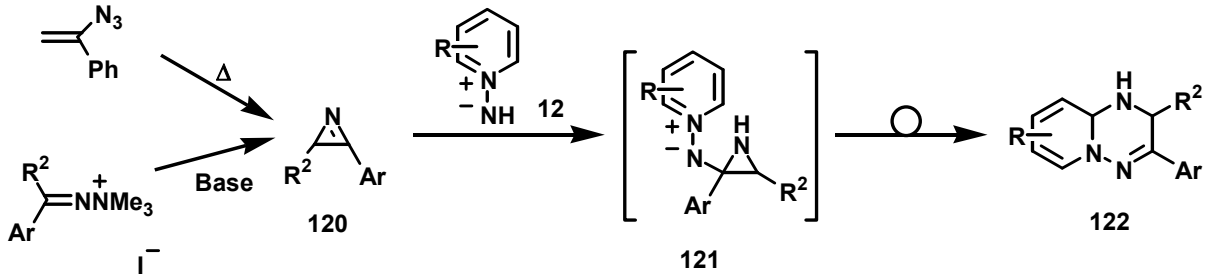
Scheme 20

alkenes was scarcely observed. However, the reactions in which the intermediacy of the 2-haloaziridine or 2*H*-azirine was strongly suggested were found by our laboratory.[47] The reactions were performed by employing two moles of pyridinium (unsubstituted)aminides **12** and one mole of ethyl 2-chlorocinnamate or methyl 2-bromocrotonate to provide 1,9a-dihydro-2*H*-pyrido[1,2-*b*]-*as*-triazines (**119**) (Scheme 21). We thought that this reaction proceeded via the first nucleophilic addition of the aminide nitrogen atom of **12** onto the β-carbon of the α-haloacrylate, the formation of 2-haloaziridine **115** from the resultingzwitterion **114** with the elimination of pyridine, the nucleophilic replacement of **115** with an another molecule of **12**, the ring opening of the resulting pyridinium (2-aziridinyl)aminide **117**, and the



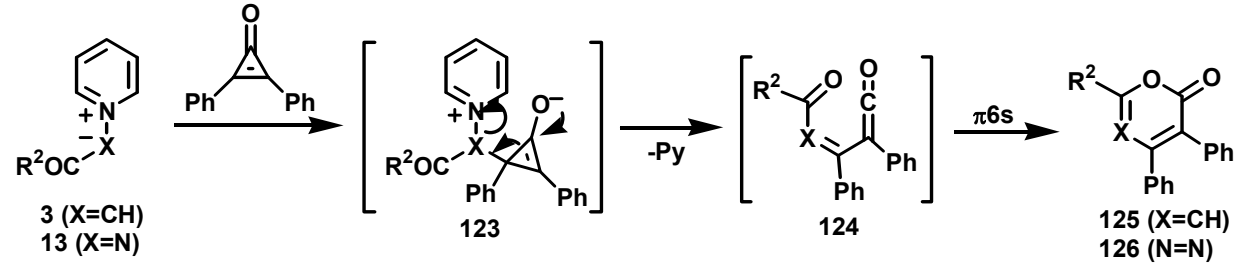
Scheme 21

1,6-cyclization of zwitterion **118** to the final products **119**. The intermediate **117** may also be formed by the nucleophilic addition of **12** to 2*H*-azirine **116** which is generated by the dehydrohalogenation of **115** under the alkaline conditions employed here. According to this mechanistic assumption we examined the reactions of various pyridinium aminides **12** with 2*H*-azirines **120**, which were isolated from the thermolysis of α-azidostyrene or generated in situ by modified Neber reaction of alkyl aryl ketone *N*,*N*-dimethylhydrazone methiodides, to develop a novel preparative method for 1,9a-dihydro-2*H*-pyrido[1,2-*b*]-*as*-triazine derivatives **122** (Scheme 22).[48]



Scheme 22

The reactions of pyridinium ylides with diphenylcyclopropenone are one of the most interesting themes in this field. Diphenylcyclopropenone is a very reactive molecule owing to the severe ring strain and behaves as a strong dienophile or dipolarophile. However, Eicher and Hansen first investigated the reactions of pyridinium acylmethylide **3** with diphenylcyclopropenone in 1969 to find the formation of 3,4-diphenyl-2-pyrone derivatives **125** in place of the expected 1,3-dipolar adducts[49] (See Scheme 23). Furthermore, Sasaki *et al*. reported the syntheses of 2-pyrone **125** and 1,3-oxazin-6-one derivatives **126** from the reactions between pyridinium ylides **3** and **13** with the same reagent.[50] Although this reaction mechanism is still not clear because of the high reactivity of the ketone carbonyl group in diphenylcyclopropenone, the reliable route at present may be one started by the first nucleophilic attack of the ylidic anion atom of ylides **3** or **13** onto the carbon-carbon double bond of diphenylcyclopropenone. The extension of this type of reaction to 1,2-diphenylcyclopropene-3-thione, and 1,2-diphenyl-3-methylenecyclopropene were also documented.[51]



Scheme 23

It can be easily realized that the development of any ring formation reaction between a 1,5-dipole **IVc** (6π) and a 2π component leads to a useful route to unsaturated seven-membered heterocycles (**VIIa** or **VIIb**) which are not readily available by other methods (See Figure 4). However, the geometrically favorable mode (π6s + π2s) of a 1,7-dipolar cycloaddition is forbidden in the ground state, and the concerted process (π6s + π2a or π6a + π2s) is unfavorable owing to severe geometrical restrictions in the transition state. On the other hand, both the nucleophilic addition (ω2s + π2a) of a 1,5-dipole **IVc** to a double or triple bond and the 1,7-cyclization (ω0s + ω2s) of the resulting zwitterion **VIb** or **VIIIb** are symmetry allowed processes though the rotation or inversion of the anion moiety in the initially generated zwitterion **VIa** or **VIIIa** is required.

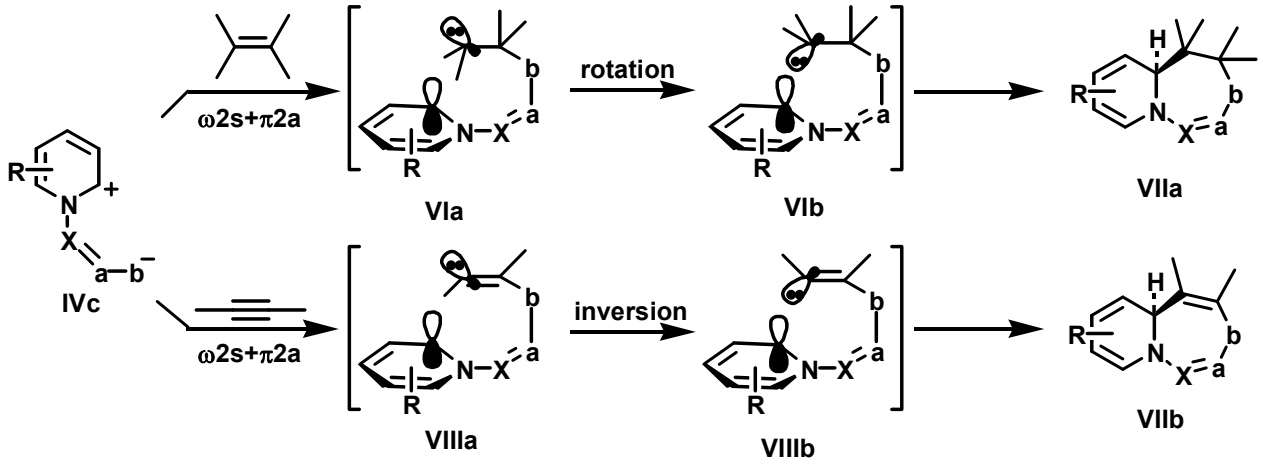
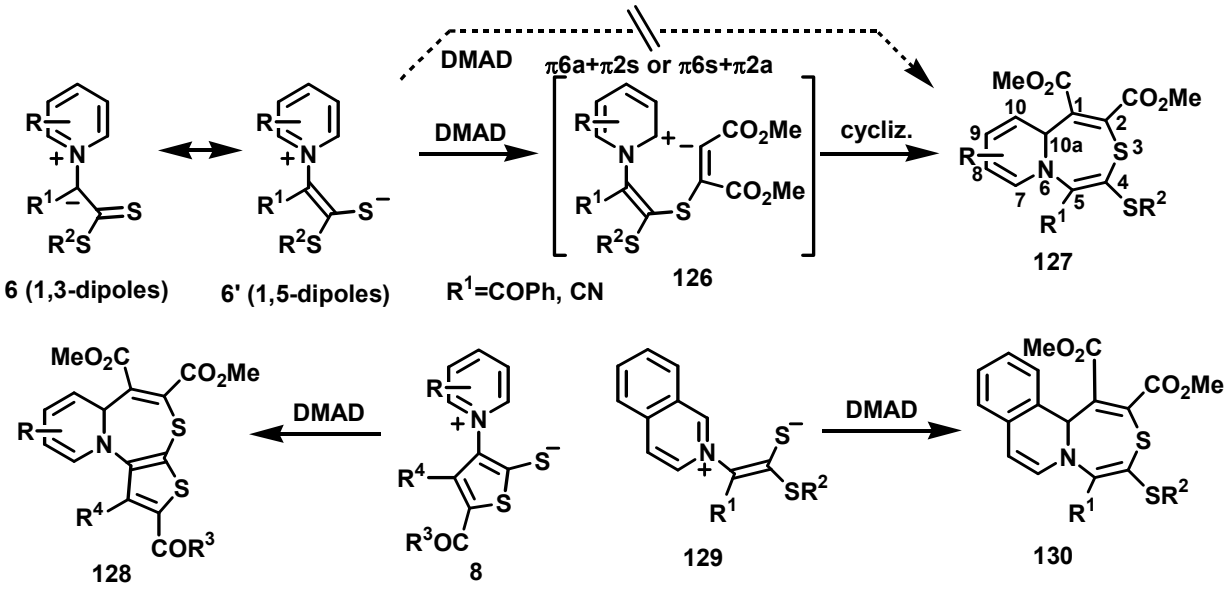


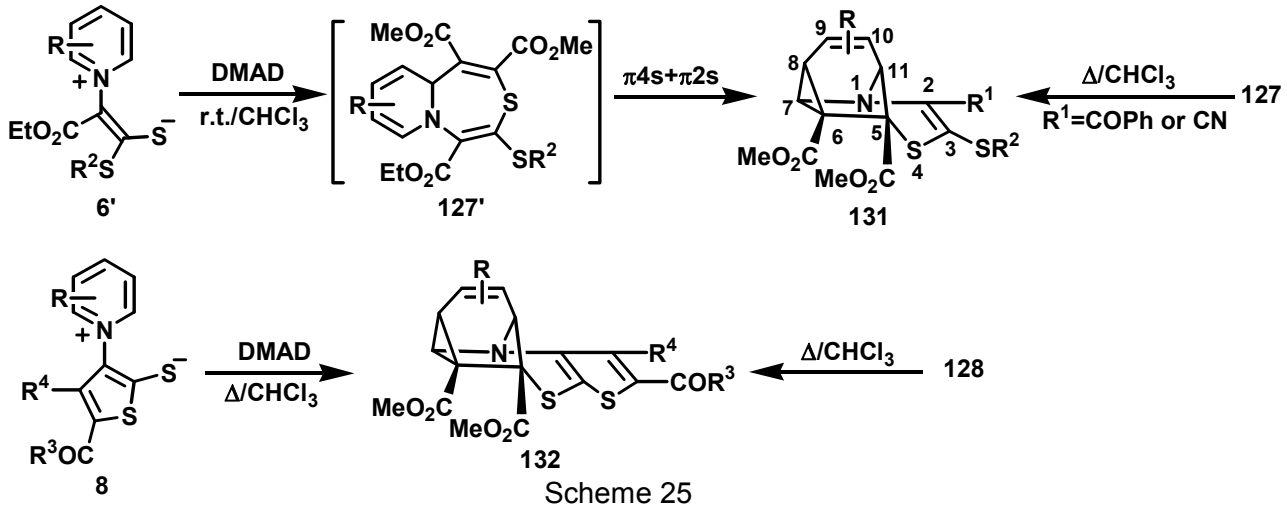
Figure 4

After some research for pyridinium ylides which can act as a 1,5-dipole we found first formation reactions of various pyrido[1,2-*d*]-1,4-thiazepine derivatives.[52] For example, the reactions of pyridinium (2-alkylthio-1-benzoyl-2-thioxo)- (R^1=COPh) and pyridinium (2-alkylthio-1-cyano-2-thioxo)ethanides **6** (R^1=CN) with DMAD in $CHCl_3$ at room temperature afforded the corresponding dimethyl 10a*H*-5-benzoyl- and 10a*H*-5-cyano-4-(alkylthio)pyrido[1,2-*d*]-1,4-thiazepine-1,2-dicarboxylates (**127**) in moderate yields (See Scheme 24). Similarly, those of 3-(1-pyridinio)thiophene-2-thiolates (**8**) and isoquinolinium 2-(thioxo)ethanides (**129**) with the same reagent provided the tricyclic 1,4-thiazepine derivatives, pyrido[1',2'-*d*]thieno[2,3-*b*]-1,4-thiazepines (**128**) and 1,4-thiazepino[5,4-*a*]isoquinolines (**130**), respectively.



Scheme 24

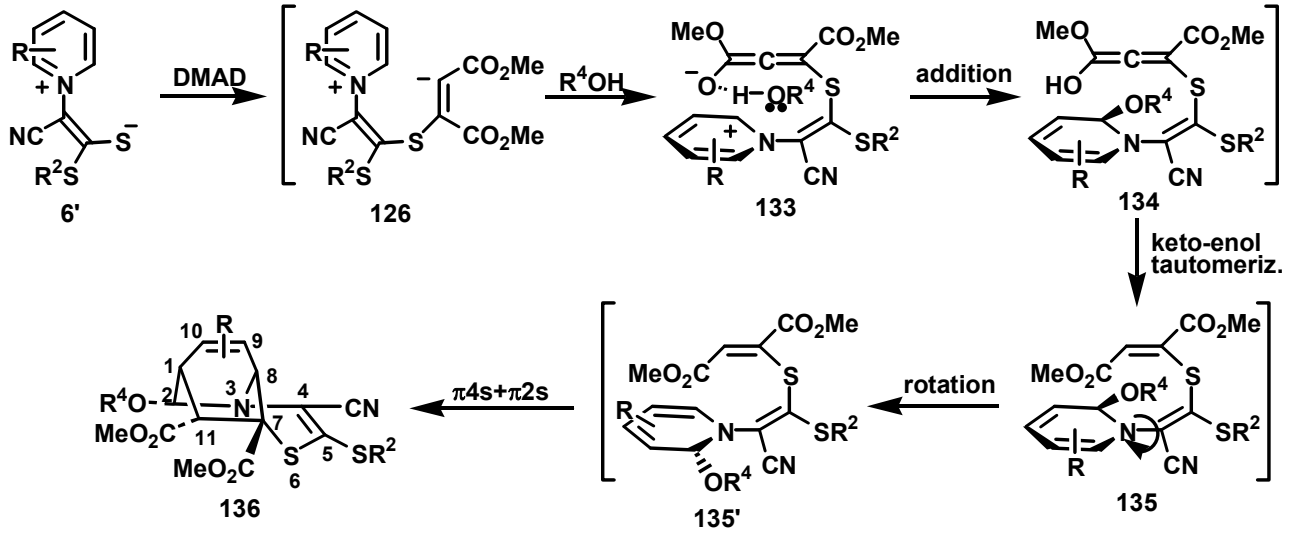
Interestingly, the reactions of pyridinium (2-alkylthio-1-ethoxycarbonyl-2-thioxo)ethanides **6'** with DMAD under the same reaction conditions did not provide the initially expected 10a*H*-pyrido[1,2-*d*]-1,4-thiazepines **127'**, but, instead of them, gave their intramolecular Diels-Alder adducts, ethyl 5,6-dimethyl 4-thia-1-azatetracyclo[5.4.0.$0^{5,11}$.$0^{6,8}$]undeca-2,9-diene-5,6-tricarboxylates (**131**)[53] (See Scheme 25). Similar types of adducts **131** and **132** were also obtained by heating 10a*H*-pyrido[1,2-*d*]-1,4-thiazepines **127** and **128** or the reactions of pyridinium methylides **6** (R^1=COPh and CN) and 3-(1-pyridinio)thiophene-2-thiolates (**8**) with DMAD in refluxing $CHCl_3$.[53]



Scheme 25

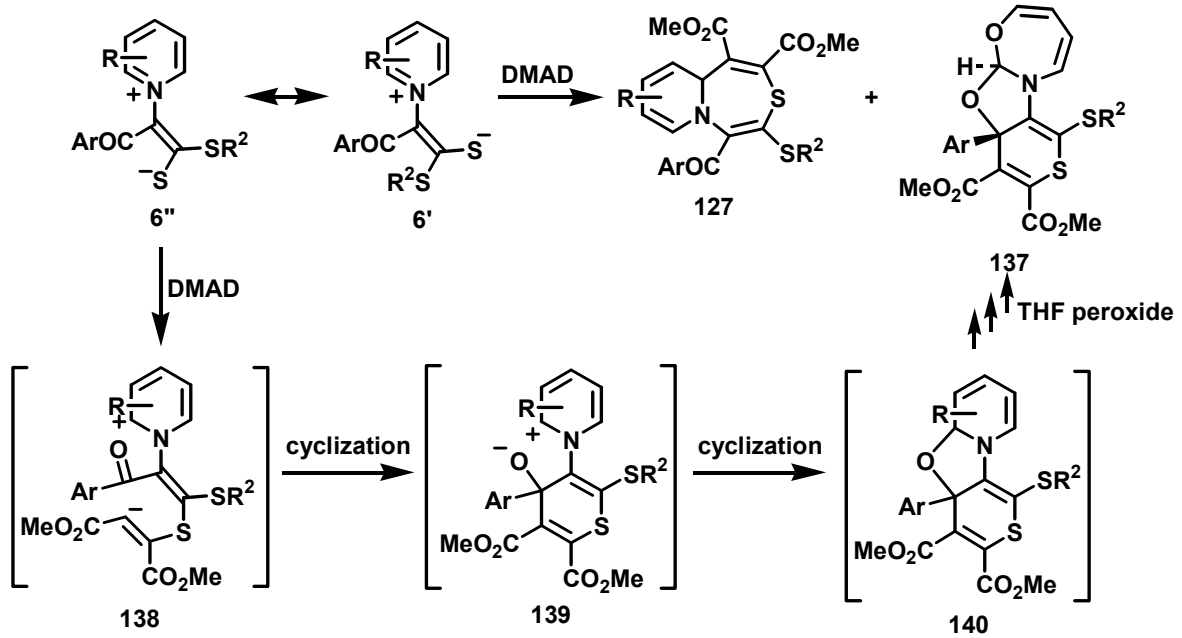
That this reaction proceeded via the nucleophilic addition—1,7-cyclization route could be proven by the reactions of pyridinium (2-alkylthio-1-cyano)ethanides (**6**) with DMAD in the presence of an alcohol, in which dimethyl 2-alkoxy-4-cycano-6-thia-3-azatricyclo[5.3.1.$0^{3,8}$]undeca-4,9-diene-7,11-dicarboxylates

(**136**) were formed by way of intramolecular Diels-Alder reaction of the adducts **135'** derived from the key intermediates **126** and alcohols (Scheme 26).[54]



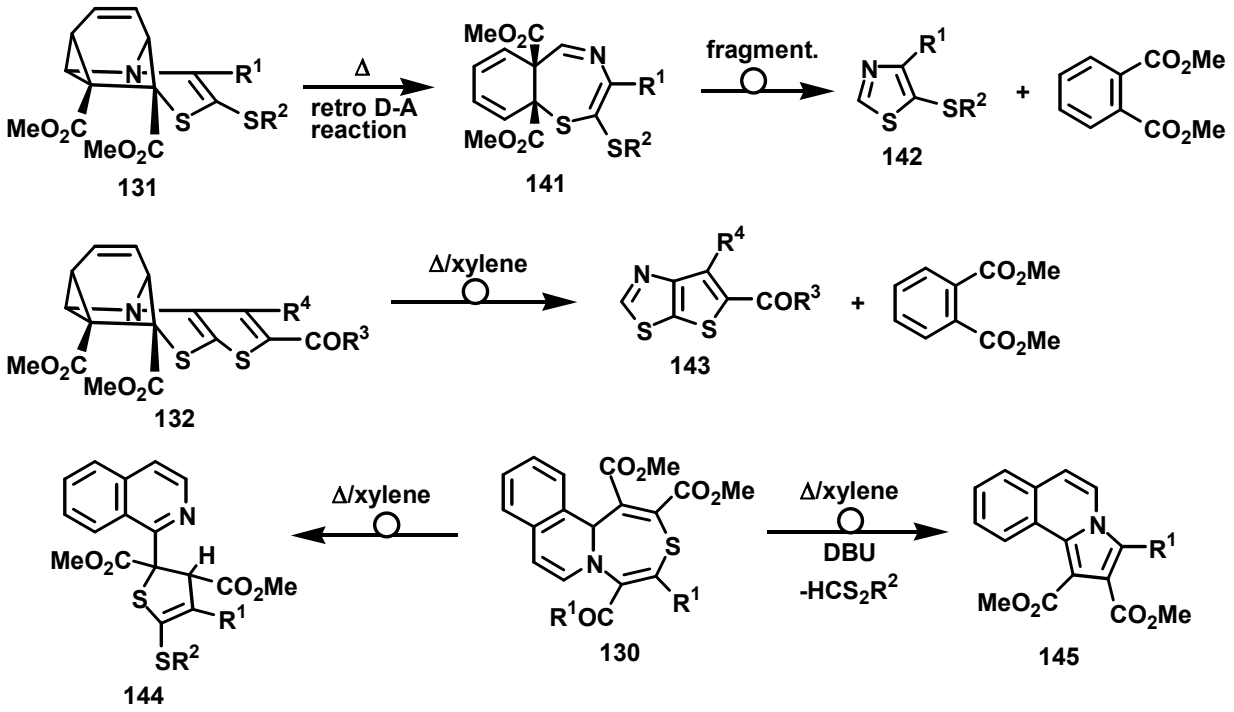
Scheme 26

Recently we could isolate the unexpected products, thiino[3',4':4,5]oxazolo[1,3-*b*]-1,3-oxazepine derivatives **137**, from the reactions of pyridinium (1-alkylthio-1-benzoyl-2-thioxo)ethanides **6** with DMAD in tetrahydrofuran involving its peroxide (THF peroxide) at the reflux temperature.[55] Though this reaction mechanism is still unclear (See Scheme 27), the high participation between the intermediate **140**, which was generated from the addition of pyridinium betaine **6"** to DMAD, followed by the successive cyclizations of zwitterion **138**, and the oxidant was suspected.



Scheme 27

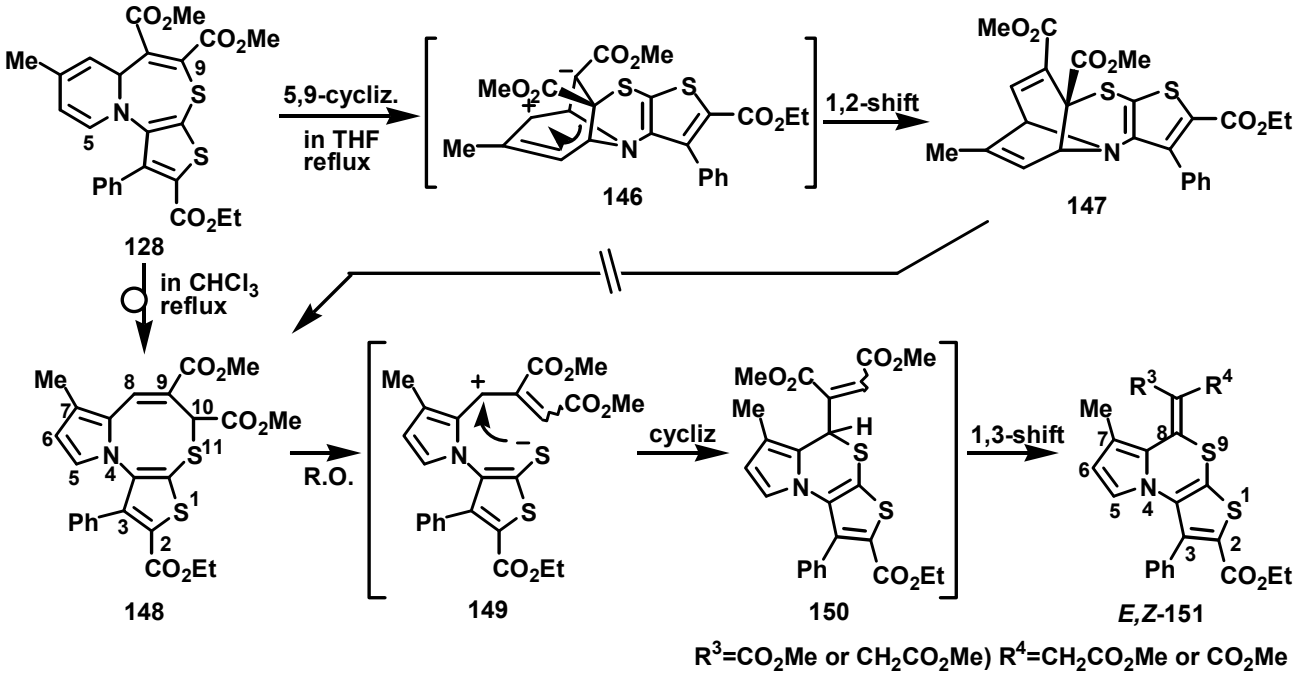
We have also reported some interesting reactions which proceeded through 10a*H*-pyrido[1,2-*d*]-1,4-thiazepines **127** and **128** and 12b*H*-1,4-thiazepino[5,4-*a*]isoquinolines **130** obtained or generated thus (See Scheme 28). For example, the thermolyses of the intramolecular Diels-Alder adducts **131** and **132** obtained from the corresponding 1,4-thiazepines **127** and **128** lead to the smooth formation of thiazole **142** and thieno[3,2-*d*]thiazole derivatives **143** by way of the retro Diels-Alder reaction and the fragmentation of the resulting benzo[*f*]-1,4-thiazepines such as **141**.[53b,56] On the other hand, the thermolyses of 1,4-thiazepino[5,4-*a*]isoquinolines **130**, which could not convert to the corresponding intramolecular Diels-Alder adducts due to the fused benzene ring, in xylene at the reflux temperature afforded 1-(1,2-dihydrothiophen-2-yl)isoquinolines **144** via the ring contraction-rearrangement route, while those in the presence of base provided the ring contraction-elimination products, pyrrolo[2,1-*a*]isoquinolines **145**.[57]



Scheme 28

Furthermore, we found two different types of rearrangements in reactions of one thiophene-fused pyridothiazepine derivative.[58] The reaction of 9,10-dimethyl 2-ethyl 7-methyl-3-phenyl-8a*H*-pyrido[1,2-*d*]thieno[2',3'-*b*]-1,4-thiazepine-2,9,10-tricarboxylate (**128**) in THF at the reflux temperature yielded 6,8-dithia-2-azatetracyclo[7.3.2.$0^{2,10}$.$0^{3,7}$]tetradeca-$\Delta^{3,7}$,4,11,13-tetraene **147**, while that in $CHCl_3$ 10*H*-pyrrolo[1,2-*d*]thieno[2',3'-*b*]-1,4-thiazocine **148.** Product **147** can be formed from the cyclization between the 5- and 9-positions in **128**, followed by the cationic 1,2-shift (ω0s+σ2s) of a carbon-nitrogen bond of the resulting zwitterion **146** with the regeneration of a carbon-carbon double bond. On the other

hand, the formation mechanism for 1,4-thiazocine **148** is unclear, because a route starting from compound **147** in which a 2,5-dihydropyrrole skeleton is present was refused. The thermal conversion from the latter product **148** to dimethyl (*Z*)- and (*E*)-2-[thieno[2',3':2,3][1,4]thiazino[4,5-*a*]pyrrol-8-ylidene]succinates **151** was shown (Scheme 29).

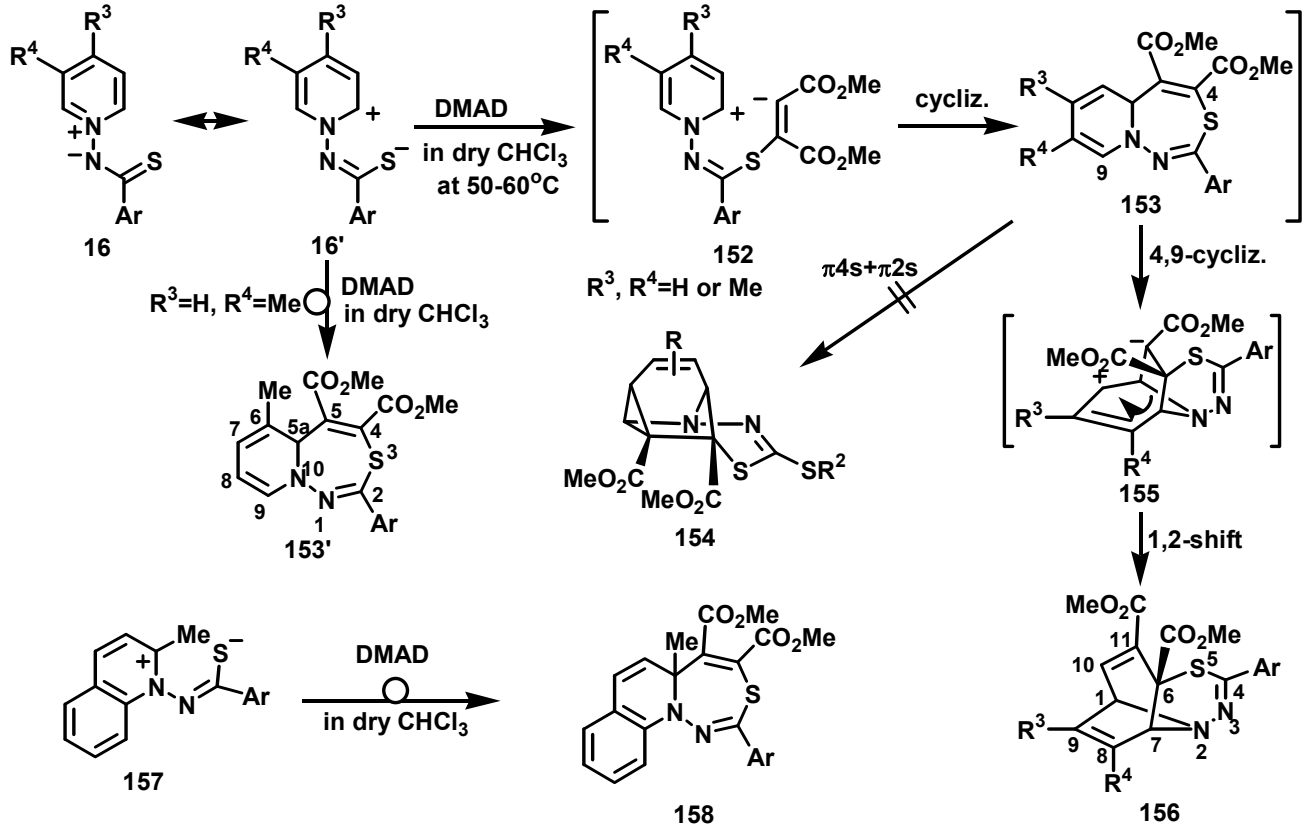


Scheme 29

The reactions of pyridinium and 4-methylpyridinium (arylthiocarbonyl)aminides (**16**) with DMAD in dry $CHCl_3$ at 50−60 ºC did not give any 5a*H*-pyrido[1,2-*d*]-1,3,4-thiadiazepine derivatives **153** and their intramolecular Diels-Alder adducts **154**, but, instead of them, provided the rearranged products, 4-aryl-5-thia-2,3-diazatricyclo[4.3.2.$0^{2,7}$]undeca-3,8,10-trienes (**156**), in low yields via similar reaction mechanisms proposed for the transformation from **128** to **147** in Scheme 29[59] (See Scheme 30). On the other hand, the reactions of 3-methylpyridinium (arylthiocarbonyl)aminides (**16**, R^3=H, R^4=Me) with DMAD formed the expected dimethyl 2-aryl-6-methyl-5a*H*-pyrido[1,2-*d*]-1,3,4-thiadiazepine-4,5-dicarboxylates (**153'**), together with dimethyl 4-aryl-8-methyl-5-thia-2,3-diazatricyclo[4.3.2.$0^{2,7}$]undeca-3,8,10-triene-6,11-dicarboxylates (**156**). Products **156** were derived from the 8-methyl-5a*H*-pyrido-[1,2-*d*]-1,3,4-thiadiazepines (**153**, R^3=H, R^4=Me). This fact strongly suggested the large effect of the 6-methyl group on the stabilization of pyridothiadiazepine structure. Similarly, 5a-methyl-1,3,4-thiadiazepino[4,5-*a*]quinolines (**158**) were isolated in moderate yields from the reactions of 2-methylquinolinium (arylthiocarbonyl)aminides (**157**) with DMAD.

The reason why 5a*H*-pyrido[1,2-*d*]-1,3,4-thiadiazepine derivatives **153** did not afford the corresponding intramolecular Diels-Alder adducts but, instead of them, gave the rearranged products,

5-thia-2,3-diazatricyclo[4.3.2.0^{2,7}]undeca-3,8,10-trienes **155**, is unclear. However, the introduction of shorter carbon-nitrogen and nitrogen-nitrogen bonds than the carbon-carbon one should cause the larger ring strain in the heterocyclic Diels-Alder adducts **154** possessing a cyclopropane ring than the rearranged tricyclic products **156**.

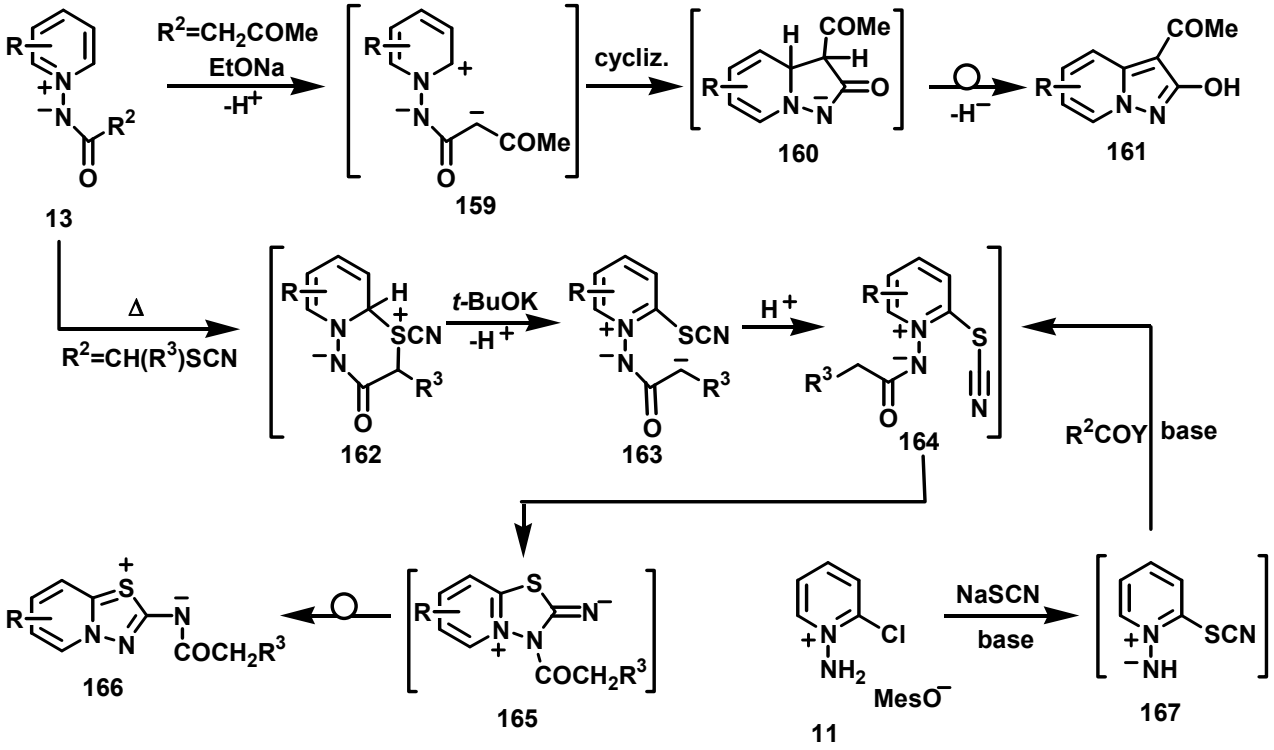


Scheme 30

3.3. REACTIONS AS ELECTROPHILES

The attack of external nucleophiles onto the 2- or 4-position of the pyridinium ring of pyridinium ylides has been scarcely known. However, a few intramolecular versions of this type of reaction were reported. In 1975 Kato and Masuda described the formation of 3-acetylpyrazolo[1,5-*a*]pyridin-2-ols (**161**) by treating pyridinium (acetoacetyl)aminides (**13**, R^2=CH_2COMe) with a strong base[60] (See Scheme 31). Products **161** were formed by way of the deprotonation from the active methylene group of **13**, the intramolecular cyclization between the resulting anion terminal and the positive 2-position of **159**, and the elimination of a hydride and the keto-enol isomerization of **160**. Similarly, we investigated the thermolyses of pyridinium (thiocyanatoacetyl)aminides (**13**, R^2=$CH(R^3)SCN$) in the presence of a strong base to obtain 1,3,4-thiadiazolo[3,2-*a*]pyridinium 2-(*N*-acetyl)imides (**166**), though their yields were low.[10b] By considering the possible reaction mechanisms and examining the independent synthesis of key

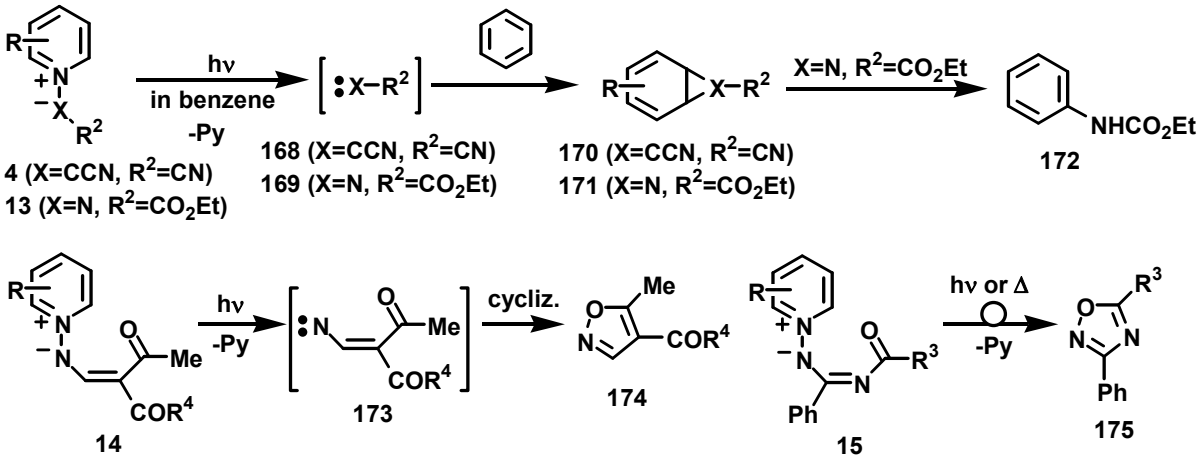
intermediates **164** starting from 1-amino-2-chloropyridinium salt (**11**) we could develop a novel and more effective synthetic method for this type of compound **166**.



Scheme 31

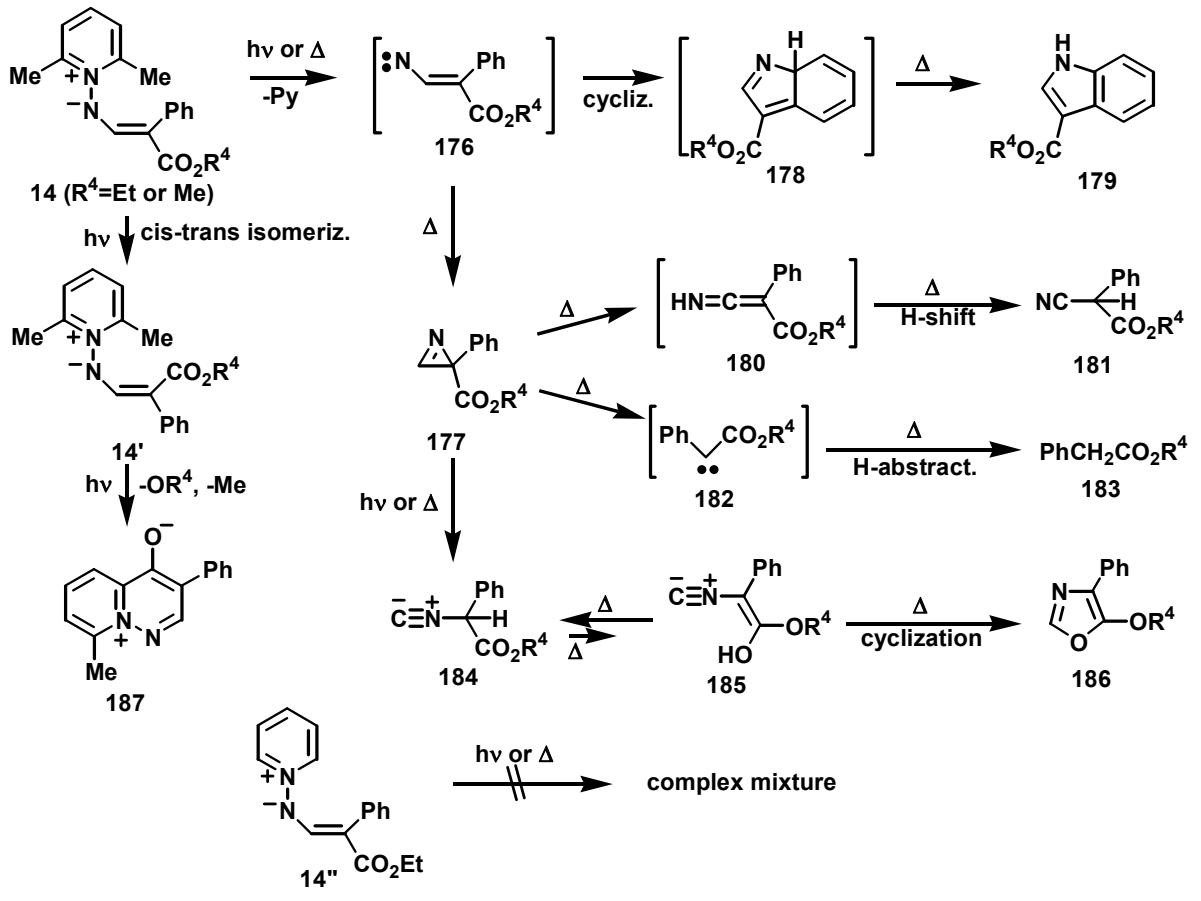
3.4. YLIDIC BOND FISSION

The cleavage of the ylidic bond is a phenomenon observed well in various thermal and photochemical reactions of pyridinium ylides. Since pyridinium ylides are not explosive, ylidic bond fission is a useful method for generating reactive carbene and nitrene species safely. The carbene and nitrene formed thus are electrophilic and react with electron-rich substrates to provide cyclopropane and aziridine derivatives or intramolecularly cyclize to give some heterocycles. For example, the photolysis of pyridinium dicyanomethylide (**4**) or pyridinium (ethoxycarbonyl)aminide (**13**) in benzene afforded 7,7-dicyanobicyclo[4.1.0]hepta-2,4-diene (**170**)[23] or ethyl *N*-phenylcarbamate (**172**)[25b] as a by-product together with each original product described earlier. It can be thought that compound **172** was formed by the isomerization of initially formed *N*-ethoxycarbonyl-7-azabicyclo[4.1.0]hepta-2,4-diene (**171**). On the other hand, the irradiation of pyridinium [(3-oxo-1-butenyl)]aminides (**14**)[6d] and pyridinium [(*N*-acyl)benzimidoyl]aminides (**15**)[7b] gave the corresponding 4-acyl-5-methylisoxazoles (**174**) and 5-acyl-3-phenyl-1,2,4-oxadiazoles (**175**) in good yields with the loss of pyridine respectively (Scheme 32). The thermolysis of ylide **15** (R^3=Ph) in xylene at the reflux temperature also provided the same compound **175** (R^3=Ph).[7b]



Scheme 32

We investigated the substituent effect which influenced ylidic bond fission and found a large promotion by the 2,6-dimethyl groups on the pyridine ring (Scheme 33).[61] The thermolyses of 2,6-dimethylpyridinium (2-alkoxycarbonyl-2-phenylvinyl)aminides (**14**) smoothly afforded indole-3-carboxylates (**179**), phenylcyanoacetates (**181**), phenylacetates (**183**), and 4-phenyloxazoles (**186**), which were derived from the vinyl nitrenes **176** or the related 2-phenyl-2*H*-azirine-2-carboxylates (**177**), and their photolysis

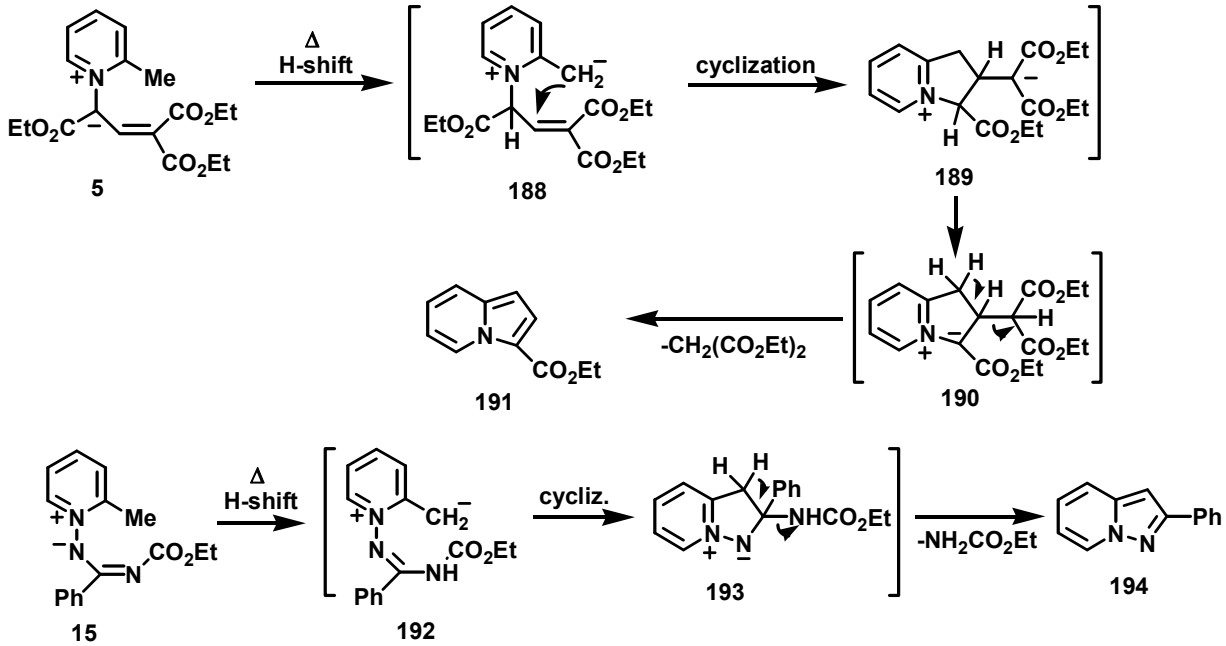


Scheme 33

gave 2*H*-azirine **177**, isonitriles **184**, and 8-methyl-3-phenylpyrido[1,2-*b*]pyridazinium-4-olate (**187**). The last compound **187** was formed by way of the first photochemical *cis-trans* isomerization of the vinyl group of ylides **14**, followed by the intramolecular cyclization-elimination of the resulting **14'**. On the other hand, the thermolysis and photolysis of parent pyridinium ylide **14"** did not provide any distinct product.

3.5. OTHER REACTIONS

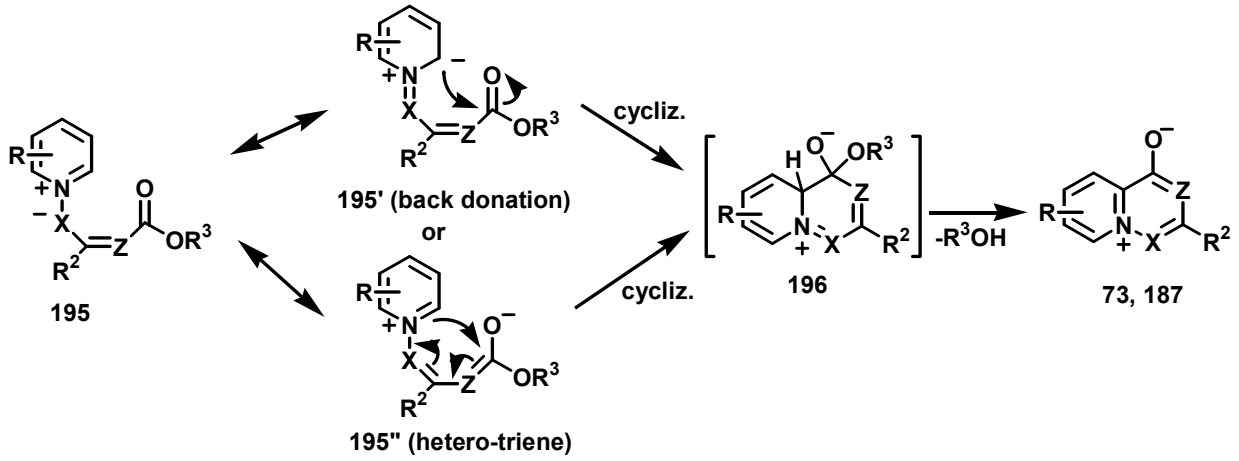
Two reactions for pyridinium ylides except those described above have been sometimes observed. The first is a smooth hydrogen shift from the 2-methyl group to the terminal anion atom of the dipole. For example, zwitterion **188** generated from the hydrogen shift of 2-methylpyridinium 1,3,3-tris(ethoxycarbonyl)allylide (**5**) undergoes the intramolecular Michael addition to form 1*H*-2,3-dihydroindolizine intermediates **189**, which in turn proceeds to ethyl indolizine-3-carboxylate (**191**) via its aromatization with the elimination of diethyl malonate[33] (See Scheme 34). Similarly, that of 2-methylpyridinium [*N*-(ethoxycarbonyl)benzimidoyl]aminide (**15**) proceeded via the hydrogen shift to the 3-nitrogen atom, the nucleophilic cyclization of **192** to **193**, and the final aromatization to 2-phenylpyrazolo[1,5-*a*]pyridine (**194**).[7]



Scheme 34

The second is the 1,6-cyclization reaction of 1,5-dipoles having an alkoxycarbonyl group at the anion terminal, and it affords the corresponding 6-membered mesoionic compound (see Scheme 12 and 33 for two examples). This reaction has been known to some extent in the field of azolium ylides and the

formation of the mesoionic compounds was elucidated by the increased nucleophilicity at the 2-position of the azole ring caused by the back donation.[62] However, the large contribution of such a back donation as seen in **195'** is not able to expect so much to the π-deficient pyridine ring, and hence an alternative route such as the 1,6-cyclization (π6s) of the hetero-triene system **195"** may be considered (Scheme 35).

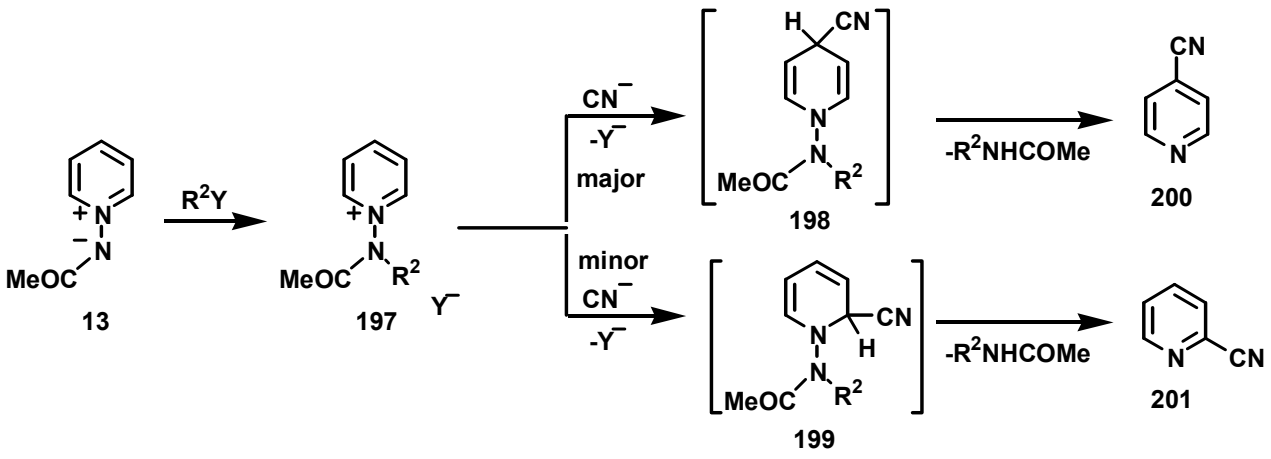


Scheme 35

4. REACTIONS OF PYRIDINIUM SALTS

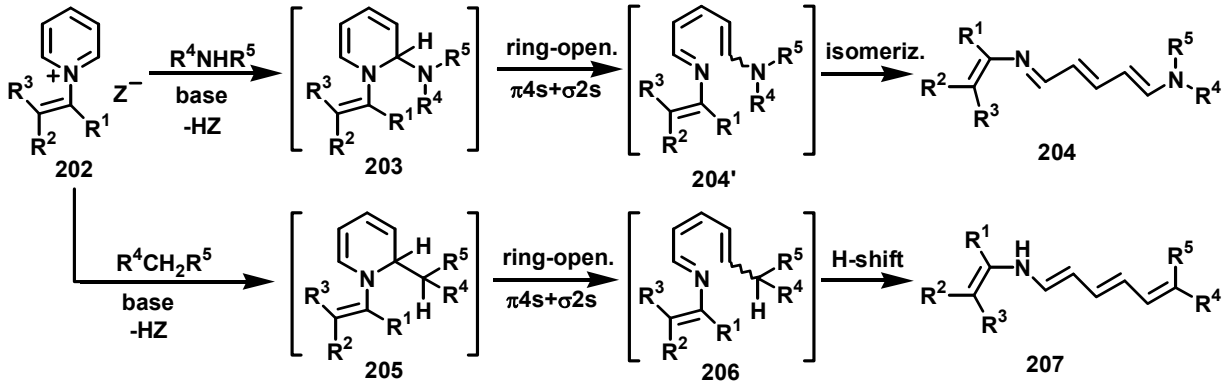
4.1. ELECTROPHLIC REACTIONS OF PYRIDIUM RING

It has been reported that 1-(disubstituted)aminopyridinium salt **197**, readily available from the alkylation of pyridinium acetylaminide **13** (R^2=Me) with alkyl halides, reacted with a cyanide ion to provide 4- (**200**) and 2-cyanopyridines (**201**) in good yields via the aromatization of the primary adducts, 4-cyano-1,4-dihydropyridine **198** and 2-cyano-1,2-dihydropyridine **199**, with the loss of an amide (Scheme 36).[63] However, the synthetic value of this type of reaction is not too high, because similar reactions can be performed by using more readily available materials such as pyridine *N*-oxides.[64]



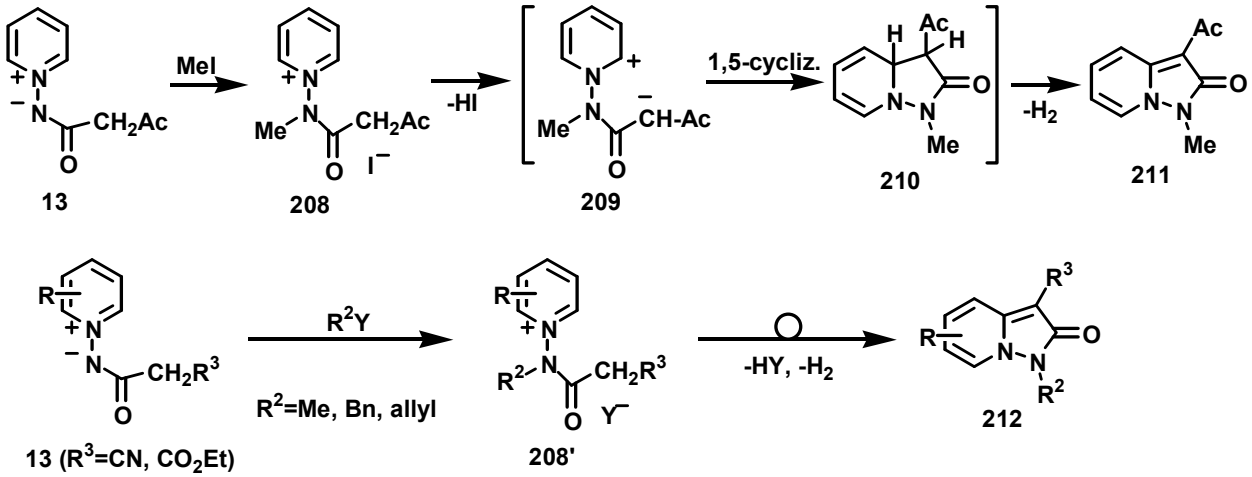
Scheme 36

The ring opening in the reactions of 1-vinylpyridinium salts **202** and some nucleophiles under alkaline conditions have been observed. For example, Aklbrecht and Kröhnke reported the formation of 3-aza-1,3,5,7-octatetraenes **204** from the reactions of salts **202** and amines such as piperidine and cyclohexylamine[65] and Kobayashi *et al*. described those of *N*-vinyl-1,3,5-hexatrienylamines **207** from their reactions with active methylene compounds (Scheme 37).[66] These products **204** and **207** should be obtained via the electrocyclic ring opening (π4s + σ2s) of the first adducts **203** or **205** between salts **202** and amine or the carbanion generated from the deprotonation of active methylene compounds, followed by the *cis-trans* isomerization of **204'** or a hydrogen shift of **206**.



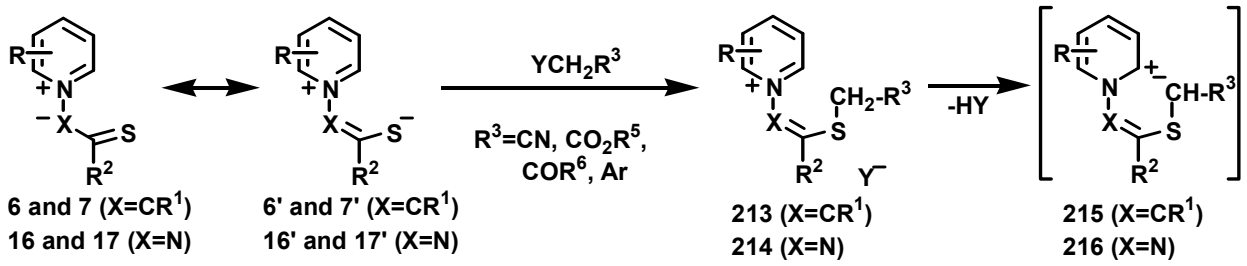
Scheme 37

Kato reported the synthesis of 3-acetyl-1-methyl-1,2-dihydropyrazol[1,5-*a*]pyridine-2-ones (**211**) from the alkaline treatment of 1-[acetoacetyl(methyl)amino]pyridinium iodide (**208**), which was obtained from the reaction of pyridinium (acetoacetyl)aminide (**13**) with iodomethane[60] (See Scheme 38). Compound **211** can be formed via the dehydriodination of salt **208**, the 1,5-cyclization of the resulting zwitterion **209**, and the dehydrogenation of cycloadduct **210**. Later, our groups also described a more common synthesis of 1-alkyl-1,2-dihydropyrazol[1,5-*a*]pyridin-2-one derivatives **212**.[10a]



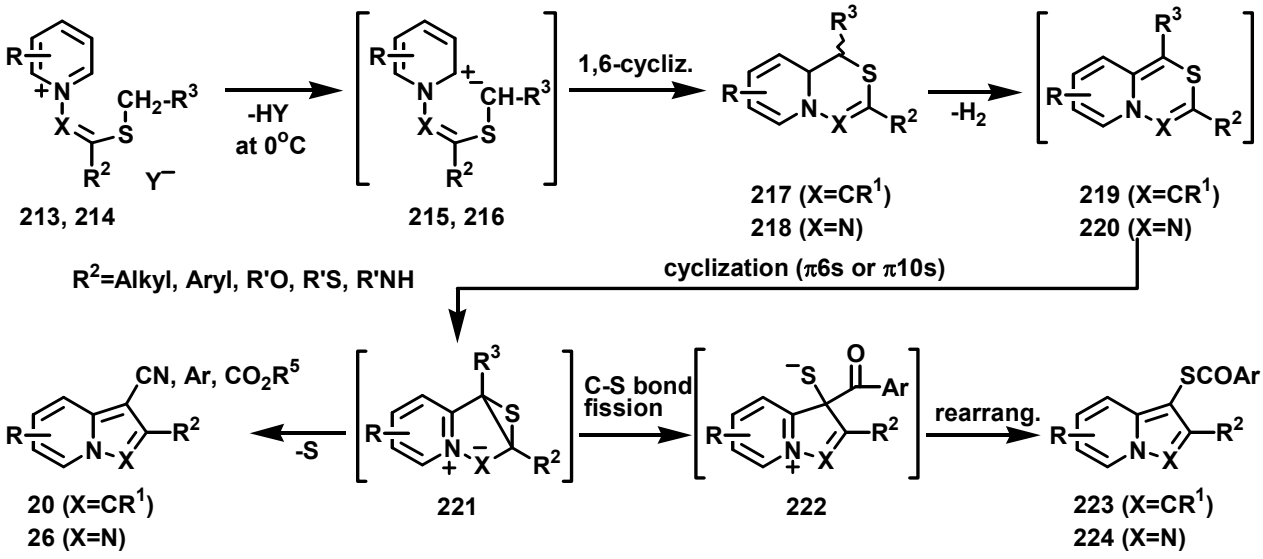
Scheme 38

As described in Section 2, pyridinium ylides **6**, **7**, **16** and **17** having a thiocarbonyl group on the ylidic atom always undergo the alkylation at the sulfur atom. When alkyl halides such as bromoacetonitrile, α-haloesters, α-haloketones and benzyl halides having an electron-poor group are employed as an alkylating agent in these reactions, the resulting pyridinium salts **213** and **214** have an active methylene group in the 1-substituent and their treatment with an appropriate base can generate new zwitterions **215** and **216** (Scheme 39).



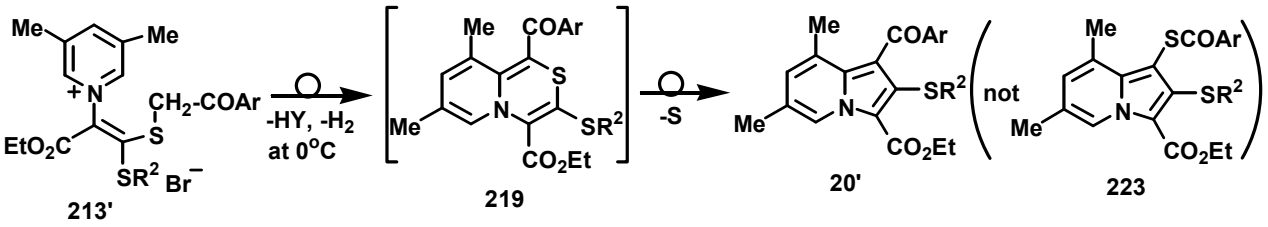
Scheme 39

We developed a quite novel synthetic method for indolizines **20** and pyrazolo[1,5-*a*]pyridines **26** through the investigation of the generation and the reaction of zwitterions **215** and **216** (Scheme 40).[67] In these reactions the generated zwitterions **215** and **216** undergo 1,6-cyclization to afford the corresponding 1,9a-dihydropyrido[2,1-*c*]-1,4-thiazine **217** or 1,9a-dihydropyrido[1,2-*d*]-1,3,4-thiadiazine intermediates **218** which can be isolated or detected by NMR spectral inspection. The treatment of **217** and **218** with a dehydrogenating agent at low temperature (0 °C) generates pyrido[2,1-*c*]-1,4-thiazines **219** or pyrido[1,2-*d*]-1,3,4-thiadiazines **220** and they are spontaneously transformed by way of the ring contraction-desulfurization (R^3=CN, CO_2R^5, and Ar) or ring contraction-rearrangement (R^3=COAr) to the corresponding indolizines **20** and pyrazolo[1,5-*a*]pyridines **26**.



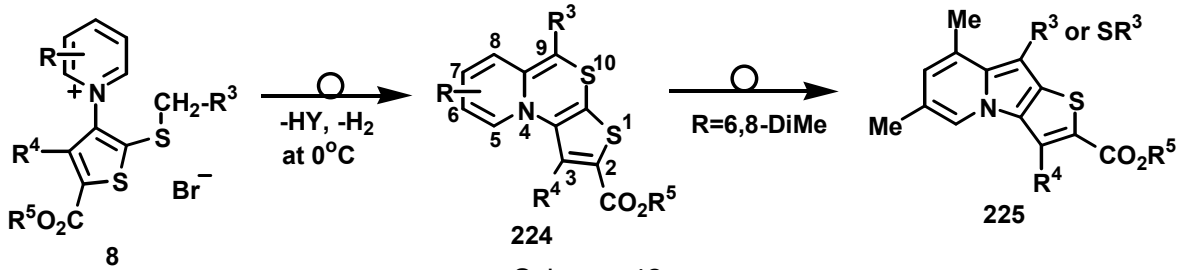
Scheme 40

The smooth desulfurization of the related species, 1,3,4-thiadiazinyl anion, is described, but the rearrangement of an arylcarbonyl group onto the sulfur atom has no precedent.[68] This method is superior to traditional ones in the introduction of a wide range of the 2-substituent such as alkyl, aryl, alkylthio, alkoxy, and alkylamino groups. Although most reactions proceeded via the ring contraction-rearrangement route when R^3=COAr, an exceptional ring contraction-desulfurization one was also observed in the reactions with 1-[2-alkylthio-2-aroylmethylthio-1-(ethoxycarbonyl)vinyl]-3,5-dimethypyridinium salts **213'** (Scheme 41).[69]



Scheme 41

These bicyclic key intermediates **219** and **220** have an unstable anti-aromatic 12π system and therefore could not be isolated and detected at all. However, pyrido[2,1-*c*]thieno[3,2-*e*]-1,4-thiazines (**224**) fused with an aromatic thiophene ring were very stable under the reaction conditions employed here, though only the 6,8-dimethyl derivatives were slowly converted to the corresponding thieno[2,3-*b*]indolizines **225** (Scheme 42).[70]

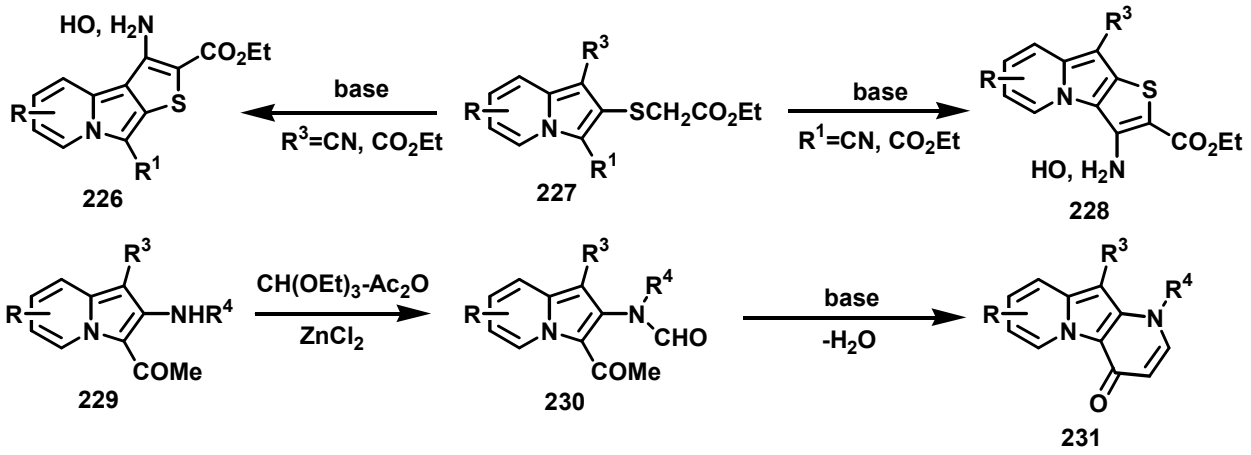


Scheme 42

Indolizines obtained thus are useful precursors for synthesizing tricyclic analogs fused with a hetero-ring. For example, thieno[3,2-*a*]indolizine **226** and thieno[2,3-*b*]indolizine derivatives **228** were prepared by the alkaline treatment of 2-(ethoxycarbonylmethylthio)indolizines **227** bearing a cyano or ethoxycarbonyl group at the 1- or 3-position,[71] and 1,4-dihydropyrido[2,3-*b*]indolizin-4-ones **231** were formed via the *N*-formylation of 3-acetyl-2-(alkylamino)indolizines **229** with triethyl orthoformate-acetic anhydride in the presence of a catalyst and the dehydration of the resulting compounds **230** under strong alkaline conditions (Scheme 43).[72]

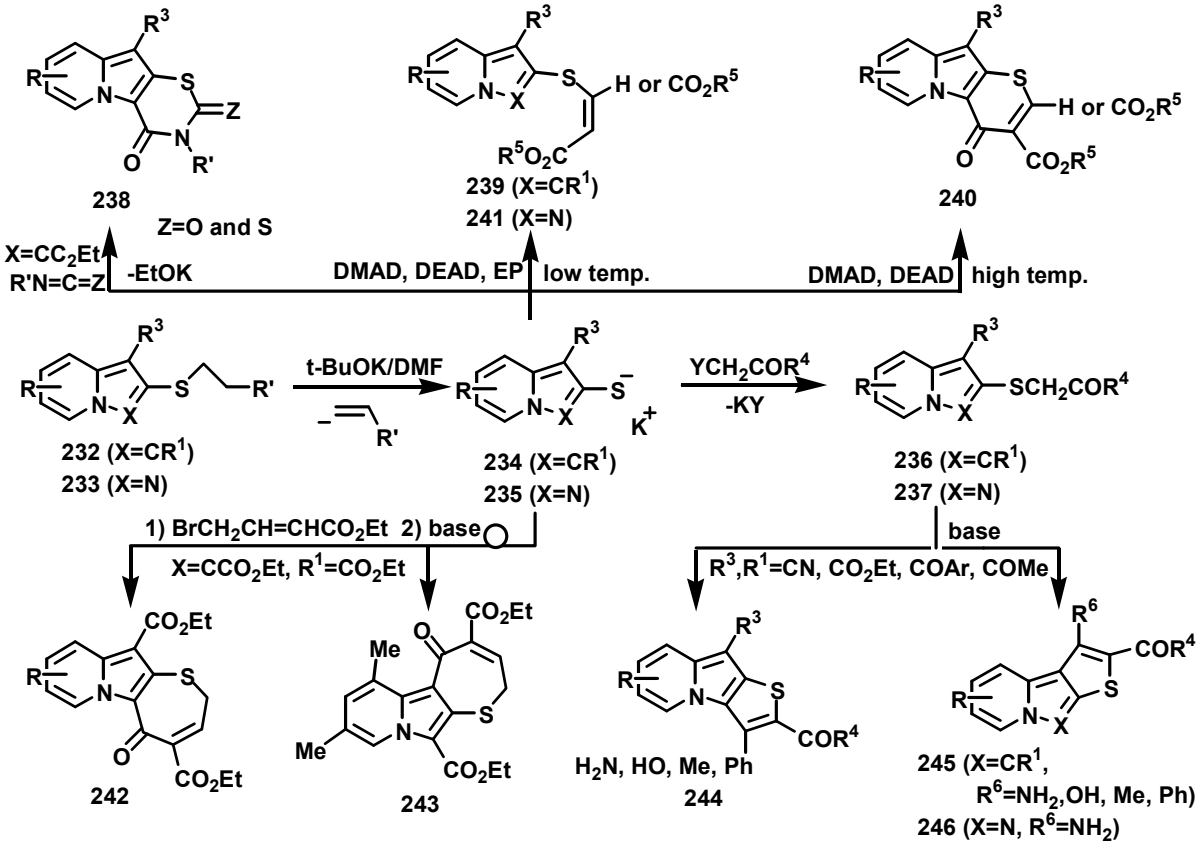
Since the introduction of the 2-substituent involving an active methylene group by this method was considerably restricted, however, we developed a novel procedure for synthesizing polyfunctionalized

indolizines **236** and pyrazolo[1,5-*a*]pyridines **237** having various acylmethylthio groups at the 2-position.



Scheme 43

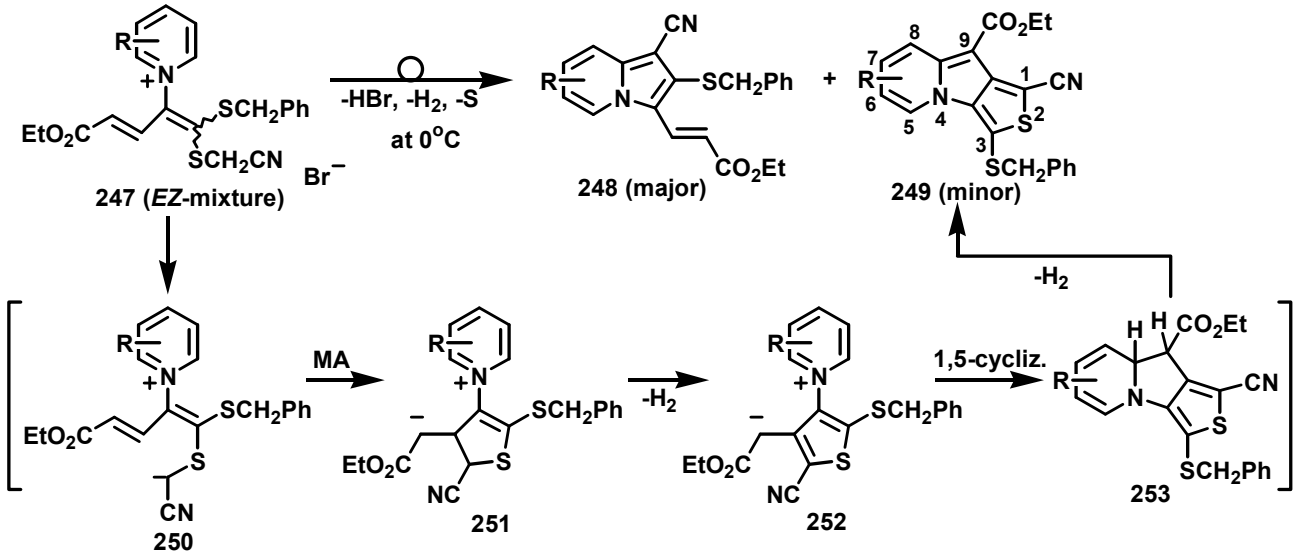
The retro-Michael addition of compounds **232** and **233** bearing a 2-cyanoethylthio or 2-(ethoxycarbonyl)ethylthio group by the treatment with a strong base (*t*-BuOK) in DMF and then the *S*-alkylation of the resulting indolizine-2-thiolates **234** and pyrazolo[1,5-*a*]pyridine-2-thiolates **235** with α-haloacetates and α-haloketones afforded the corresponding 2-(acylmethylthio)indolizines **236** and 2-(acylmethylthio)pyrazolo[1,5-*a*]pyridines **237**.[73]



Scheme 44

The reactions of thiolates **234** and **235** with isocyanates and isothiocyanates afforded 1,3-thiazino[6,5-*b*]indolizines **238**,[74] and those with DMAD, diethyl acetylenedicarboxylate (DEAD), ethyl propiolate (EP), yielded the Michael adducts **239** and **241** and/or thiazino[2,3-*b*]indolizin-4-ones **240** depending upon the reaction conditions used.[75] Similarly, the *S*-alkylation of 1,3-bis(ethoxycarbonyl)indolizine-2-thiolates (**234**) with ethyl 4-bromocrotonate and subsequent alkaline treatment of the resulting indolizine derivatives gave thiepino[2,3-*b*]- **242** and thiepino[3,2-*a*]indolizine **243**.[76] The functionalized indolizines **236** were transformed in the presence of a base to the corresponding thieno[2,3-*b*]indolizines **244** or thieno[3,2-*a*]indolizines **245** depending upon the substituents at the 1- and 3-positions, and 2-(acylmethylthio)pyrazolo[1,5-*a*]pyridine-3-carbonitriles **237** were similarly converted to thieno[2',3':2,3]pyrazolo[1,5-*a*]pyridines **246**.[77] These results are summarized in Scheme 44.

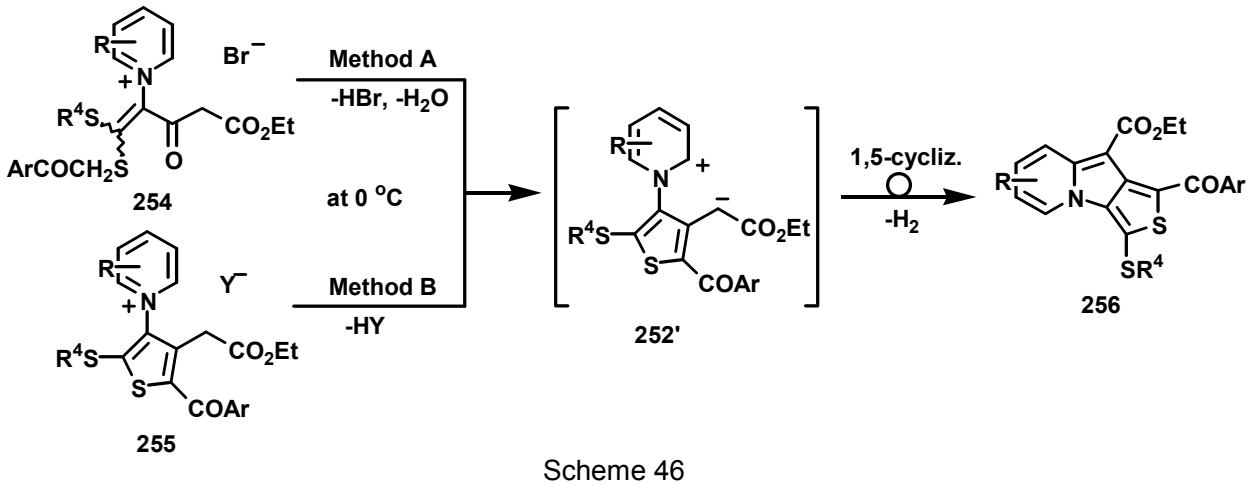
In the attempts to synthesize 2-benzylthio-3-(2-ethoxycarbonylvinyl)indolizine-1-carbonitrile (**248**) from the *EZ*-mixtures of 1-(1-benzylthio-1-cyanomethylthio-4-ethoxycarbonyl-1,3-butadien-2-yl)pyridinium bromides (**247**) we noticed the formation of the byproducts, ethyl 3-benzylthio-1-cyanothieno-[3,4-*b*]indolizine-9-carboxylates (**249**), in low yields together with the target compounds.[78] We assumed that compounds **249** were formed by way of the Michael addition (MA) of the carbanion atom of **250** generated by the dehydrobromination of the *Z*-isomers of salts **247**, the aromatization of dihydrothiophenes **251**, the 1,5-cyclization of zwitterions **252**, and the dehydrogenation of 8a,9-dihydrothieno[2,3-*b*]indolizine intermediates **253** (Scheme 45).



Scheme 45

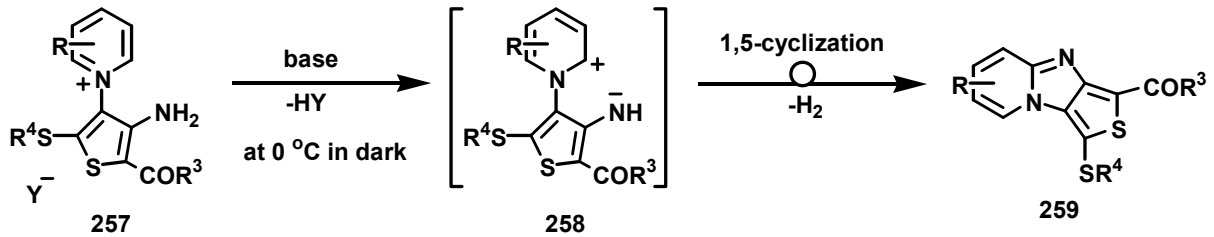
To confirm this assumption we planned two independent syntheses of thieno[2,3-*b*]indolizines such as **256** (Scheme 46). The first route (method **A**) involved the generation of the common key intermediates **252'** by the dehydrobromination and the dehydration of 1-[2-alkylthio-2-arylcarbonylmethylthio-1-

(ethoxycarbonylacetyl)vinyl]pyridinium bromides (**254**) in the presence of a base,[79] and the second (method **B**) can also form the same intermediates **252'** by the dehydrohalogenation of 1-[2-alkylthio-5-arylcarbonyl-4-(ethoxycarbonylmethyl)thiophen-3-yl]pyridinium halides (**255**), which were readily available from the *S*-alkylation of 3-(1-pyridinio)thiophene-2-thiolates (**9**) with various alkylating agents.[80] The experimental results made the high effectiveness of method **B** clear. The thieno[2,3-*b*]indolizine molecules **256** having an arylmethylthio, allylthio, propargylthio, or acylmethylthio group at the 3-position exhibited an interesting arene-arene, arene-π, or arene-cation interaction in their gauche conformation in the relation of the sulfide linkage.[81]



Scheme 46

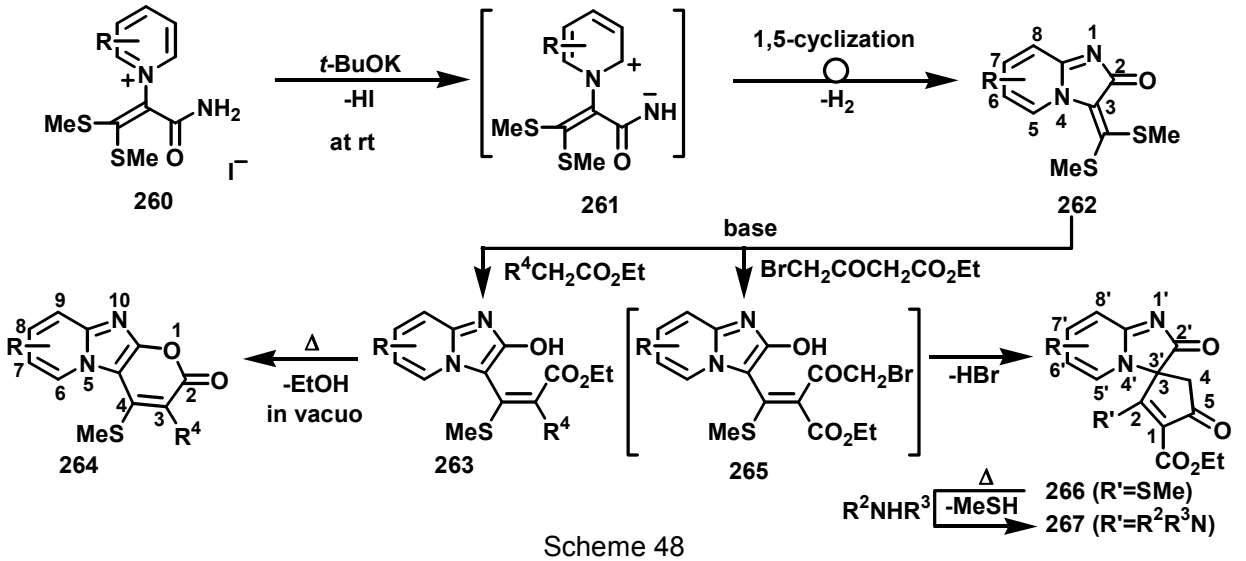
Similarly, we found that the alkaline treatment of 1-[2-alkylthio-4-amino-5-(arylcarbonyl)thiophen-3-yl]pyridinium halides (**257**), readily available from 4-amino-3-(1-pyridinio)thiophene-2-thiolates (**10**) and alkyl halides, smoothly generated the corresponding 3-(1-pyridinio)thiophen-4-imides **258** and then their 1,5-cyclization and the aromatization afforded thieno[3',4':4,5]imidazo[1,2-*a*]pyridine derivatives **259** (Scheme 47).[82]



Scheme 47

The smooth deprotonation from an aromatic primary amino group described above encouraged us to extend this type of reaction to pyridinium salts bearing a carbamoyl group in the 1-substituent. As expected, the treatment of 1-[1-carbamoyl-2,2-bis(methylthio)vinyl]pyridinium iodides (**260**), prepared

from the reactions of pyridinium methylides **6** (R^1=$CONH_2$) with iodomethane, with a strong base afforded 3-[bis(methylthio)methylene-2(3*H*)-imidazo[1,2-*a*]pyridines (**262**) with the loss of a molecule of hydrogen[83] (See Scheme 48). Compounds **262** reacted with several active methylene compounds such as diethyl malonate, ethyl acetoacetate, and ethyl cyanoacetate in the presence of a base to provide 3-vinylimidazo[1,2-*a*]pyridin-2-ols **263**, and the products, in turn, on heating at reduced pressure were transformed to the corresponding pyrano[2',3'-*b*]imidazo[1,2-*a*]pyridin-2-ones **264**.[83] Furthermore, compounds **262** reacted with ethyl 4-bromoacetoacetate to give directly spiro[2-cyclopentene-1,3-imidazo[1,2-*a*]pyridine] derivatives **266** via the dehydrobromination of the initially formed 3-vinylimidazo[1,2-*a*]pyridin-2-ols **265**. The smooth replacement of the 2-methylthio group of **266** by primary and secondary amines was also reported. The proton signals of compounds **260** and their 2-amino derivatives **267** showed an interesting concentration-dependency in their ^{1}H-NMR spectra in $CDCl_3$.[84]

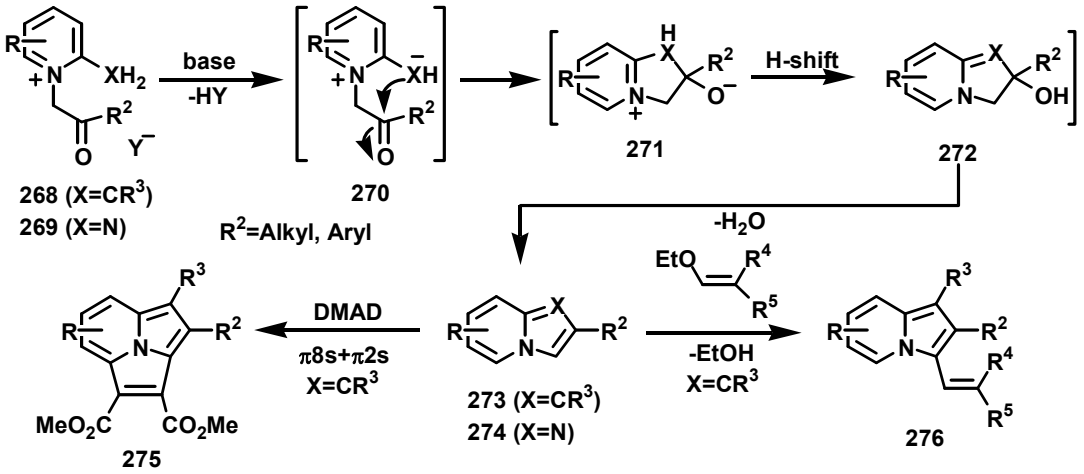


Scheme 48

4.2. REACTIONS OF 2- OR 4-METHYL OR AMINO GROUP ON PYRIDIUM RING

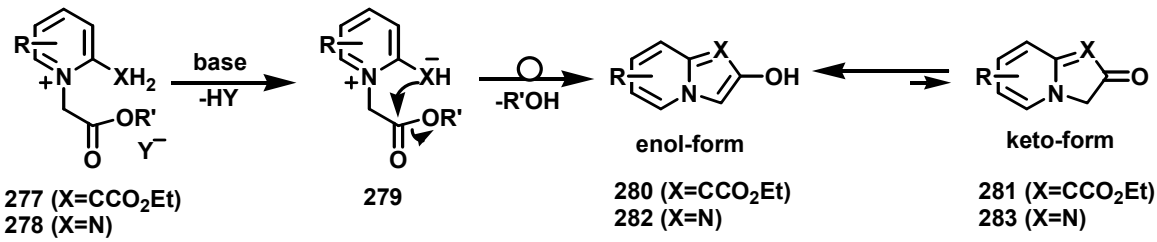
The increased acidity of the methyl and amino group at the 2- and 4-positions of the pyridinium salts is well realized by seeking their resonance structures (see Figure 1) and, in particular, various reactions of the activated 2-methyl, 2-methylene, and 2-amino groups have been investigated. For example, Tschitschibabin reaction is a representative method for obtaining 3-unsubstituted indolizines **273**[85] (See Scheme 49). This reaction affords compounds **273** via the intramolecular nucleophilic addition of the methanide ion **270** (X=CR^3), generated from the alkaline treatment of 1-acylmethyl-2-methyl- or 2-(substituted methyl)pyridinium halides **268**, to the ketone carbonyl group, the proton shift of the resulting **271** (X=CR^3), and the aromatization with the loss of water from **272** (X=CR^3). Indolizines **273** obtained thus may be useful precursors for cycl[3.2.2]azines **275**[86] and 3-vinylindolizines **276**.[87] Similarly,

the use of 2-aminopyridinium salts **269** in this reaction gave the corresponding 3-unsubstituted imidazo[1,2-*a*]pyridines **274**.[88]



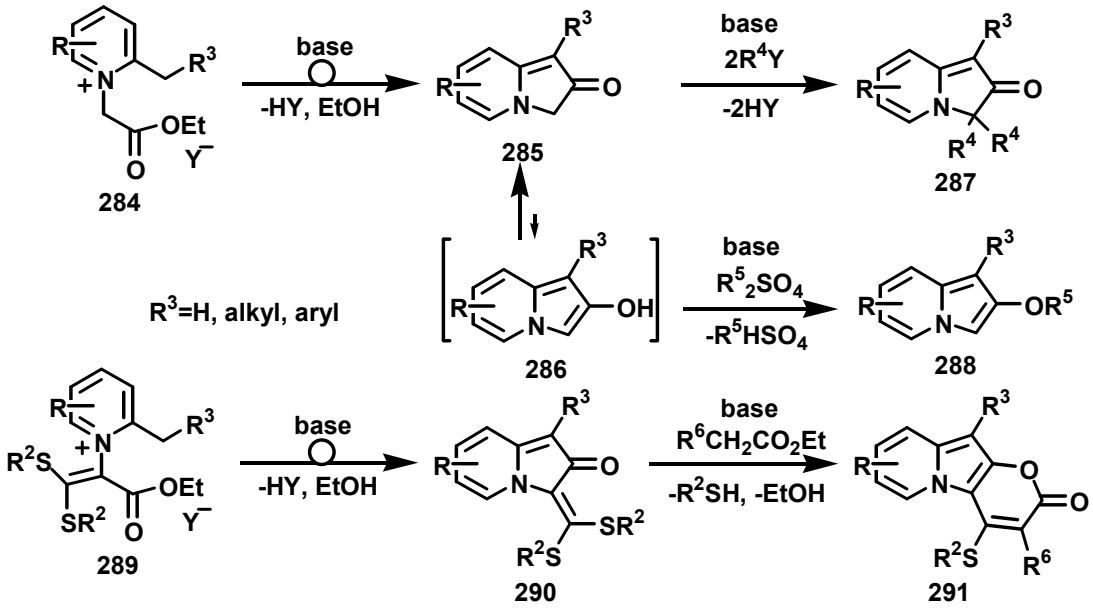
Scheme 49

The alkaline treatment of 1-ethoxycarbonylmethyl-2-(substituted methyl)pyridinium salts **277** and 2-amino-1-(ethoxycarbonylmethyl)pyridinium halides **278** afforded the corresponding 2-indolizinols **280**[89] and imidazo[1,2-*a*]pyridin-2-ols **282**[90] with the elimination of a hydrogen halide and an alcohol. The keto forms such as **281** and **283** in these reactions were not confirmed (Scheme 50).



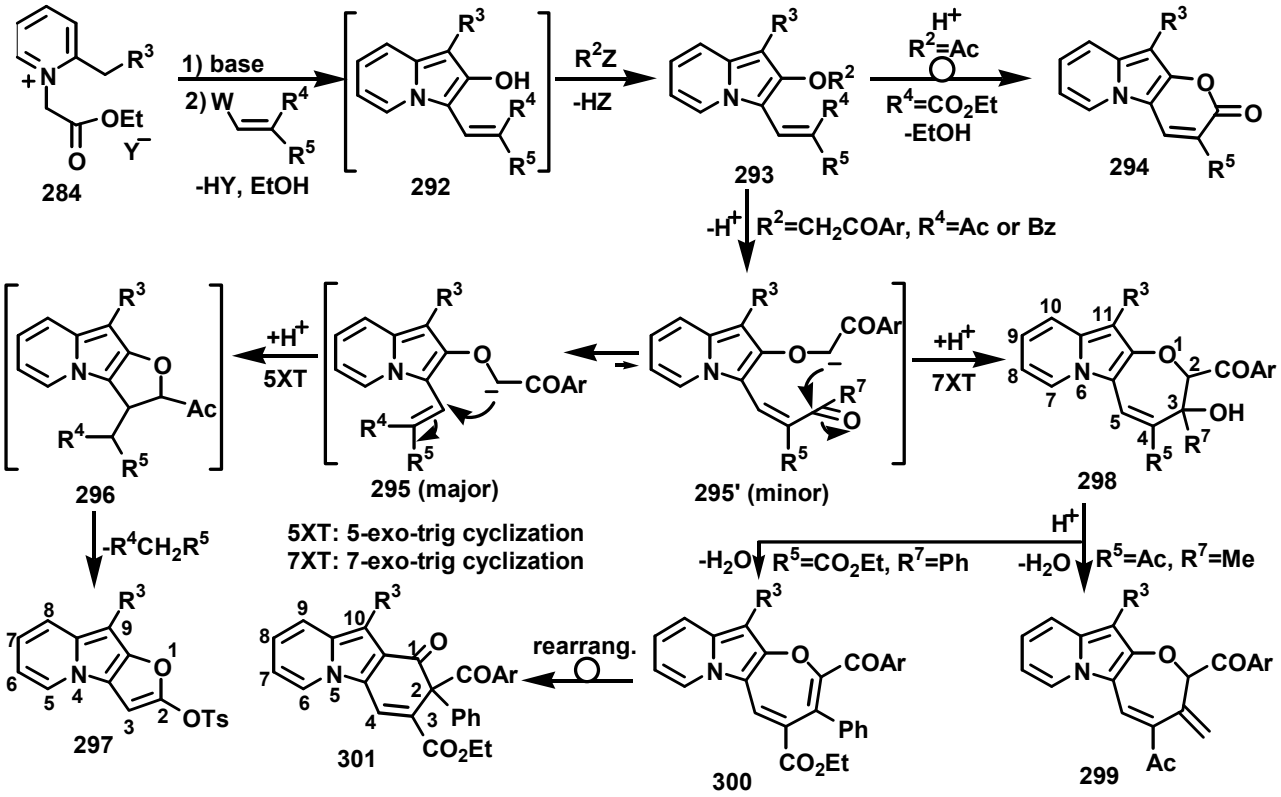
Scheme 50

When the alkaline treatment of 1-(ethoxycarbonylmethyl)pyridinium salts (**284**) or 1-[2,2-bis(alkylthio)-1-ethoxycarbonylvinyl]pyridinium salts (**289**) having an alkyl or benzyl group at the 2-position was examined, we found the formation of the corresponding 2(3*H*)-indolizinones (**285**) or 3-[bis(alkylthio)methylene]-2(3*H*)-indolizinones (**290**) but 2-indolizinols **286** which were enol forms of **285** could not be detected at all.[91] The reactions of 2(3*H*)-indolizinones **285** with various alkyl halide in the presence of a base afforded the expected 3,3-dialkyl-2(3*H*)-indolizinones (**287**) but those with dialkyl sulfates reacted in the enol forms **286** to yield 2-alkoxyindolizines (**288**).[91c] On the other hand, bifunctionalized 3-methylene-2(3*H*)-indolizinones **290** reacted with some acetates activated with an electron-withdrawing or aryl group in the presence of a base to provide the corresponding pyrano[2,3-*b*]indolizin-2-one derivatives **291**.[91a,b] These results are summarized in Scheme 51.



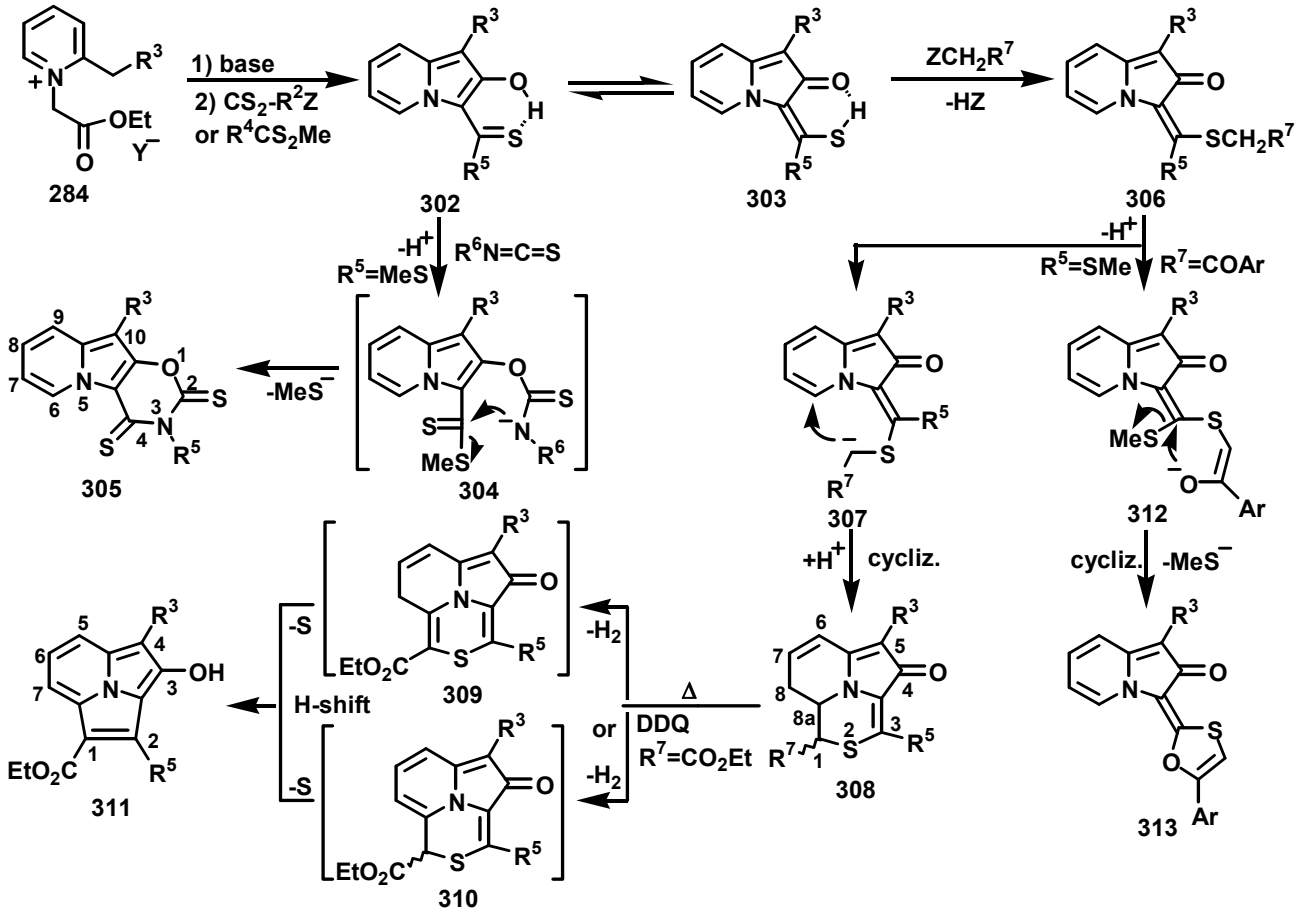
Scheme 51

We further examined this reaction to find a novel synthetic method for functionalized 3-vinylindolizines **293** by employing a combination of the vinylation of 2(3*H*)-indolizinone intermediates **285** and alkylation or acylation of the resulting 3-vinyl-2-indolizinols **292**.[91d] These functionalized 3-vinylindolizines **293** have been proven to be important precursors or intermediates for forming 3-acylpyrano[2,3-*b*]indolizin-2-ones **294**,[92] 2-(arylcarbonyl)furo[2,3-*b*]indolizines **297**,[93] and 4-acyl-2-arylcarbonyl-2,3-dihydrooxepino[2,3-*b*]indolizin-3-ols **298** (Scheme 52).[94] Compounds **297** and **298** were formed via the 5-exo-trig cyclization (Michael addition) of the major carbanions **295** generated by the deprotonation of 2-arylcarbonylmethoxy-3-vinylindolizines **293** onto the 2-vinyl group and then aromatization of the resulting **296** with the elimination of an active methylene compound, and the 7-exo-trig cyclization (nucleophilic addition) of the minor carbanions **295'** to the ketone carbonyl group on the 3-vinyl group, respectively. Interestingly, the acid-catalyzed dehydration of 4-acetyl-2-arylcarbonyl-3-methyl-2,3-dihydrooxepino[2,3-*b*]indolizin-3-ols **298** (R^5=Ac, R^7=Me) did not afford the initially expected full-conjugated oxepino[2,3-*b*]indolizines, but, instead of them, only 3-methylene derivatives **299** were obtained. On the other hand, similar treatment of 4-ethoxycarbonyl-3-phenyl-2,3-dihydrooxepino[2,3-*b*]indolizin-3-ols **298** (R^5=CO_2Et, R^7=Ph) gave the corresponding full-conjugated products **300**. These full-conjugated oxepino[2,3-*b*]indolizines **300** were considerably unstable and, on heating in ethanol, underwent the smooth rearrangement to 2-arylcarbonyl-2-phenylpyrido[1,2-*a*]indol-1-ones **301**. From these facts we could realize a trend to evidently avoid the formation of compounds with an unfavorable 4nπ-electron system, though the oxepine ring of the full-conjugated oxepino[2,3-*b*]indolizines **300** was not planar.



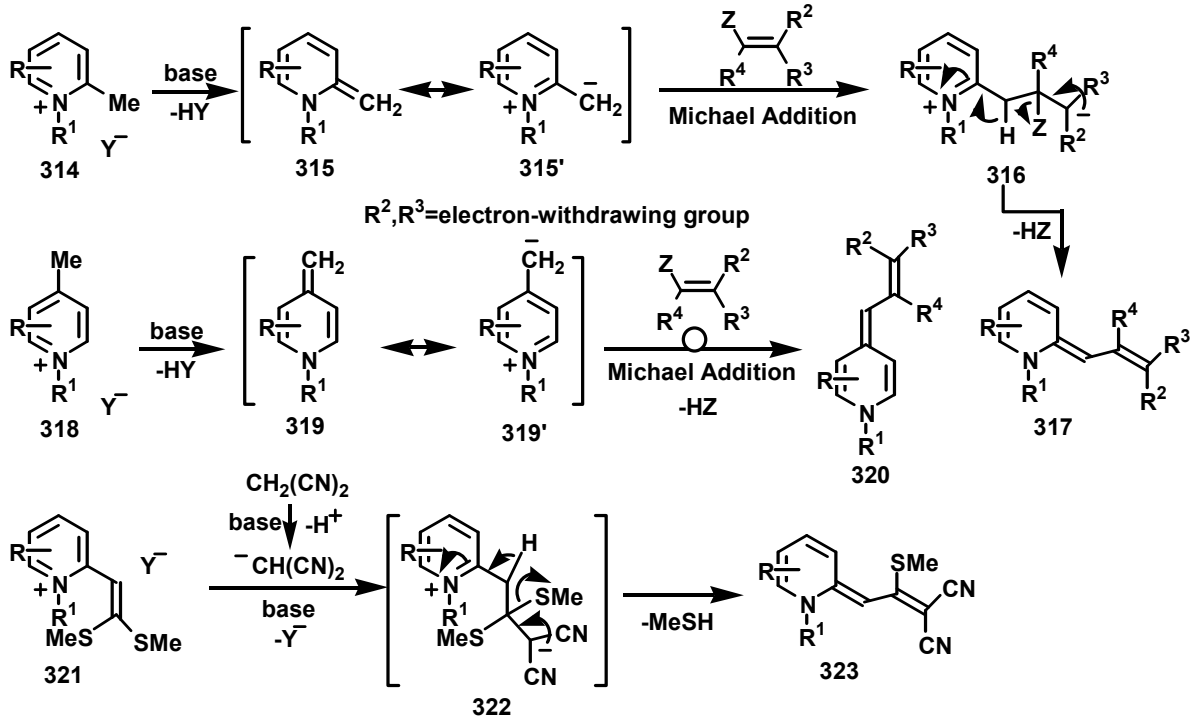
Scheme 52

Some 3-(mercapto)methylene-2(3*H*)-indolizinones **302**, readily available from the reactions of pyridinium salts **284** and carbon disulfide and alkylating agents or dithioesters in the presence of a base, are also useful materials for obtaining new nitrogen-bridged heterocycles such as 1,3-oxazino[6,5-*b*]indolizines **305**,[95] 4(1*H*)-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizinones **308**[96] and cycl[3.2.2]azin-3-ols **311**,[97] and 3-(1,3-oxathiol-2-ylidene)-2(3*H*)-indolizinones **313**[98] (See Scheme 53). An equilibrium is present between thiol compounds **303** and enol ones **302**, and they reacted at the sulfur atom of the thiol group with soft alkylating agents and at the oxygen atom of the hydroxyl group with hard electrophiles. For example, when compounds **302** were allowed to react with some isothiocyanates in the presence of a base, 2*H*-3,4-dihydro-1,3-oxazino[6,5-*b*]indolizine-2,4-diones (**305**) were formed via the intramolecular addition of the imide atom onto the carbon atom of the thiocarbonyl group of the initially generated adducts **304** with a loss of methanethiolate ion. On the other hand, the reactions of **303** with α-bromoacetonitrile, ethyl bromoacetate, and phenacyl bromides in the presence of a base proceeded via the *S*-alkylation followed by the deprotonation of the resulting **306** to provide products **308** or **313** depending upon the nature of the substituents R^5 and R^7. Furthermore, the dehydrogenation of compounds **308** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) under the heating conditions caused to the ring contraction-desulfurization to yield cycl[3.2.2]azin-3-ols **311** by way of the dehydrogenated derivatives **309** or **310**.



Scheme 53

In 1968 Severin and Böhme reported the first synthesis of 2-allylidene-1,2-dihydropyridines **317** and 4-allylidene-1,4-dihydropyridines **320** from the reactions of some 1,2- **314** (R^1=Me) and 1,4-dimethylpyridinium salts **318** (R^1=Me) with 1-dimethylamino-2-nitro-2-phenylethylene in the presence of a base[99] (See Scheme 54). We[100] and other researchers[101] described the preparation of various allylidenedihydropyridine analogs **317** and **320** by using more common vinylating agents such as ethoxymethylene and ketene dithioacetal compounds. Similar compounds **323** were also synthesized by the reactions of 2-[2,2-bis(methylthio)vinyl]-1-methylpyridinium salts (**321** (R^1=Me)) with malondinitrile in the presence of a base.[102] These products **317** and **320** were formed via the Michael addition of zwitterions **315'** and **319'**, which are the resonance contributors of 2-methylene-1,2- **315** and 4-methylene-1,4-dihydropyridines **319** and generated by the dehydrohalogenation of salts **314** and **318**, onto a vinylating agent and the elimination of a HZ molecule. On the other hand, the formation of **323** proceeded by way of the nucleophilic addition of dicyanomethanide ion generated from the deprotonation of malondinitrile onto the positive carbon atom of ketene dithioacetal **321**, followed by the loss of a methanethiol from adduct **322**.



Scheme 54

As shown in Figure 5, a remarkable structural feature of 2-allylidene-1,2-dihydropyridines **317** is the presence of the nucleophilic centers at the 2(1)- and 2(3)-position. Actually, the structural data of 2-(3-cyano-3-ethoxycarbonylallylidene)-1-methyl-1,2-dihydropyridine supported a pyridinium ring form rather than a 1,2-dihydropyridine one and the high double bonded character of the C(2(1))─C(2(2)) and C(2(2))─C(2(3)) bonds, and hence exhibited a larger contribution of the allyl anion structures **317b** and **317c** than the allylidene one **317a**. It can be readily realized that 2-allylidene-1,2-dihydropyridines bearing an electron-poor reaction site in the R^1 substituent should be useful precursors for some heterocycles.

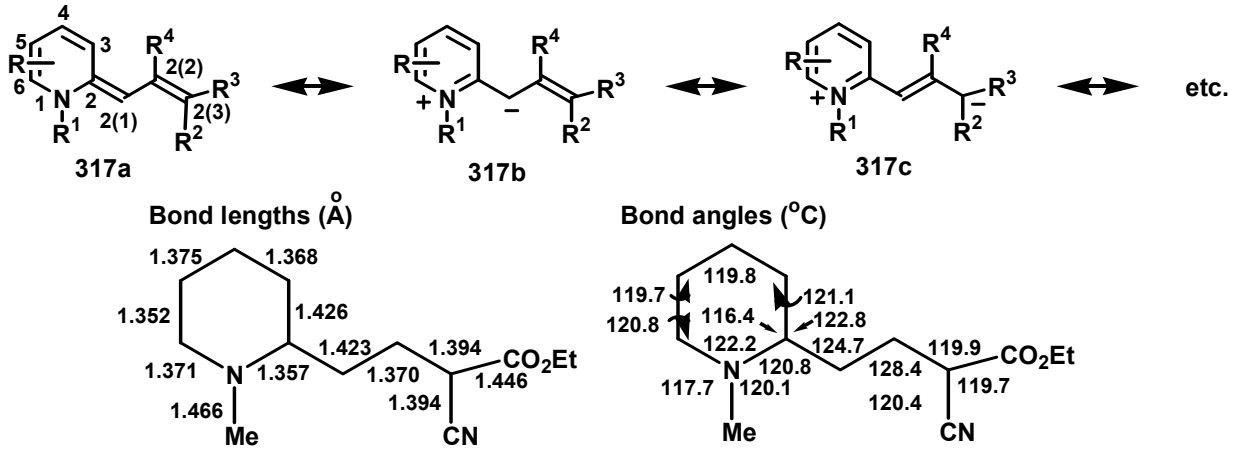
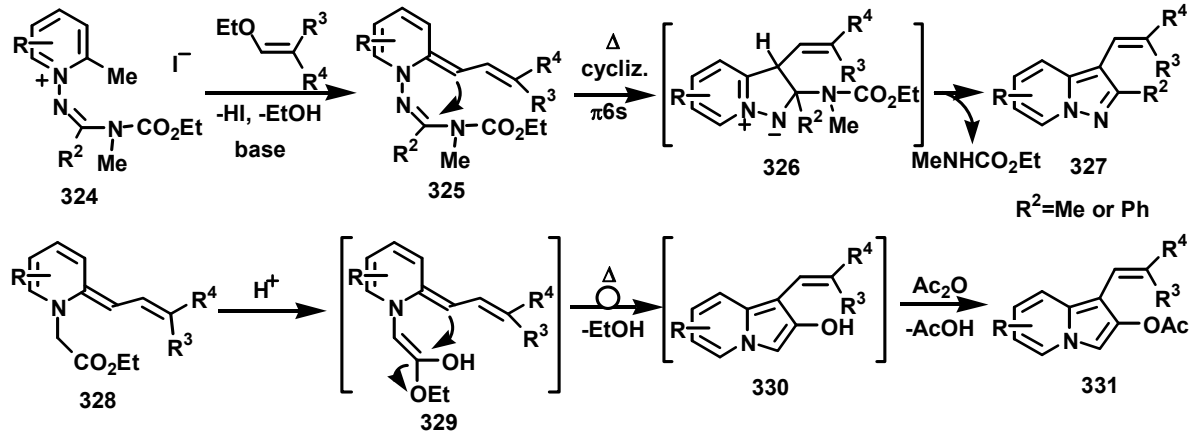


Figure 5

In 1977 we first reported the synthesis of functionalized 3-vinylpyrazolo[1,5-*a*]pyridine derivatives **327** from the thermolysis of 2-[3-cyano-3-(ethoxycarbonyl)allylidene]-1-(disubstituted methyleneamino)-1,2-dihydropyridines (**325**), which could be readily synthesized via the *N*-alkylation of pyridinium 1-[(*N*-ethoxycarbonyl)imidoyl]aminides **15** with iodomethane and subsequent vinylation of the resulting pyridinium salts with ethoxymethylene compounds, in xylene at the reflux temperature[103] (See Scheme 55). Similarly, we could obtain some functionalized 1-acyloxy-1-vinylindolizines **331** by the reactions of 2-allylidene-1-ethoxycarbonylmethyl-1,2-dihydropyridines **328** and anhydride.[104] Products **327** and intermediates **330** were formed by the electrocyclic cyclization (π6s) of **325** and **329** and subsequent aromatization with the elimination of ethyl *N*-methylcarbamate and ethanol respectively. Compounds **331** were formed by the acetylation of 2-indolizinol **330** with acetic anhydride.



Scheme 55

We could realize the high possibility of the transformation from a divinylamine or its aza-analogue system **332** to a pyrrole or pyrazole skeleton **334** through the mechanistic consideration of these reactions (Figure 6).

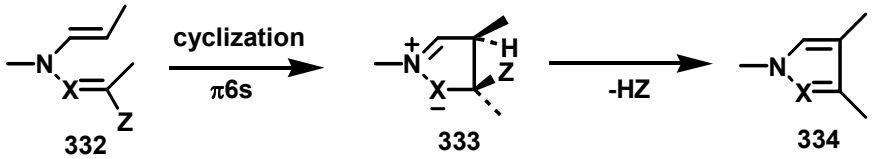
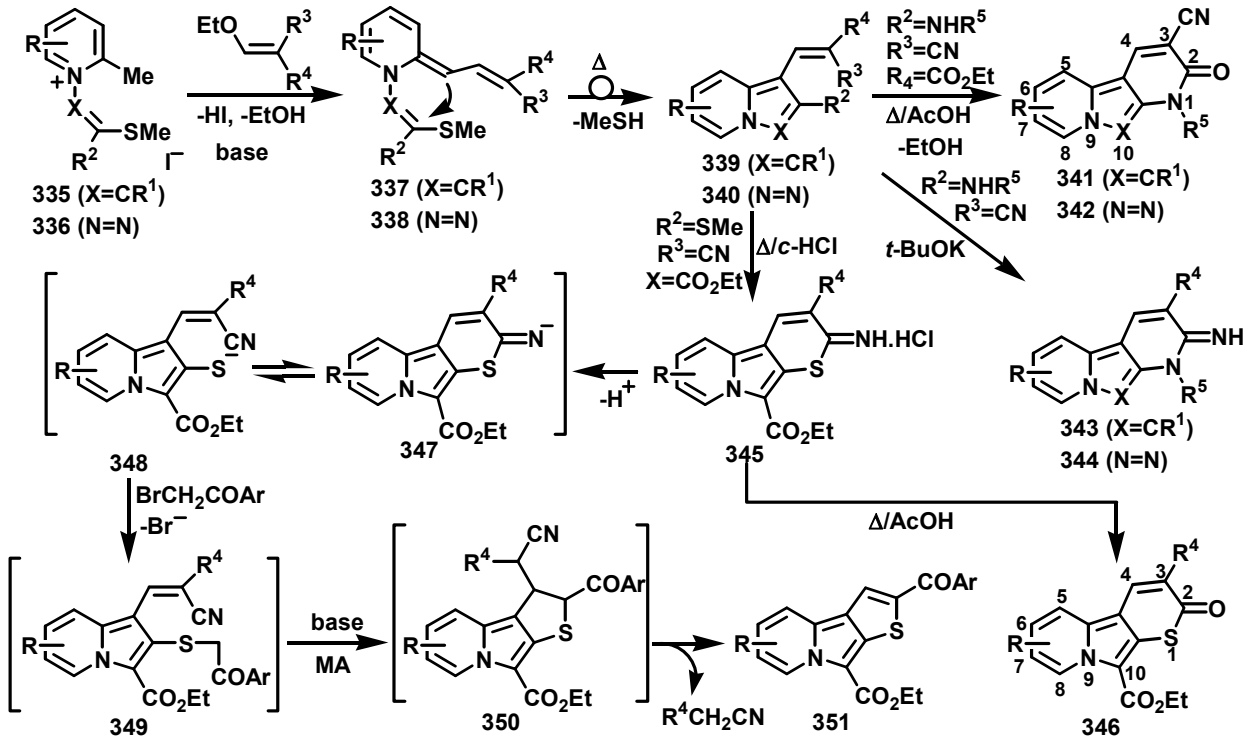


Figure 6

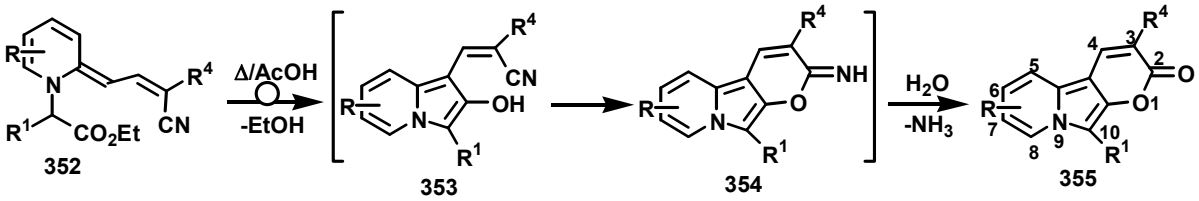
So we synthesized 2-methylpyridinium salts **335** and **336** having a vinyl or methyleneamino group at the 1-position from the alkylation of 2-methylpyridinium (2-thioxo)ethanides **6** or (thiocarbonyl)aminides **16**, and examined their reactions with ethoxymethylene compounds. As expected, we could obtain various 1-vinylindolizines **339** or 3-vinylpyrazolo[1,5-*a*]pyridines **340** bearing an alkylthio[105] and alkylamino group[106] at the 2-position (See Scheme 56). The 2-alkylamino compounds **339** and **340** could be

converted to 1-alkyl-1,2-dihydropyrido[3,2-*a*]indolizin-2-ones **341** and their 10-aza-analogs **342** in acetic acid under the reflux conditions or to the corresponding 2-imine derivatives **343** and **344** by the treatment of potassium *t*-butoxide.[106] The treatment of 2-(methylthio)indolizine derivatives **339** (X=CCO_2Et) with conc. hydrochloric acid afforded 2*H*-thiino[3,2-*a*]indolizin-2-imine hydrochlorides **345**, which were then converted to carbonyl derivatives **346** on heating in acetic acid.[107] On the other hand, the reactions of **345** and phenacyl bromides in the presence of a strong base provided thieno[3,2-*a*]indolizines **351** via the reaction sequence shown below.[108]



Scheme 56

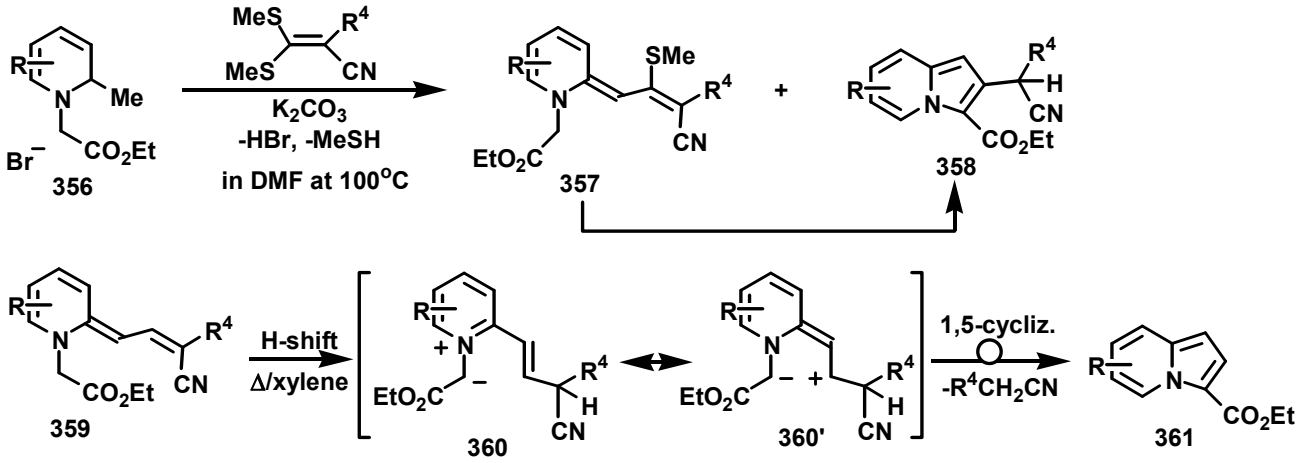
We also found a one-pot synthesis of 2*H*-pyrano[3,2-*a*]indolizin-2-ones **355** which was performed by refluxing 2-[3-cyano-3-(ethoxycarbonyl)allylidene]-1-ethoxycarbonylmethyl-1,2-dihydropyridines (**352**) in acetic acid (Scheme 57).



Scheme 57

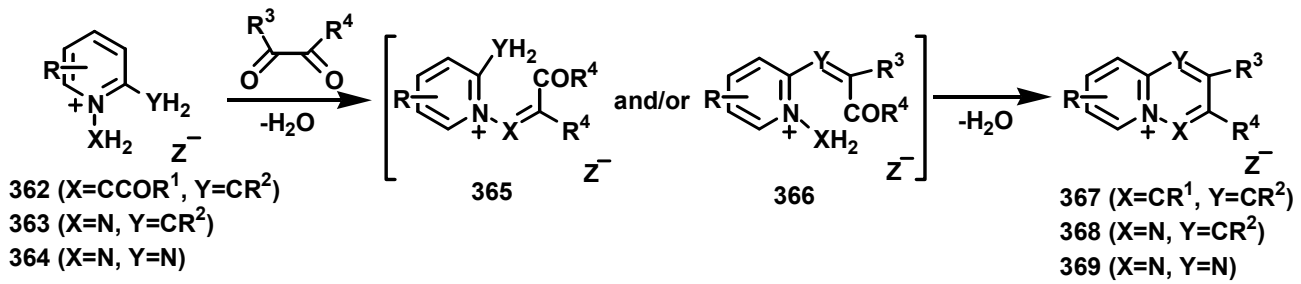
Another reaction is a 1,6-hydrogen shift from the *N*-methylene group of 2-allylidene-1,2-dihydropyridine derivatives, and it generates in situ reactive 1,5-dipoles and the 1,5-dipolar cyclization gives indolizines.

In 1977 Kobayashi et al. described a one-pot synthesis of the corresponding 2-[3-cyano-2-(methylthio)allylidene]-1-ethoxycarbonylmethyl-1,2-dihydropyridines **357** and ethyl 2-(disubstituted methyl)indolizine-3-carboxylates **358** in the reactions of 2-methylpyridinium salts **356** and 3,3-bis(methylthio)propenenitriles in the presence of a base in DMF at 100 °C[101b] (See Scheme 58). They reported that indolizines **358** were formed by way of 2-allylidene-1,2-dihydropyridines **357**, though the mechanisms were not described until 1981.[109] On the other hand, we found the formation of ethyl indolizine-3-carboxylate **361** in the thermolysis of allylidene-1,2-dihydropyridine **359** in 1978, and showed the possible reaction routes via the 1,5-dipolar cyclization of the intermediates **360** and **360'** generated from the hydrogen-shift of **359** and subsequent aromatization to final product **361**.[104]



Scheme 58

Some condensation reactions of 2-alkyl- or 2-aminopyridinium salts with various bifunctional reagents such as α-diketones and α-ketoesters have been well documented. For example, quinolizinium salts **367** were prepared by the stepwise dehydrations between 1-acylmethyl-2-alkylpyridinium salts **362** and 1,2-dicarbonyl compounds in the presence of a base[110] (See Scheme 59). Similar treatment of 2-alkyl-1-amino- **363** and 1,2-diaminopyridinium salts **364** gave the corresponding pyrido[1,2-*b*]pyridazinium salts **368**[111] and pyrido[1,2-*b*]-*as*-triazinium salts **369** respectively.[112]



Scheme 59

5. CONCLUSION

In this review I briefly described some of more common and practical reactions of pyridinium ylides and their closely related pyridinium salts. The chemistry is now changing from the traditional syntheses of bicyclic heterocycles such as indolizine and pyrazolo[1,5-*a*]pyridine to those of more complex and functionalized compounds. Although many novel methods for preparing such compounds have been developed, it is important to notice that no method is almighty and the scope of the application is severely restricted. To expand further this chemistry of pyridinium ylides and related pyridinium salts I sincerely hope the development of novel methodologies in this field continue.

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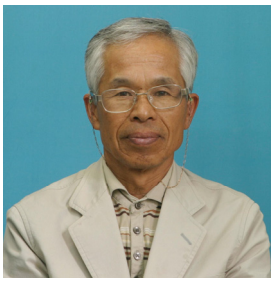

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