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THE REACTIVITY OF N-SUBSTITUTED PYRIDINIUM SALTS

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Abstract — Reactions of N-substituted pyridinium salts, along with some data concerning their properties and applications are described.

I. INTRODUCTION

The theme of the present paper, a continuation of our former one, dealing with syntheses of N-substituted pyridinium salts[1] is their reactivity. Reactions of pyridinium salts will be presented according to following topics :

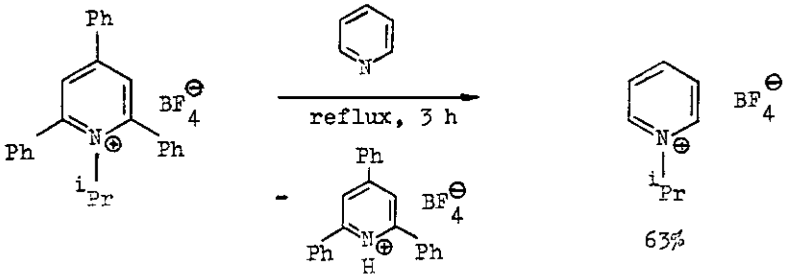
- nucleophilic displacement
- cyclization
- oxidation
- reduction
- reactions proceeding on the N-substituent
- reactions proceeding on the ring substituent

Some literature data concerning syntheses, physicochemical properties and applications of these compounds will be also given.

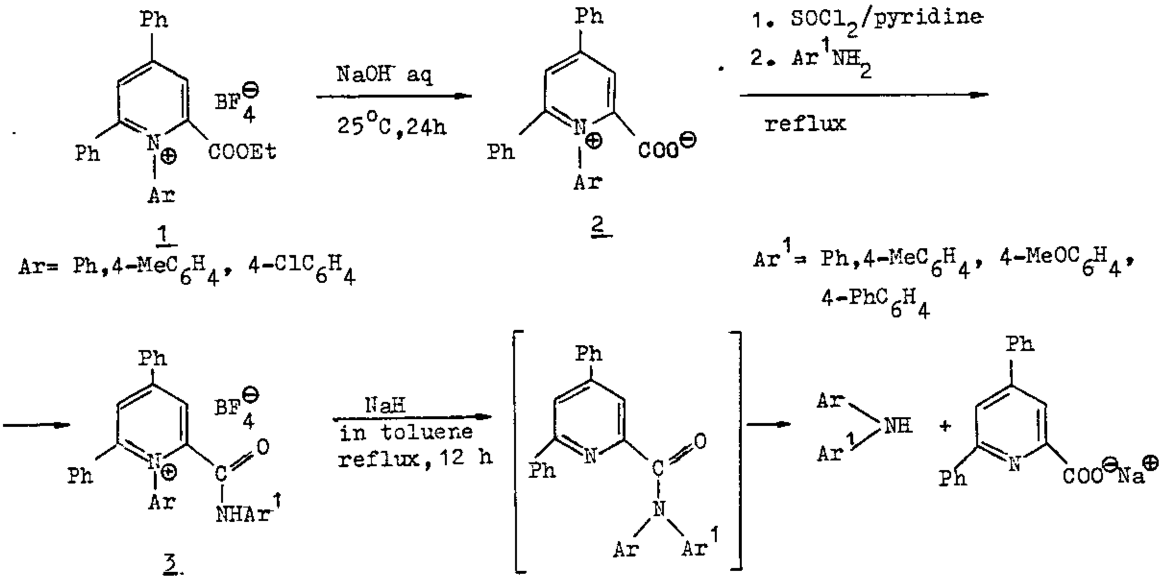
II. REACTIVITY OF PYRIDINIUM SALTS

A. NUCLEOPHILIC DISPLACEMENT REACTIONS

There are known numerous reactions of nucleophilic displacement performed on pyridinium salts[2-9], the following one can serve as an example.[10]



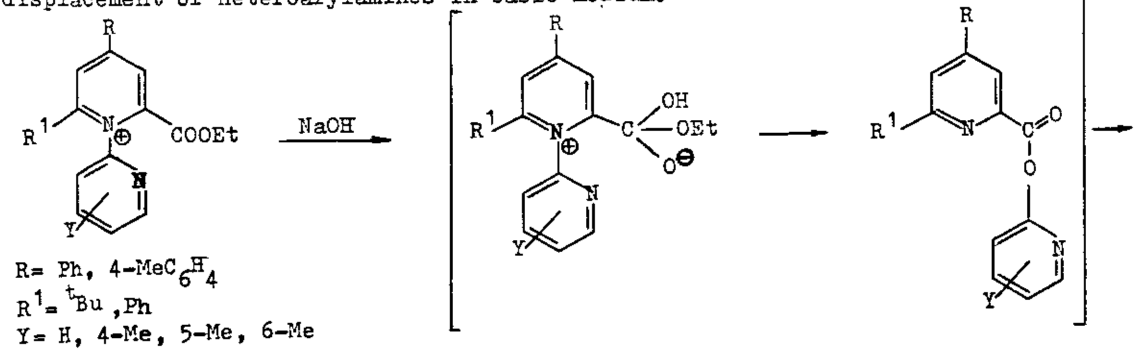
Unsymmetrical diarylamines can be prepared by the hydrolysis of 1 to pyridinium betaine 2, whose treatment with thionyl chloride, followed by condensation with an aniline gives rise to the amide 3 which in the reaction with sodium hydride transfers intramolecularly the 1-aryl group to the nitrogen of the amide.[11]



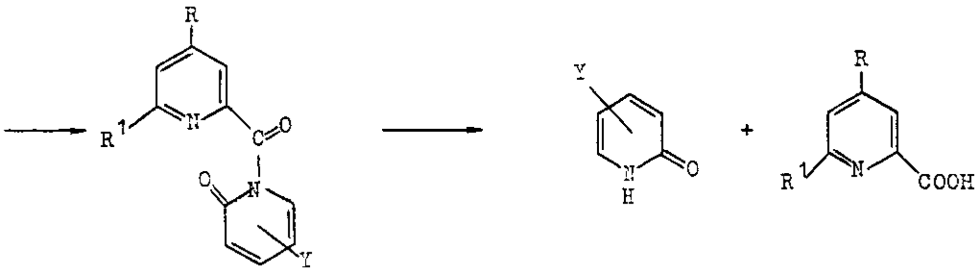
Ar= Ph, 4-MeC_6H_4, 4-ClC_6H_4

Ar^1= Ph, 4-MeC_6H_4, 4-MeOC_6H_4, 4-PhC_6H_4

Conversion of 2-aminopyridines into 2-pyridones involves the intramolecular displacement of heteroarylamines in basic medium.[12]

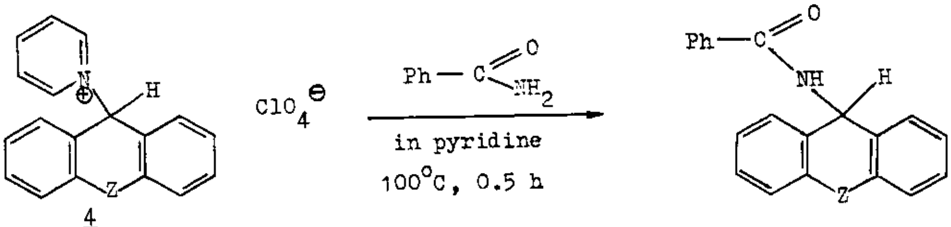


R= Ph, 4-MeC_6H_4
R^1= ^{t}Bu, Ph
Y= H, 4-Me, 5-Me, 6-Me



Study of the mechanism and kinetics of nucleophilic displacement reactions of pyridiniums is the topic of numerous papers ; as nucleophiles were used piperidine,[13-18] pyridine,[17,18] N,N-dimethylthiourea,[17] morpholine[18] and nitroalkane anions.[19,20]

Salts of the type 4 are useful for introduction of xanthyl and thioxanthyl groups into amides.[21]

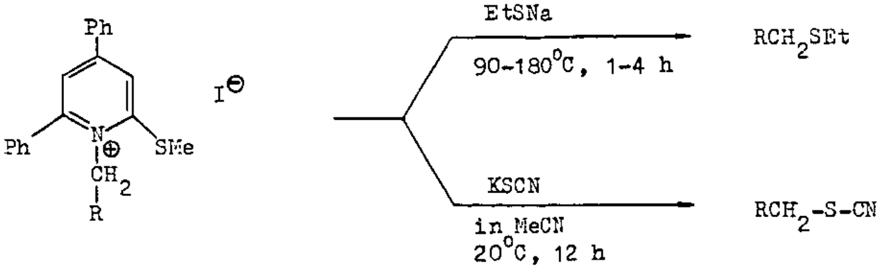


4

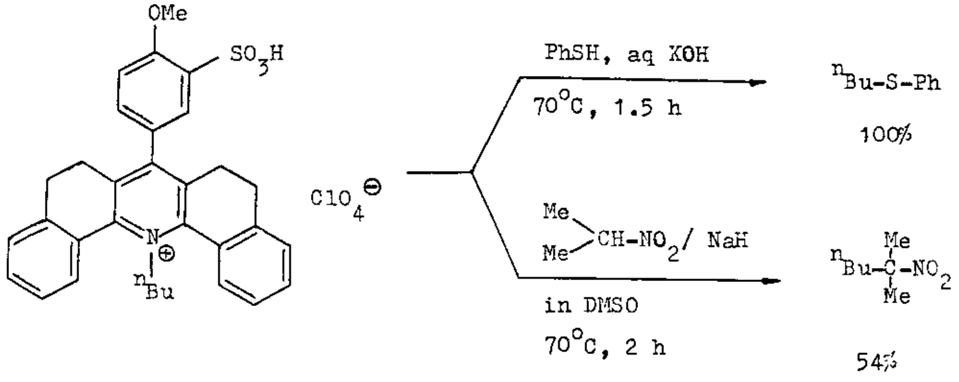
Z = O, S

Similar reactions were performed on quinoline analogues.

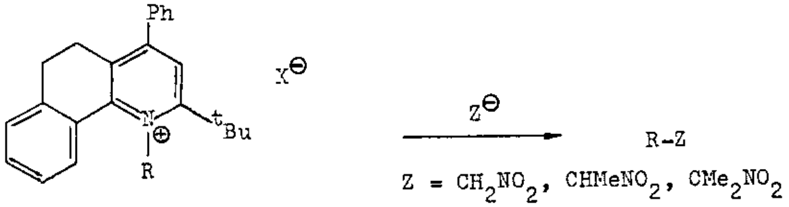
Pyridinium salts undergo displacement reactions by sulphur nucleophiles and by 2-nitropropane anion.[22,23]



R = Ph, 4-MeC_6H_4, 4-ClC_6H_4



Transfer of the N-substituent from N-alkyl and N-benzyl-2,4,6-triphenylpyridinium cations proved to be a convenient method for the C-alkylation of nitroalkane anions, there was shown however that the following reactions proceed under milder conditions, and nitroalkanes are formed in a high yield.[24]

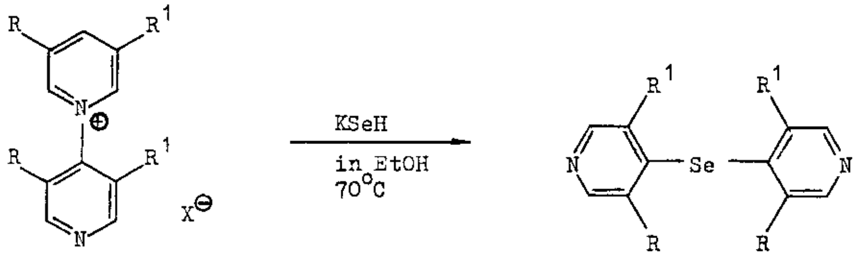


$Z = CH_2NO_2, CHMeNO_2, CMe_2NO_2$

$R = {}^{n}Pr, {}^{n}Bu, CH_2Ph, C_5-C_7$ alkyl

$X = BF_4, CF_3SO_3$

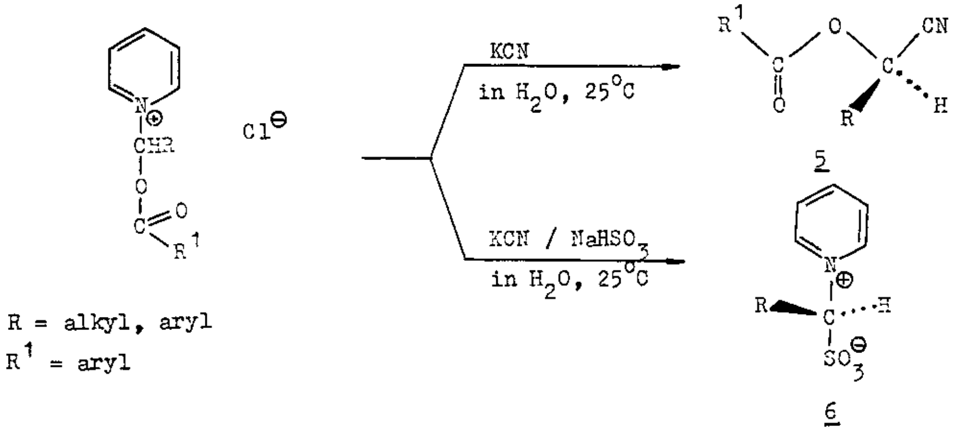
Among nucleophilic displacement reactions one ought to mention the synthesis of di-(4-pyridyl)selenides, carried out with the use of pyridinyl pyridinium salts.[25,26]



R, R^1 = H, Me, Et

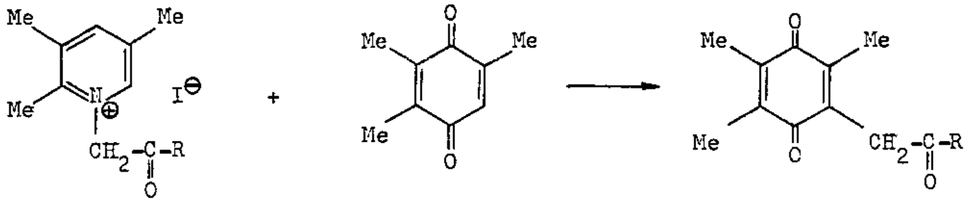
X = Cl, Br

Acylated cyanohydrines 5 and betaines 6 can be obtained by the following procedures.[27]



R = alkyl, aryl
R^1 = aryl

A convenient method of introducing acetonyl and similar groups into quinone nuclei utilizes pyridinium salts.[28]

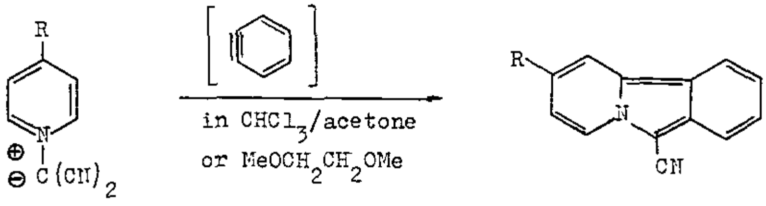


R = Me, OEt, Ph, 4-$NO_2C_6H_4$

Naphthoquinones react in an analogous manner. The mechanism of the above reactions is given.

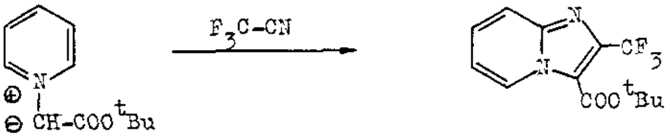
B. CYCLIZATION REACTIONS

Numerous cyclization reactions of pyridinium salts are known, among which 1,3-dipolar cycloaddition reactions form a large group and they will be presented at first. As examples of 1,3-dipolar cycloaddition reactions the following ones ought to be mentioned.

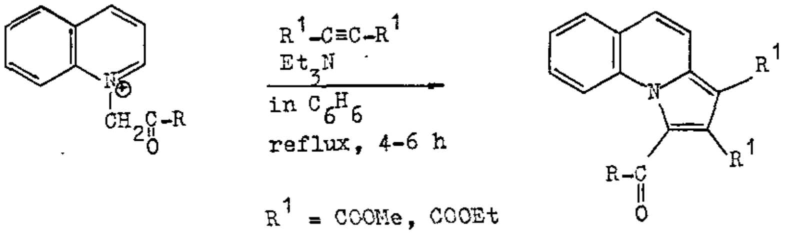


refs 29,30

R = H, Me, Ph, PhCO



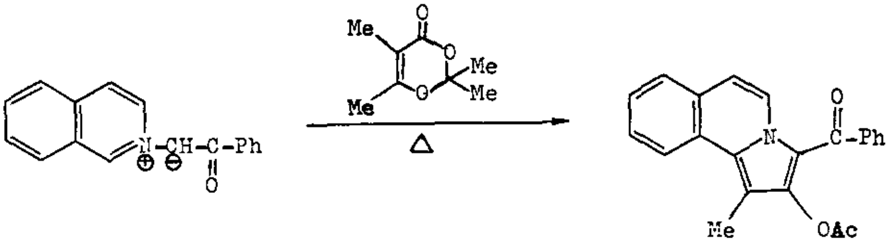
ref. 31



ref. 32

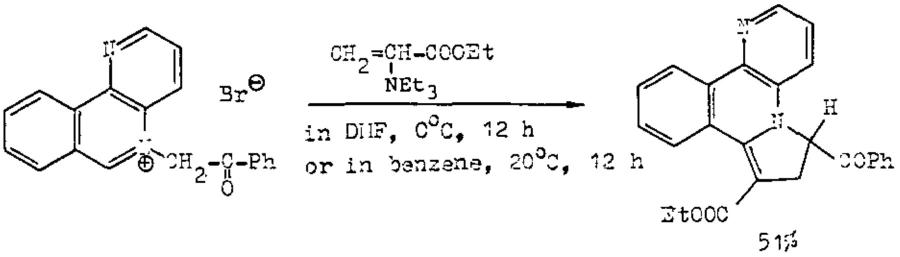
R^1 = COOMe, COOEt

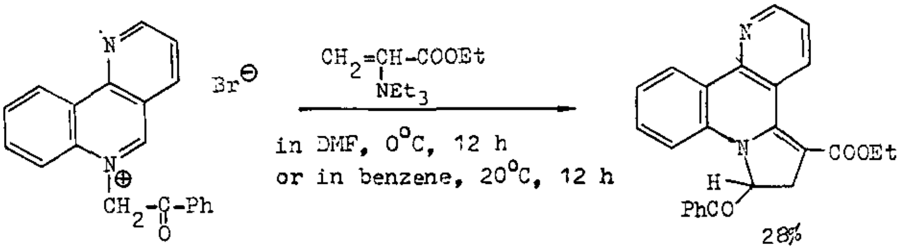
R = 4-ClC$_6$H$_4$, 2-naphthyl



ref. 33

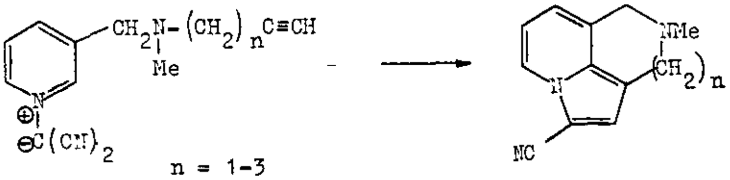
In the study of 1,5-(and 1,6)-benzo[h]naphthyridinium 5(and 6)-phenacylides, their 1,3-dipolar cycloaddition reactions were performed, using ethyl acrylate, acrylonitrile and DMAD as dipolarophiles[34], for instance





Similar 1,3-dipolar cycloaddition reactions of N-ethoxycarbonylmethyl analogues of these compounds have been also investigated.[35]

Intramolecular 1,3-dipolar cycloaddition reactions of pyridinium methylides give rise to some pyrido-, azepino- and azocino[3,4,5-hi]indolizines, for instance 7 can be obtained from 8 having non-activated acetylenic dipolarophiles in the same molecule.[36]

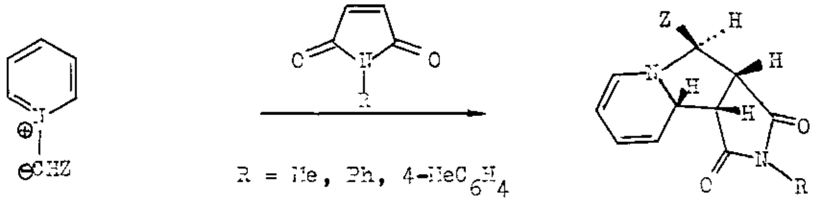


8 7

The 1,3-dipolar cycloaddition reactions of pyridinium N-ylides have been also performed in the two-phase system.[37]

Double cycloaddition reaction of pyridinium methylides to methylenecyclopropenes, leading to cage compounds of the new type has been reported.[38]

The [3+2] cycloaddition reaction of pyridinium methylides with electron-deficient olefins proceeds in the following way.[39]

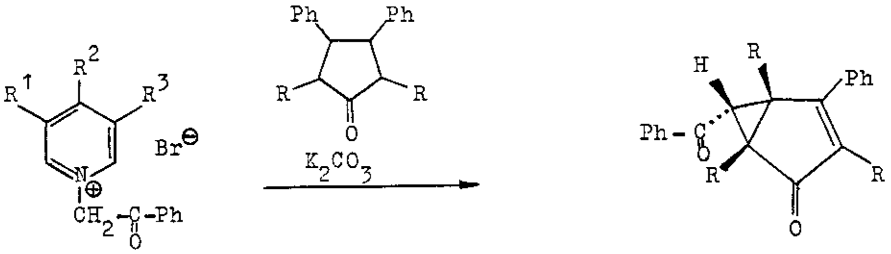


R = Me, Ph, 4-MeC$_6$H$_4$

Z = COOMe, COOEt, 4-NO$_2$C$_6$H$_4$ and other

There was observed that only anti-ylides participate in this reaction. The stereochemistry of the above processes is discussed.

In the study of pyridinium salts also their cyclization reactions which do not proceed by 1,3-dipolar cycloaddition mechanism have been studied. For instance, 9 was treated with cyclopentadienones to yield bicycloderivatives ; the reaction involves the nucleophilic addition and subsequent pyridine elimination.[40]

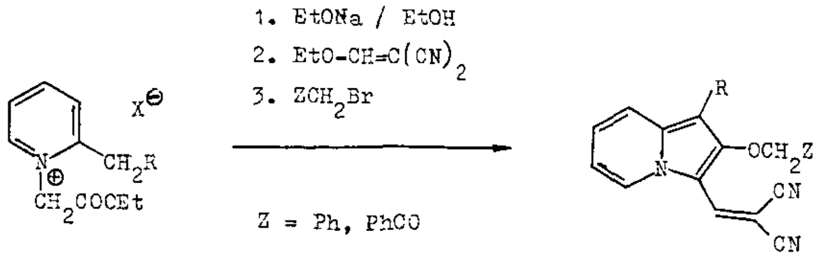


9

R = Me, Et, Ph

$R^1 = R^2 = R^3 = H$
$R^1, R^3 = H \; ; \; R^2 = Me$
$R^2 = H \; ; \; R^1 = R^3 = Me$

The following reaction leading to substituted indolizine systems 10 has been investigated.[41]

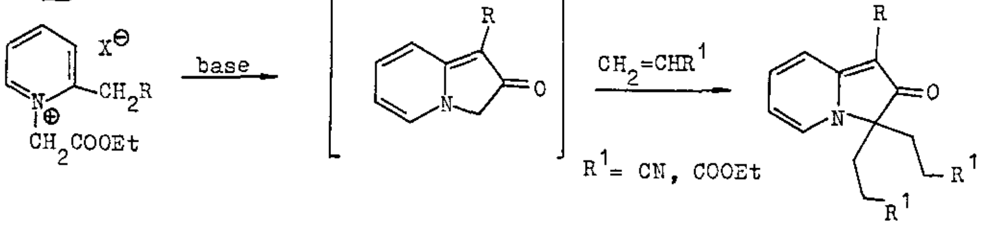


10

R = H, Me, Et, Ph

X = Cl, Br

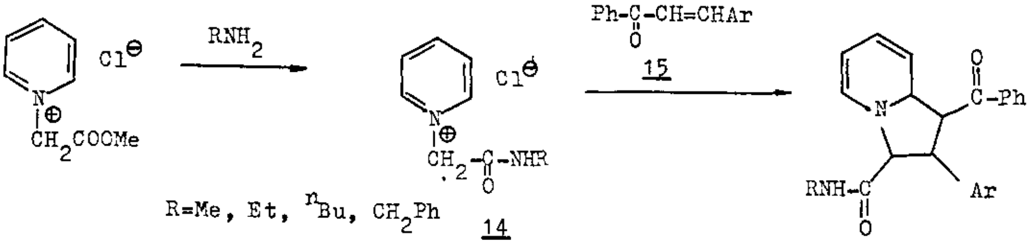
Indolizinone derivatives can be obtained in one-pot synthesis by way of a double Michael addition to 3-unsubstituted 2(*3H*)-indolizinones generated in situ from pyridinium salts. For instance, the intermediate 11 which formed from 12 by alkali treatment reacted with acrylonitrile and ethyl acrylate to afford 1:2 adducts 13.[42]



12 11 13

R = H, Me, Et, Ph
X = Cl, Br

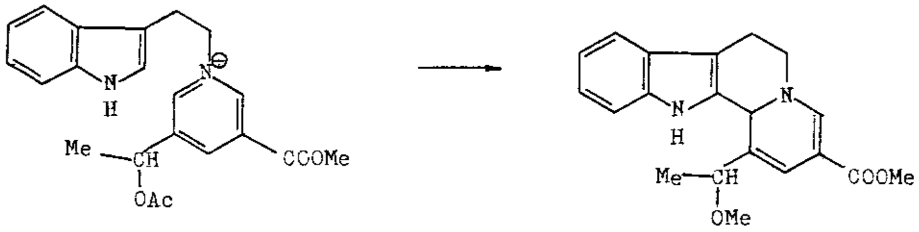
Methoxycarbonylmethylpyridinium chloride can be converted by treatment with alkyl amines into 14, which with chalcone 15 undergoes Michael addition and subsequent ring closure.[43]



R=Me, Et, ^{n}Bu, CH_2Ph 14

Ar=Ph, 4-ClC_6H_4, 4-MeC_6H_4

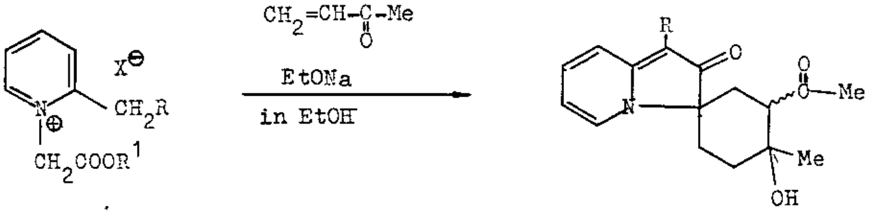
Reaction of 16 with aqueous alkali, proceeding via open ring intermediate, provides a synthetic method of indoloquinolizine derivatives 17.[44]



16

17

Spiroindolizines 18 have been obtained in the following way.[45]



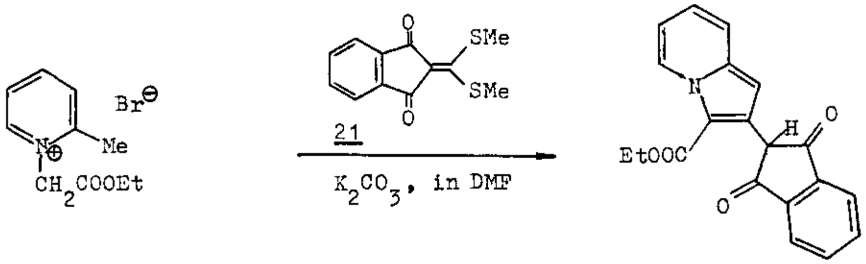
18

R = Me, Et, Ph, 4-ClC_6H_4

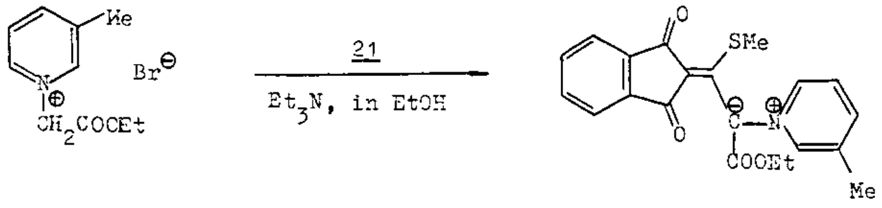
R^1 = alkyl

X = halo

Investigating N-ylides there was found that the first of the following reactions proceeds by the ring closure resulting in 19, while the second one gives rise to stable N-allylides 20.[46]

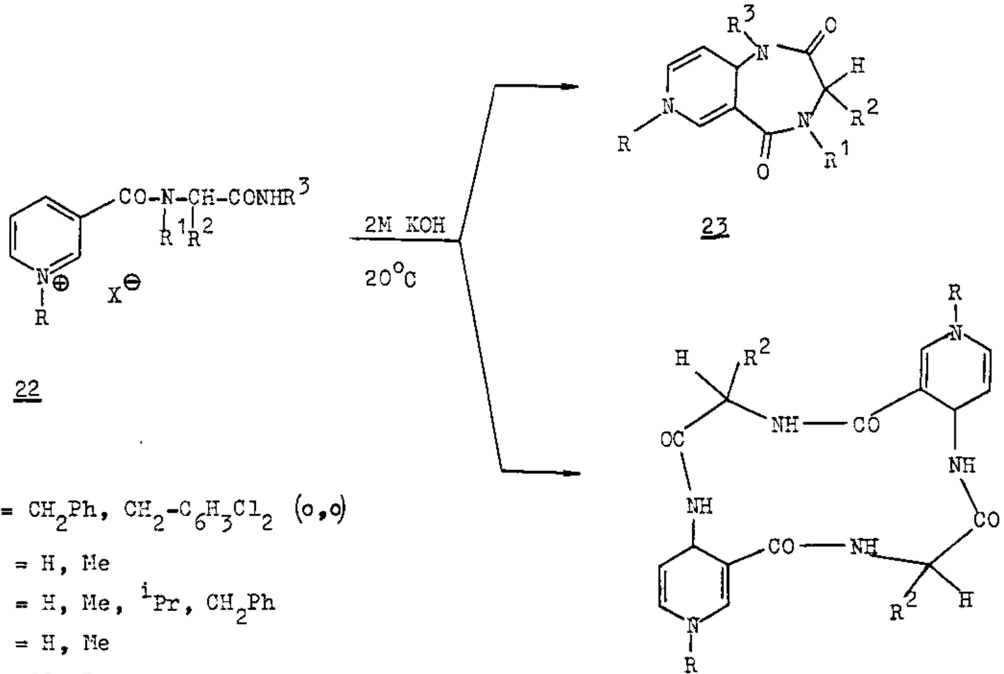


19



20

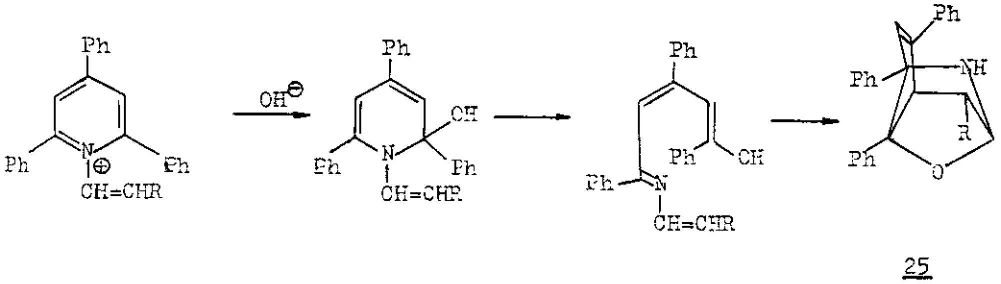
In the study of quaternary salts of nicotinamides 22 there was performed their cyclization under the influence of bases giving rise to cyclopeptides 23 or 24, according to the kind of substituents in 22.[47]



R = CH_2Ph, CH_2-$C_6H_3Cl_2$ (o,o)
R^1 = H, Me
R^2 = H, Me, ^{i}Pr, CH_2Ph
R^3 = H, Me
X = Cl, Br

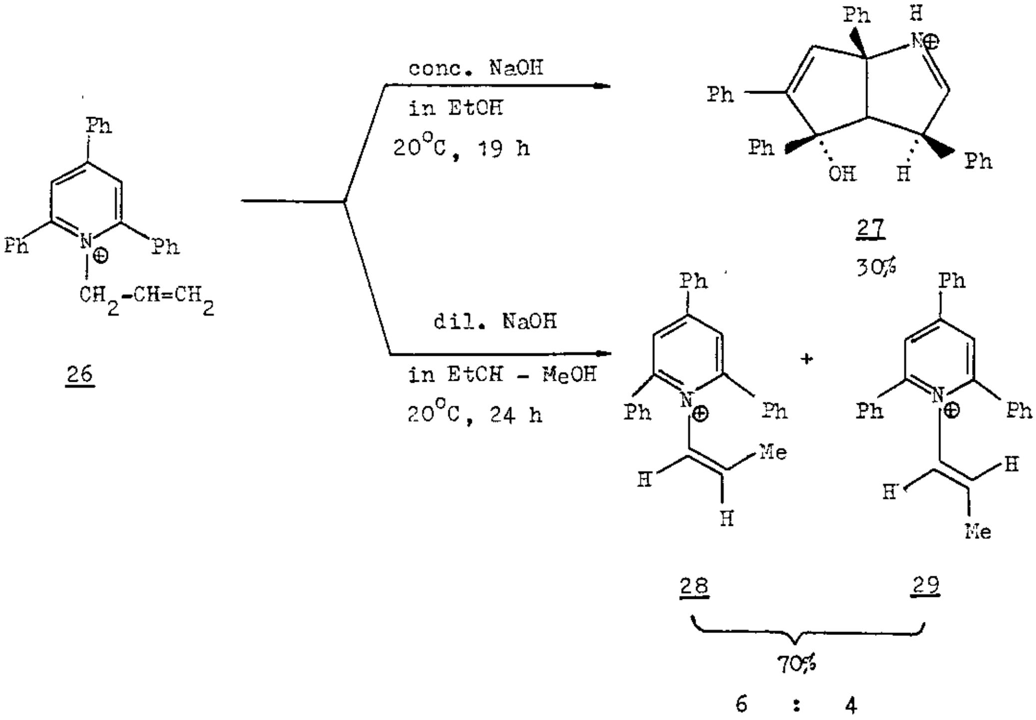
for $R^1 = R^3 = H$

1-Vinyl and 1-propenyl-2,4,6-triphenylpyridinium salts treated with alkali undergo a rearrangement to cage compounds of the type 25 [48]



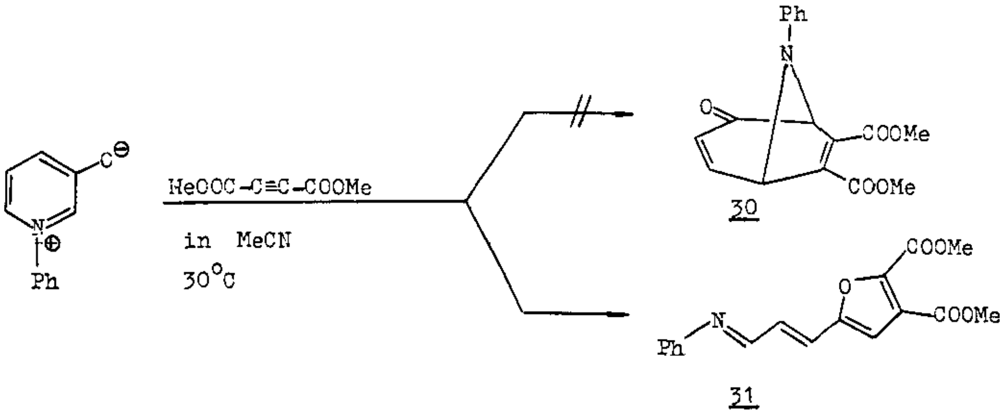
R = H, Me

Investigating N-allylpyridinium salts there was found, that 26 was treated with concentrated alkali in ethanolic solution to give 27, while the reaction with dilute alkali yielded the 6:4 mixture of Z and E propenyl isomers 28 and 29.[49]

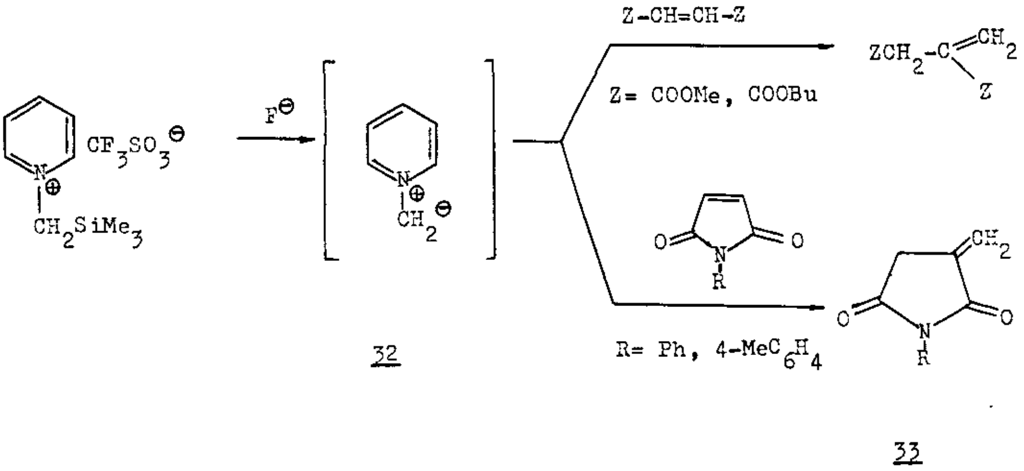


In the papers concerning quaternary salts, the other cyclization reactions of pyridinium salts,[50-52] as well as cyclization reactions of pyrimidinium,[53] phthalazinium[54] and quinoxalinium salts[55-57] are also described.

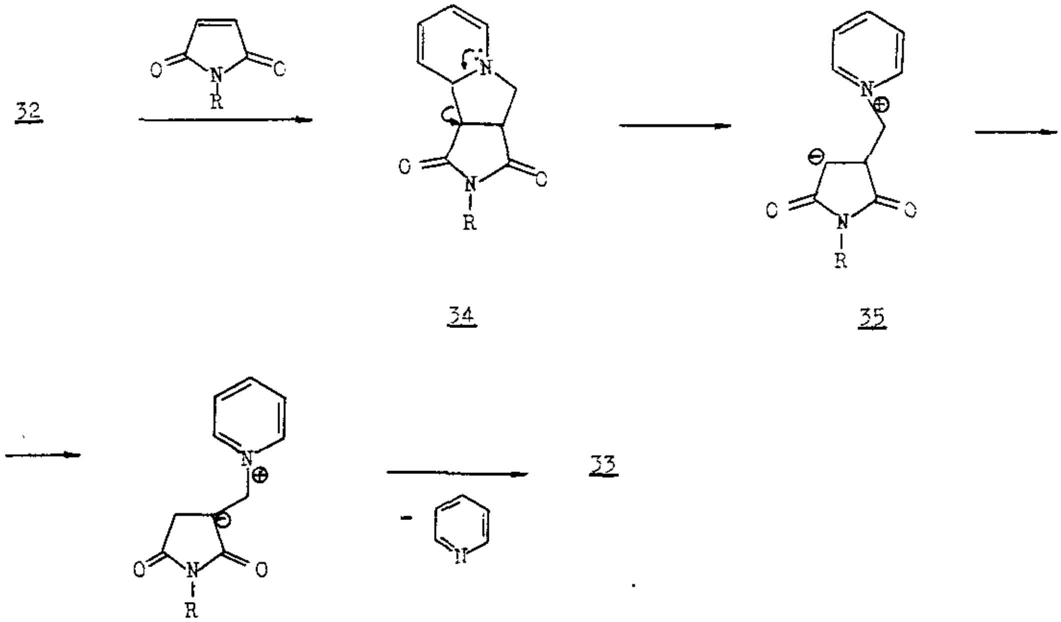
Among reactions of pyridinium ylides which do not yield cyclized products, the following ones will be presented.
The reaction of 1-phenyl-3-oxidopyridinium with DMAD instead of the expected 30 affords 31, which formed by the opening of the pyridine ring.[58]



The reaction of nonstabilized pyridinium methylide 32 with electron deficient olefins results in their hydromethylenation.[59]



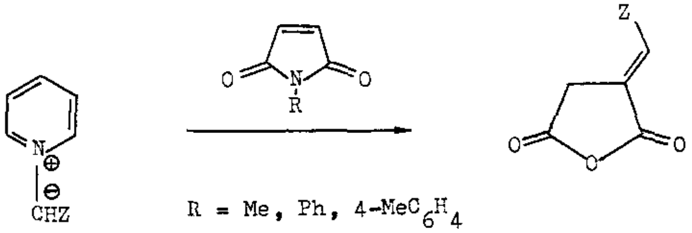
The proposed mechanism, shown on the reaction with N-substituted maleimide, involves as the initial step the 3+2 cycloaddition reaction, giving rise to 34, this undergoes the ring opening to afford the zwitterionic intermediate 35. The next 1,2-proton migration, followed by the elimination of pyridine, yielded **33.**



34

35

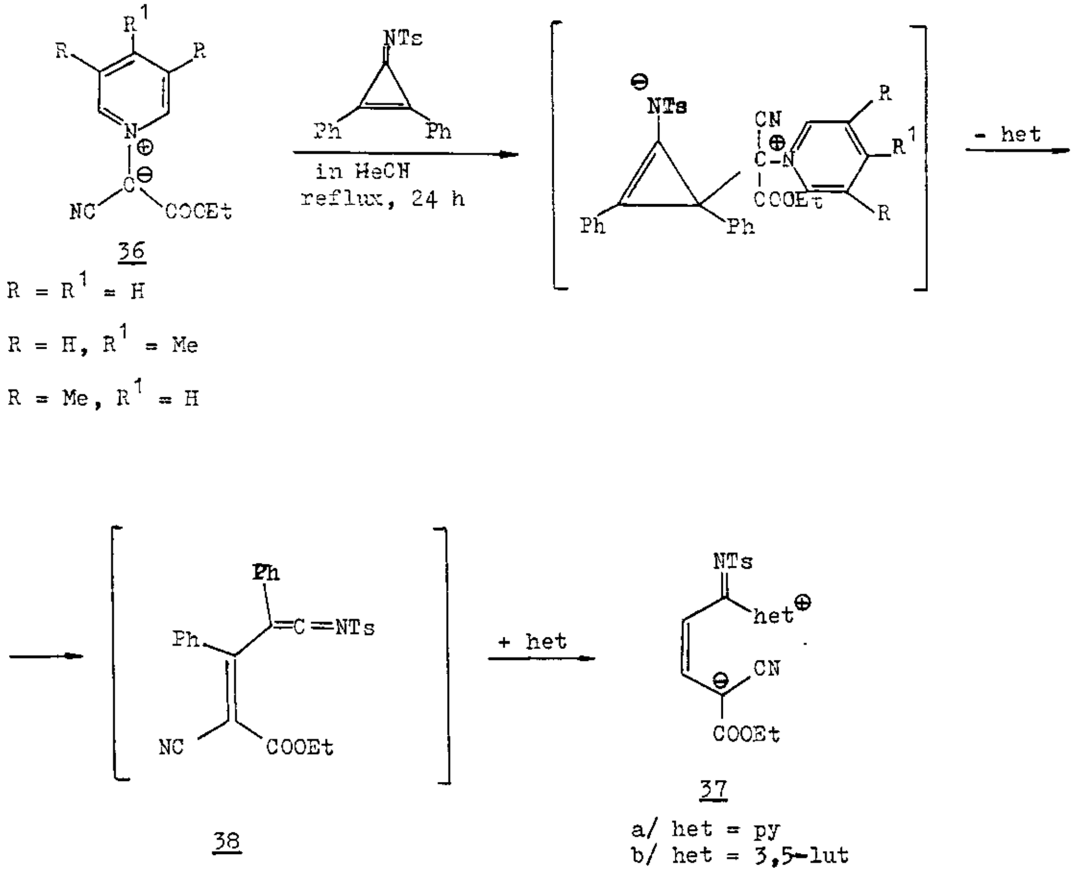
In a similar procedure with stabilized pyridinium N-methylides, olefins **undergo** hydroalkylidenation.[60,61]



R = Me, Ph, 4-MeC$_6$H$_4$

Z = COOMe, PhCO, CN

Studying pyridinium N-ylides, the reaction of 36 with substituted cyclopropenimine, resulting in internal salts 37 , has been performed.[62]



36

$R = R^1 = H$

$R = H, R^1 = Me$

$R = Me, R^1 = H$

38

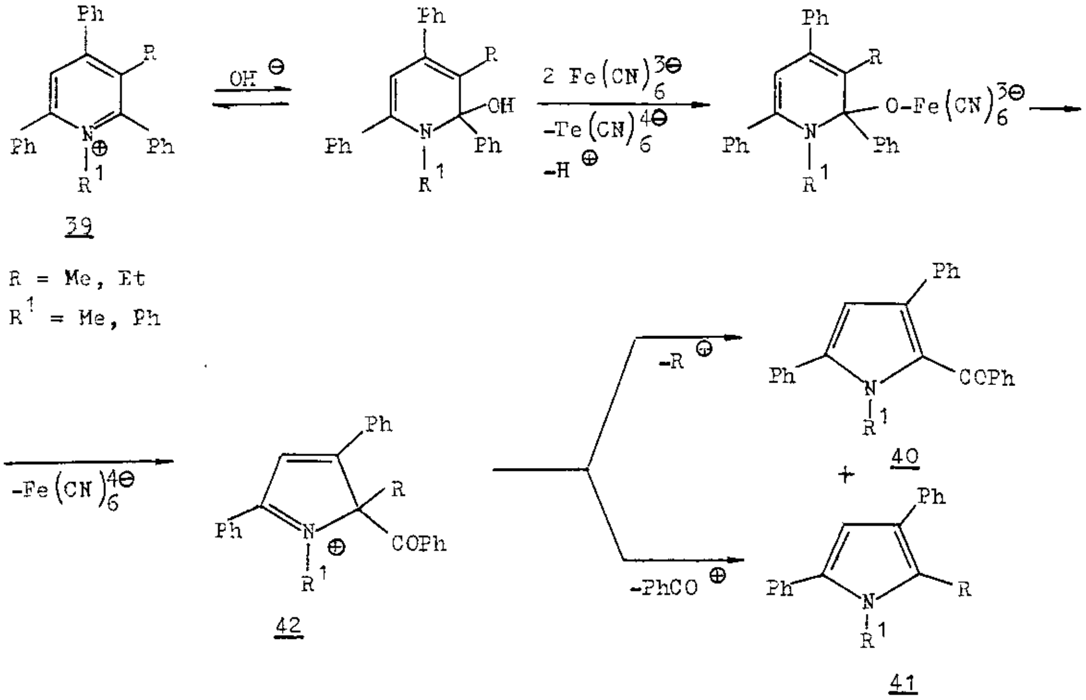
37

a/ het = py
b/ het = 3,5-lut

There was observed that in the presence of 3,5-lutidine, 37b was formed in 68 % yield, thus confirming the participation of a heterocycle-free intermediate 38 in the reaction mechanism.

C. OXIDATION REACTIONS

Oxidation of 39 with alkaline solution of potassium ferricyanide yields a mixture of pyrroles 40 and 41. The mechanism of the above reaction involves the formation of a common precursor 42.[63,64]

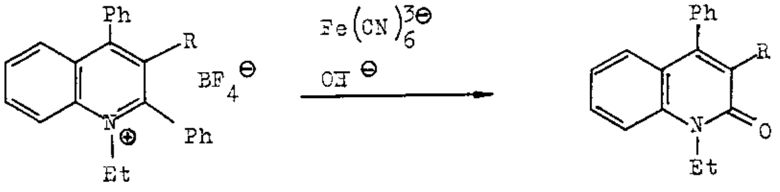


39 42 40 + 41

R = Me, Et

R^1 = Me, Ph

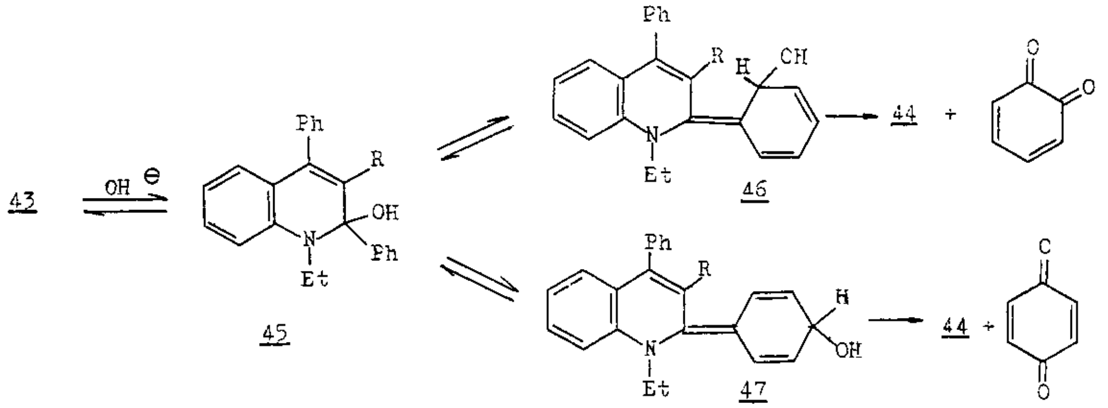
In the case of 43, however, such contraction of heteroaromatic ring does not take place, due to steric and electronic effects of the adjacent benzene moiety, and the reaction results in quinolone 44.[65]



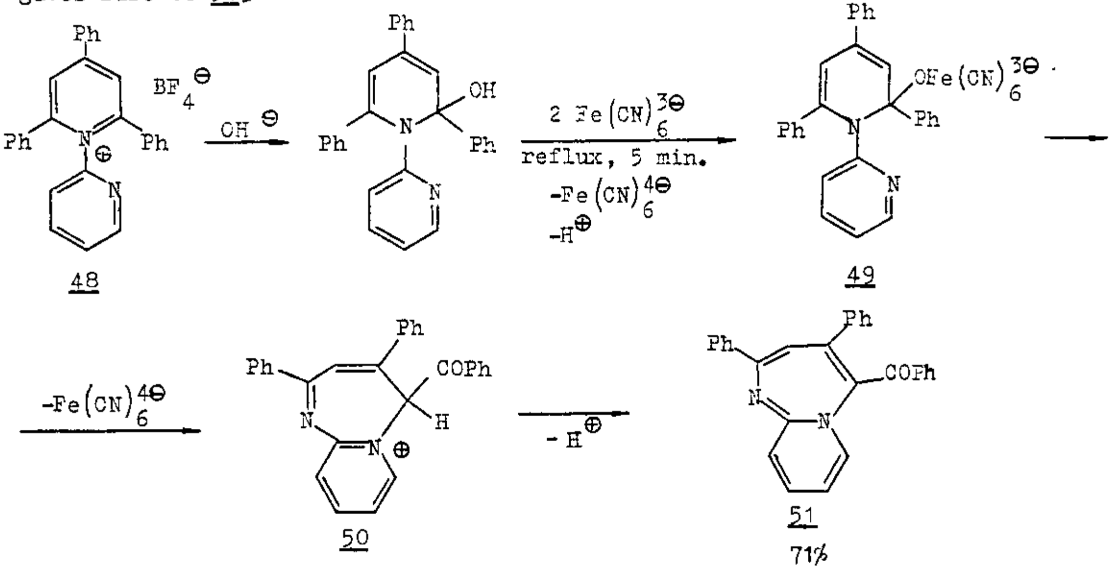
43 44

R = H, Me, Ph

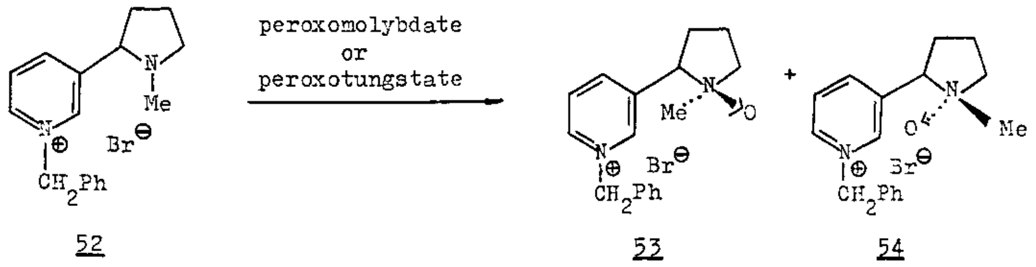
The mechanism involves the splitting off of 2-phenyl substituent from 1,2-dihydro-intermediate 45. Oxidation of 46 and 47 gives rise to 44, along with 1,2- and 1,4-benzoquinones, unstable in the alkaline oxidation medium.



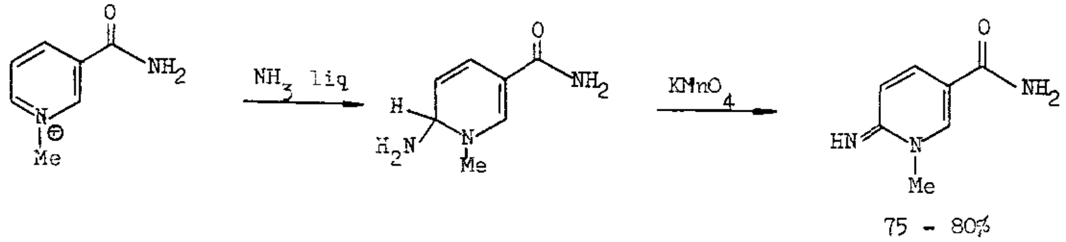
In the similar oxidation of 48, the nitrogen atom of the 1-substituent acts as a nucleophilic centre of 49, enabling its cyclization to 50, which under deprotonation gives rise to 51.[66]

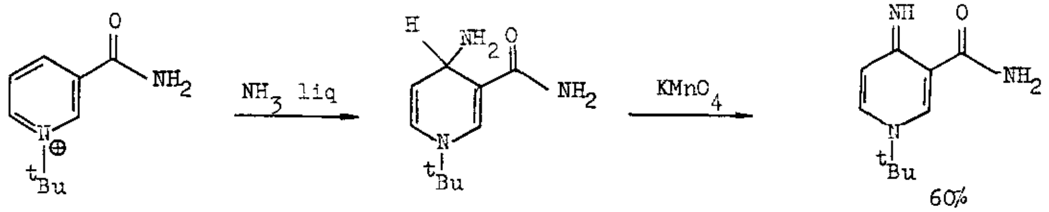


The oxidation of 52 with peroxomolybdate or peroxotungstate gave cis and trans N-oxides 53 and 54 in the ratio of 1:14 and 1:15, respectively.[67,68]

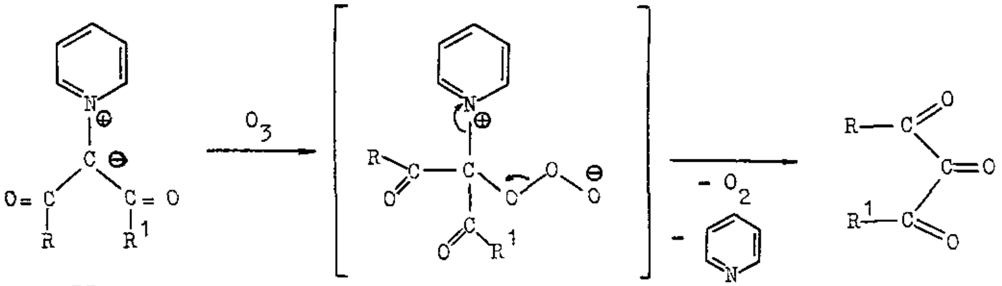


For the introduction of an imino group in N-alkylpyridinium and quinolinium salts in α or γ positions, their low temperature oxidation with potassium permanganate in liquid ammonia can be used. In the case of bulky N-substituents, for example tertial butyl group, 4-iminoproducts are formed.[69-71]





Here will be also mentioned the reaction of pyridinium methylides 55 with ozone in aprotic medium, involving their cleavage to vicinal triketones.[72]

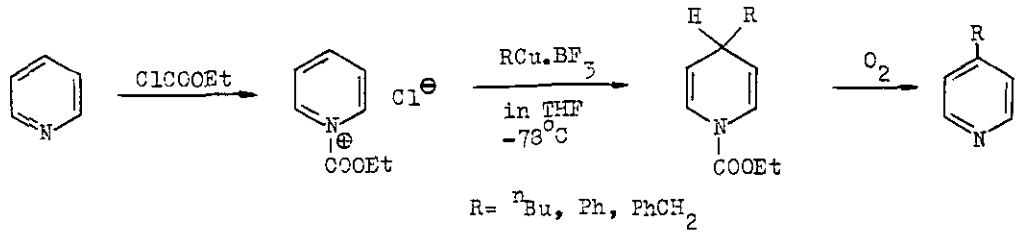


55

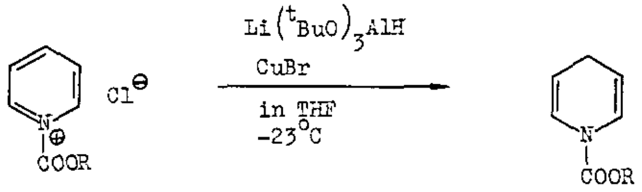
$R, R^1 = Ph, 4\text{-}ClC_6H_4, 4\text{-}MeOC_6H_4$

D. REDUCTION REACTIONS

The following reactions are examples of reduction leading to 1,4-dihydro derivatives. The reaction of 1-ethoxycarbonylpyridinium chloride with $RCu.BF_3$ provides a convenient route of introducing substituents into 4-position of pyridine starting from pyridine itself. The formed 1,4-dihydroderivative undergoes the subsequent oxidation with oxygen to give 4-substituted pyridine.[73-76]

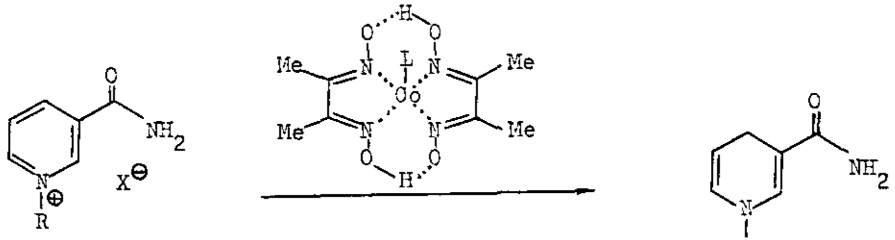


The following reaction leading to 1-substituted 1,4-dihydropyridines has been performed.[77-83]



R = Et, Ph, CH_2Ph

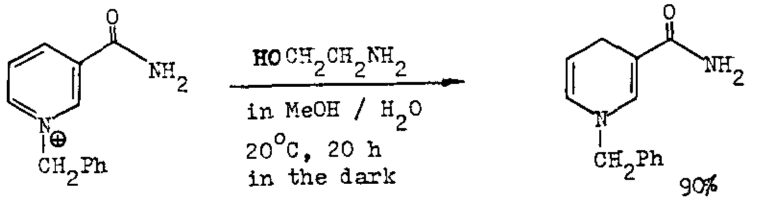
Selective reduction of 3-carbomoylpyridinium salts mediated by low valent cobalt complexes gave 1,4-dihydropyridines with high regioselectivity.[84]



R = Pr, Ph, CH_2Ph L= pyridine, piperidine

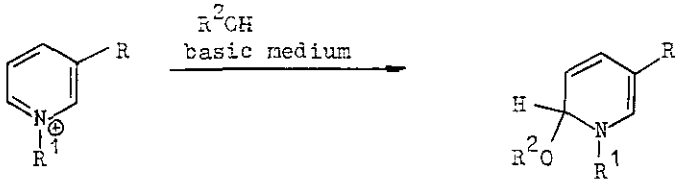
X = Cl, Br

In order to compare the mechanism of nonenzymic formation of 1,4-dihydropyridines by amines with that of enzymic process, the following reduction was studied in the investigation of NAD(P)$^+$-NAD(P) models.[85-88]



Other examples of reduction reactions leading to 1,4-dihydro derivatives are reported.[89-91]

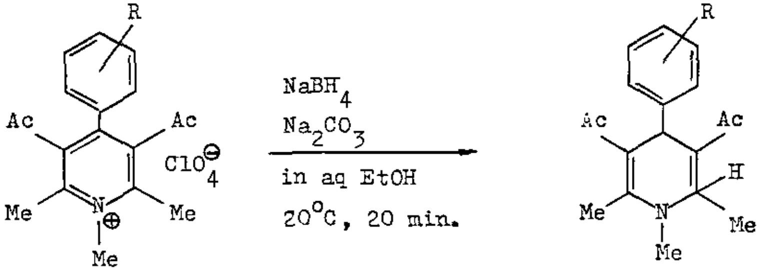
In numerous reactions 1,2- and 1,6-dihydropyridines are formed, for instance pyridinium salts 56, which were substituted at 3-position with electron withdrawing substituents, treated with alcohols under basic conditions to yield 6-alkoxy-1,6-dihydropyridines.[92]



56

R = CN, PhCO, $CONH_2$, SO_2NMe_2 and other
R^1 = Me, $4\text{-}FC_6H_4$, $CH_2\text{-}C_6H_3Cl_2$ (o,o')
R^2 = Me, Et, Pr, ^{i}Pr, ^{t}Bu

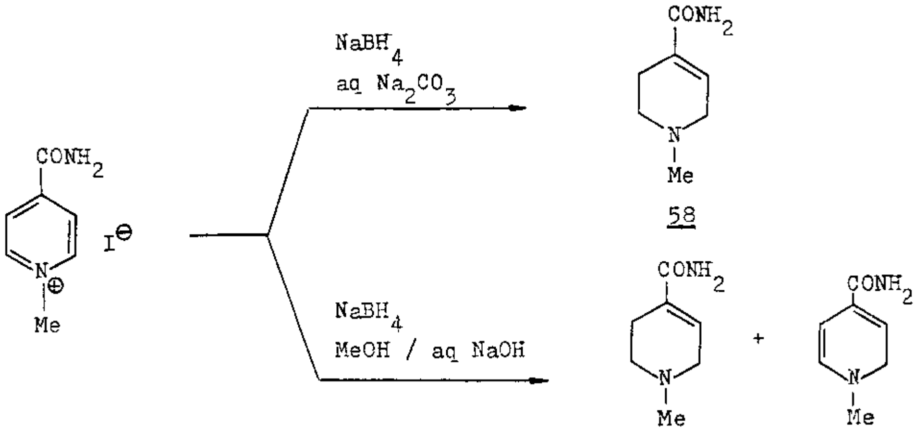
The following reduction of 57 has been performed.[93]



57

R = H, 4-Me, 4-Br, 2,3-$(OMe)_2$

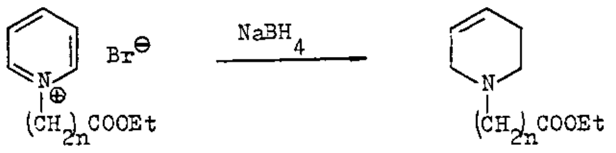
The hydrogenation of substituted pyridinium salts depends on the reaction conditions, for instance, 1-methyl-4-carbamoylpyridinium iodide was treated with sodium borohydride in aqueous sodium carbonate to give 58, while in aqueous methanolic sodium hydroxide a significant amount of 59 is also formed.[94]



58

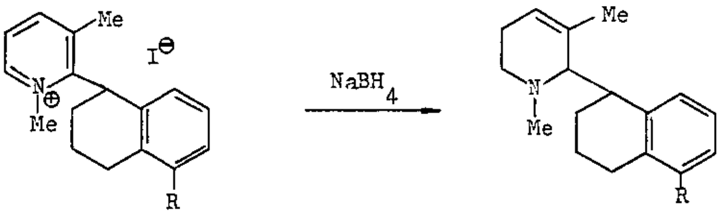
58 59

Tetrahydropyridines have been obtained in following reactions.



n = 1-4

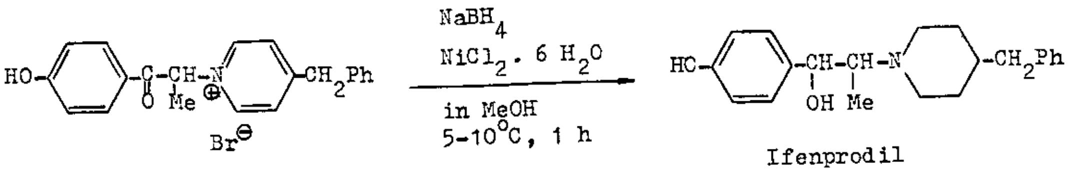
ref. 95



ref. 96

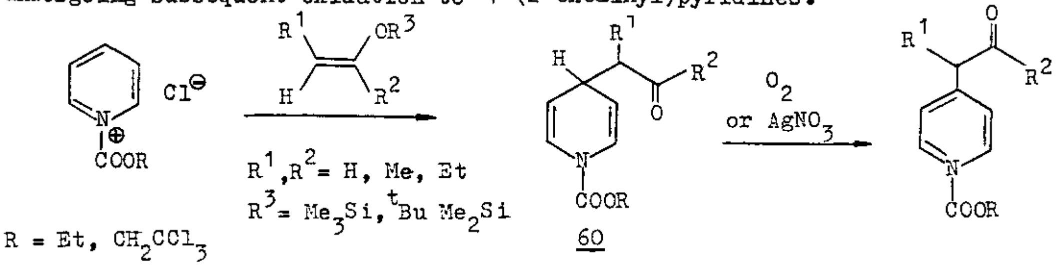
R = H, OH

The synthesis of Ifenprodil[97] is presented as an example of reduction reactions of pyridinium salts resulting in piperidine derivatives.



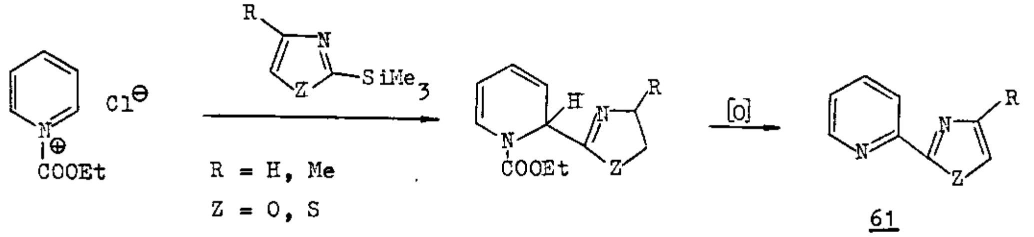
Ifenprodil

Pyridinium salts react with silyl enol ethers to give 1,4-dihydropyridines 60, undergoing subsequent oxidation to 4-(2-oxoalkyl)pyridines.[98]

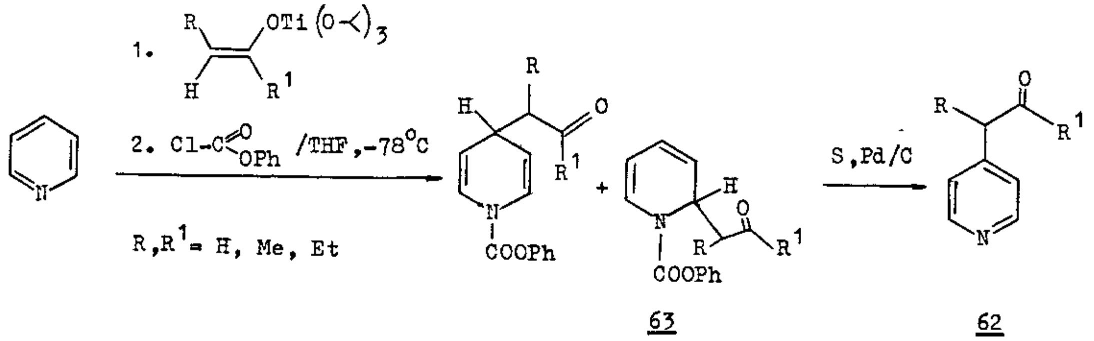


Analogous reaction was carried out on quinolines to afford mixtures of 1,2- and 1,4-dihydroquinolines,[99] and in the case of isoquinoline the 2-oxoalkyl group was introduced into 1-position.[100,101]

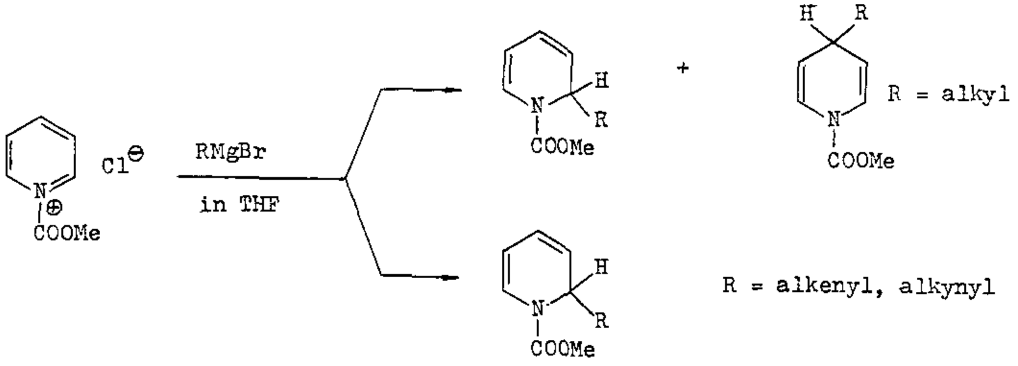
In a similar manner, using pyridinium, quinolinium or isoquinolinium salts as starting materials, the unsymmetrical azadiaryls 61 can be obtained.[102]



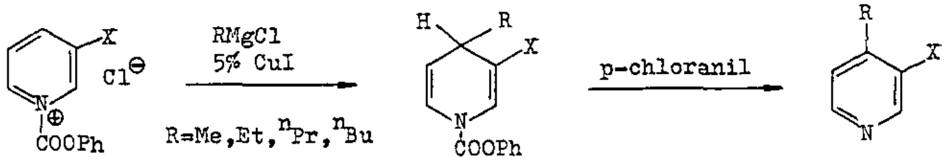
1-Phenoxycarbonylpyridinium salts add titanium enolates at the 4-position to give 1,4-dihydropyridines, which when heated with sulphur and Pd/C undergo aromatization resulting in 4-(2-oxoalkyl)pyridines 62; this reaction proved to be a convenient synthetic method for these compounds. As the minor 1,2-dihydro derivative 63 decomposes under reaction conditions, the only product is 62.[103,104]



Studying the reactivity of pyridinium salts towards Grignard reagents, in the reaction of 1-methoxycarbonylpyridinium chloride with alkyl Grignard reagents the mixture of 1,2- and 1,4-adducts was obtained, while in the similar reaction with alkenyl or alkynyl Grignard reagents only 1,2-addition took place.[81,105]



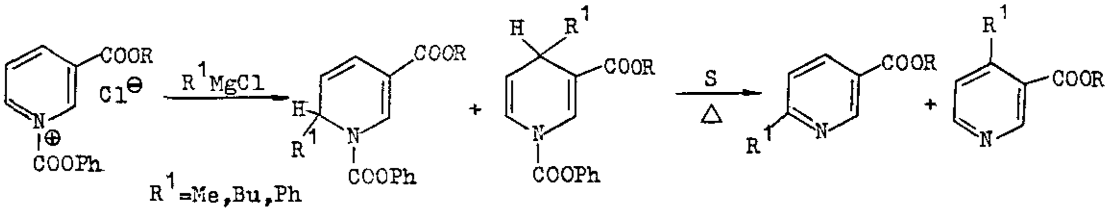
Addition of Grignard reagents to 1-phenoxycarbonyl salts of 3-halopyridines was performed in the presence of a catalytic amount of cuprous iodide to yield 1,4-adducts, undergoing subsequent aromatization to 64.[106,107]



64

X = Cl, Br

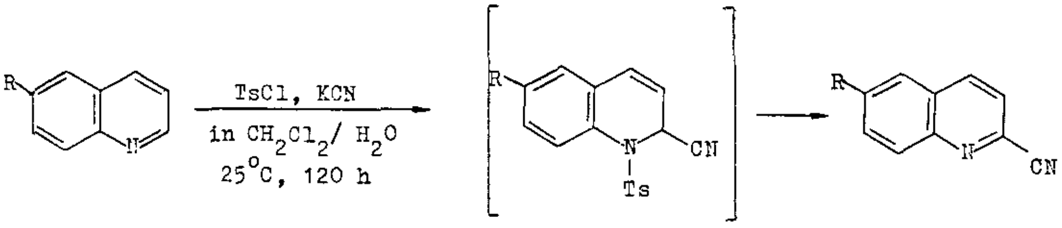
Treatment of 65 with Grignard reagents resulted in 66 and 67 which are aromatized by heating with sulphur.[108]



65 66 67

R = Me, ^{i}Pr, ^{t}Bu

There exists a deal of Reissert reactions of pyridinium salts, recently reviewed.[109] The following reaction, which proceeds via unstable Reissert intermediates 68, provides a convenient method of direct introduction of cyano group into quinolines.[110] Isoquinolines behave similarly, giving rise to 1-cyanoisoquinolines.[110]



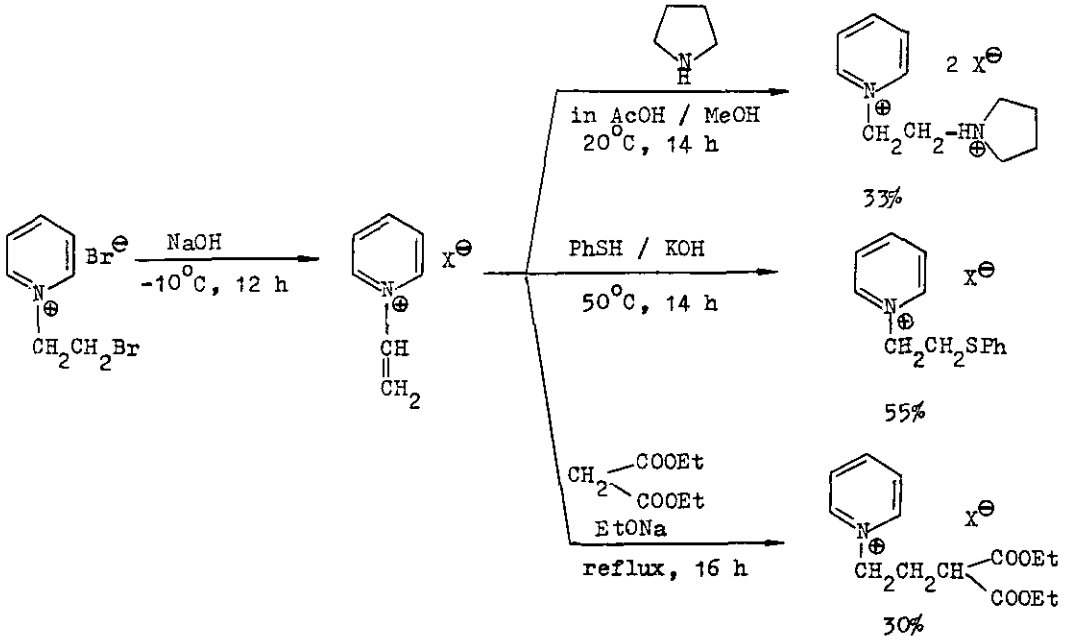
R = H, OMe

68

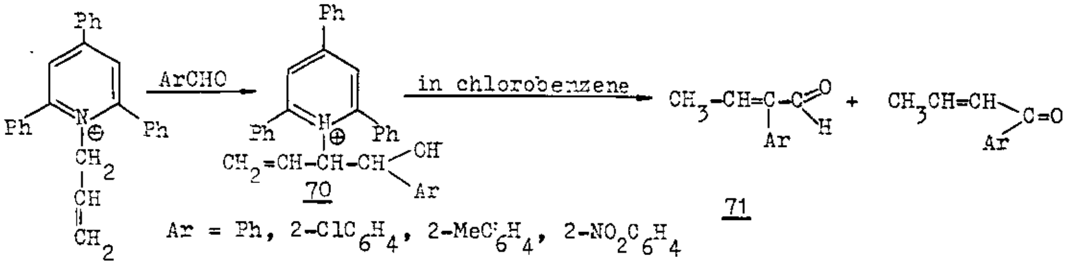
The rate constants and equilibrium constants of the cyanide ion addition to pyridinium salts have been measured.[111]

E. REACTIONS PROCEEDING ON THE N-SUBSTITUENT

1-Vinylpyridinium salts, readily available from 1-(2-bromoethyl)pyridinium bromide by treatment with alkali, and isolated as perchlorates or tetrafluoroborates add N,S and C nucleophiles in Michael-type reactions.[112]



Treatment of 69 with aromatic aldehydes yields aldol 70, which refluxed in chlorobenzene to afford crotonaldehyde 71 along with isomeric aryl propenyl ketone.[113]



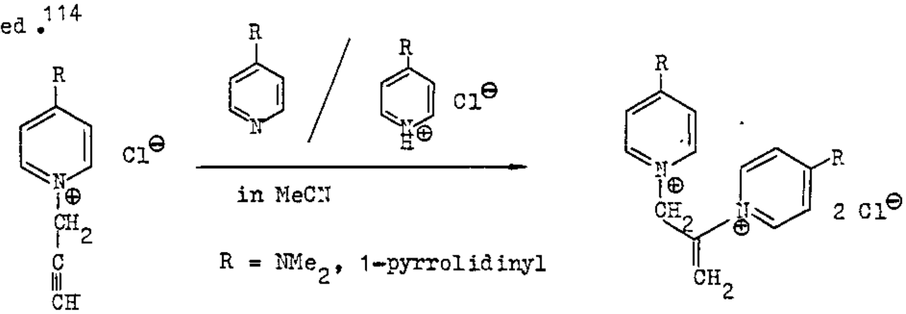
70

71

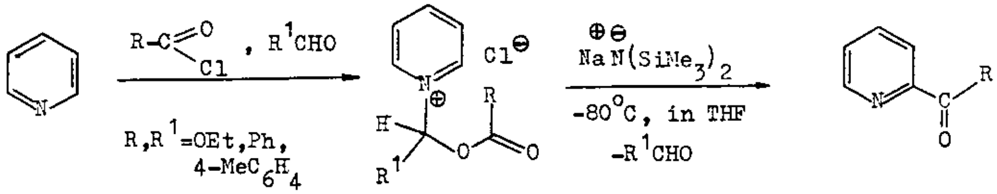
Ar = Ph, 2-ClC$_6$H$_4$, 2-MeC$_6$H$_4$, 2-NO$_2$C$_6$H$_4$

69

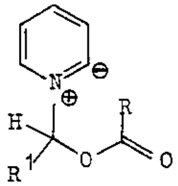
In the study of 1-(2-propynyl)pyridinium salts, the following reaction has been performed.[114]



Treatment of pyridinium and isoquinolinium salts with **sodium-bis(trimethylsilyl)amide** allows to introduce RCO- or ROCO- groups in the 2-position of these azaaromatics.[115]

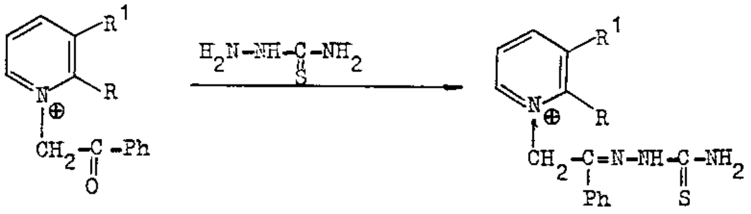


The mechanism involves the formation of ylide intermediate 72.



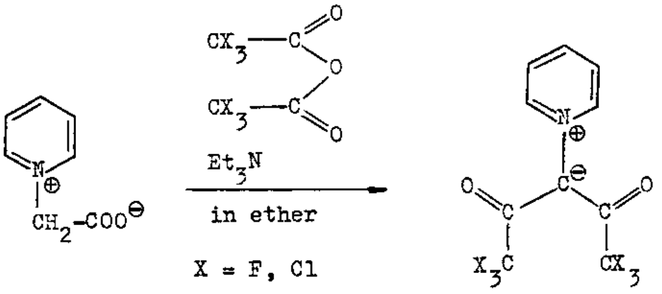
72

Other examples of reactions proceeding on the N-substituent are reported as follows



ref.116

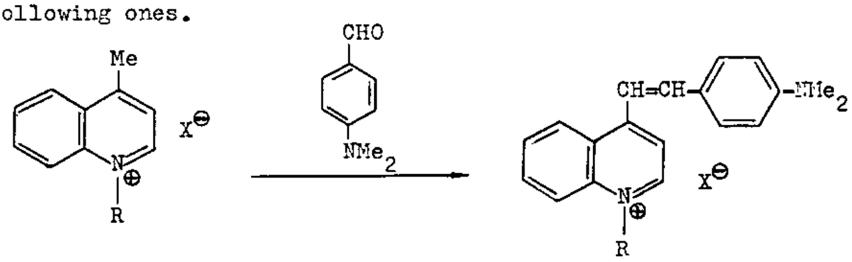
R = H, Me
R^1 = H, $PhCONHCH_2NHCO$



ref. 117

F. REACTIONS PROCEEDING ON THE RING SUBSTITUENT

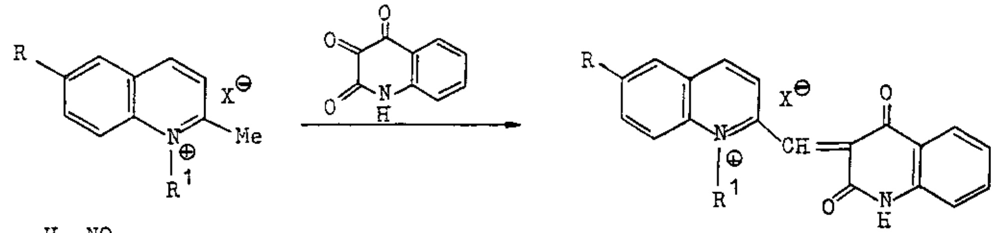
Among reactions of the ring substituent of pyridinium salts one ought to mention the following ones.



ref.118

R = Me, Et, ^nPr, ^nBu, CH_2Ph
X = Cl, Br, I, ClO_4

73



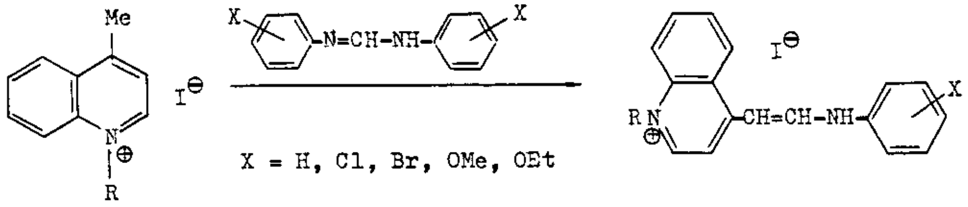
ref.119

$R = H, NO_2$

$R^1 = Me, Ph$

$X = I, ClO_4$

74



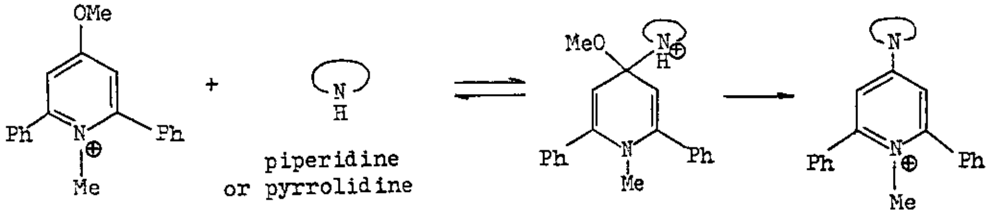
X = H, Cl, Br, OMe, OEt

ref.120

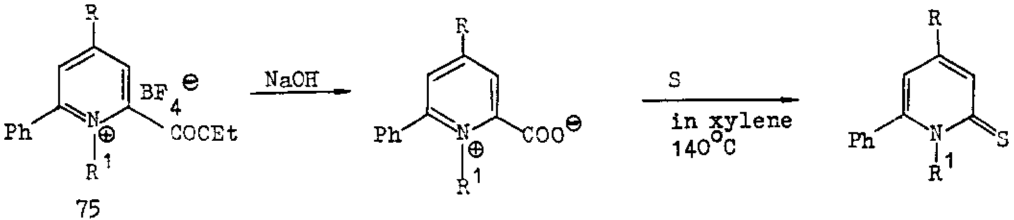
R = Me, Et

In the investigation of the latter reaction, the influence of substituents in both substrates on the reaction rate has been discussed.

The kinetics of the following demethoxylation has been investigated ; for this reaction a specific base - general acid (SB-GA) mechanism is suggested.[121]



Pyridine-2-thiones can be obtained from pyridinium salts 75 by their hydrolysis and subsequent treatment with sulphur.[122]



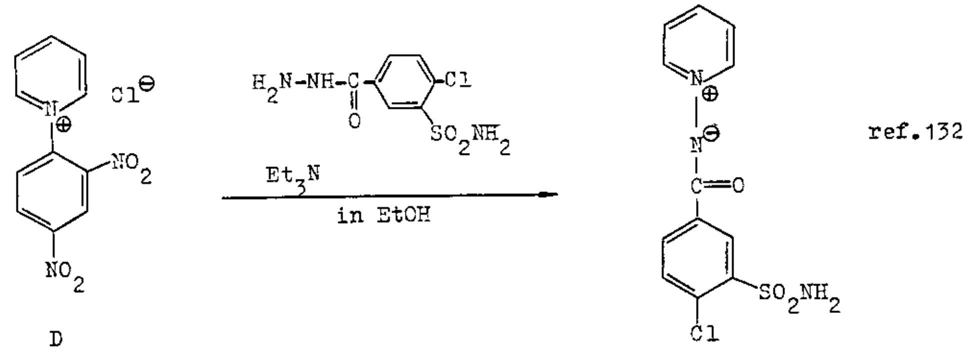
75

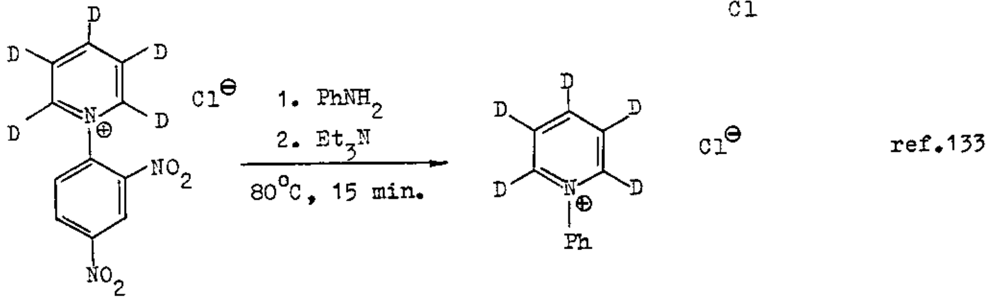
$R = H, Ph, 4\text{-}MeC_6H_4$

$R^1 = Me, Et, Ph$

The kinetics of the substitution reactions of 2-halogeno-N-alkylpyridinium salts with aliphatic and aromatic amines has been investigated.[123,124]

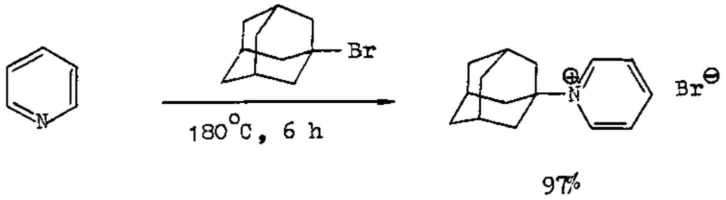
A great deal of other reactions of pyridinium salts has been performed [125-131] ; two following transformations proceeding via ring opening of 1-(2,4-dinitrophenyl) derivatives will be presented here.



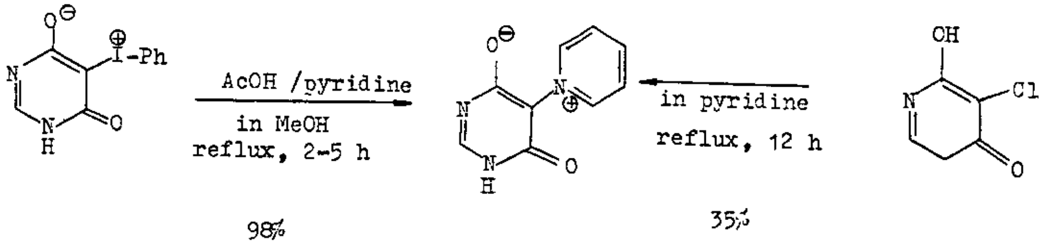


III. SYNTHESES, PROPERTIES AND APPLICATIONS OF PYRIDINIUM SALTS

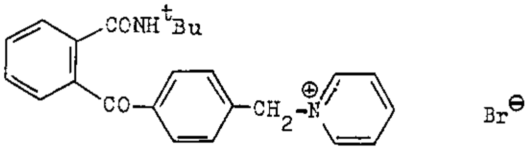
Among synthetic approaches to pyridinium salts one ought to mention a rather uncommon example of quaternization reaction with a halogeno derivative bearing halogen at the bridgehead position.[134]



Pyridinium ylide 76 can be obtained on two following routes [135], and 77 is prepared by the quaternization reaction of pyridine.[136]



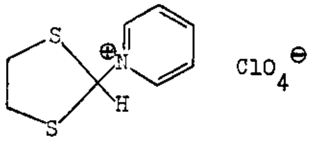
76



77

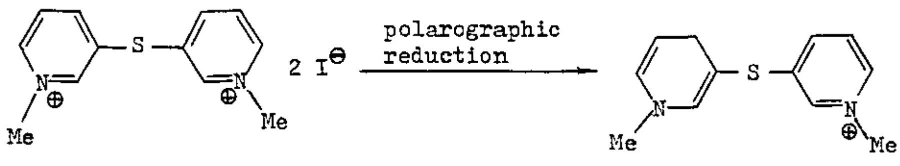
The following investigations concerning physicochemical properties of pyridinium salts have been reported.

Rates of dissociation of the C-N bond in 78 have been obtained by the dynamic NMR technique.[137]



78

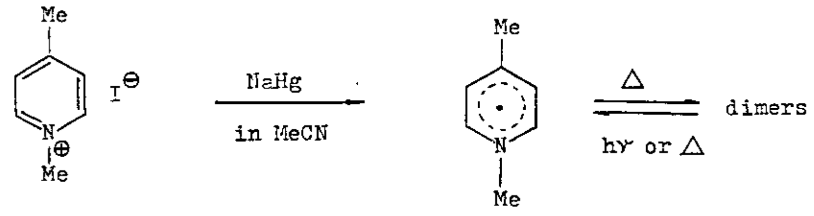
Compound 79 was reduced polarographically by a one electron transfer not involving hydrogen to an unstable radical cation 80 .[138]



79

80

1,4-Dimethylpyridinyl radical 81 has been obtained by photolysis of its dimer with a N_2 laser, as the sodium amalgam reduction of 82 afforded the radical undergoing an immediate dimerization. Time-resolved ESR spectra of 81 are discussed.[139]

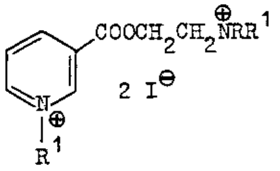


82

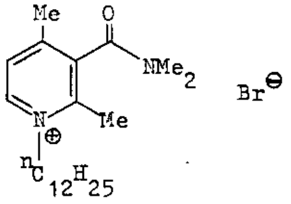
81

^{13}C and ^{1}H NMR spectra of N-alkylmethylquinolinum salts have been studied [140], and structures of N-methylpyridinium cations were calculated utilizing MINDO/3 procedure.[141]

IR spectra of 83 [142] and the CD study of an optically active detergent 84 [143] have been reported.



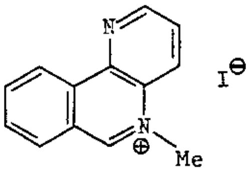
83

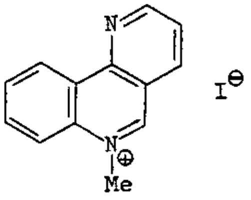


84

R, R^1 = Me, Et

Compounds 73[118] and 74[119] as well as 85 and 86[144] show antibacterial properties.





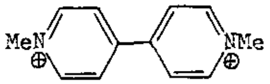
85

86

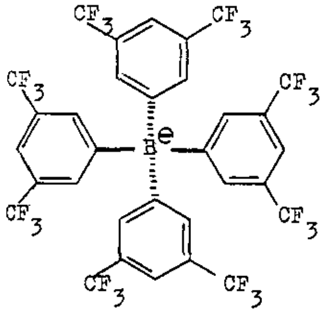
Reviewing applications of pyridinium salts one ought to mention their use as condensing agents, for example, 2-fluoro-1-methylpyridinium tosylate is utilized in the synthesis of α-ribonucleosides [145], and 2-chloro-1-methylpyridinium iodide in the construction of β-lactam skeleton.[146]

N-Alkyl-4-dialkylaminopyridinum salts were found to be effective phase transfer catalysts, up to 100 times more stable than tetrabutylammonium bromide.[147]

The redox behaviour of methylviologen radical cation $MV^{+\bullet}$ incorporated into a hydrophobic organic phase by lipophilic anions was studied. $MV^{+\bullet}$ incorporated with $TFPB^-$ can easily transfer the electron to an acceptor at the interface between the organic and aqueous phases, and is an efficient catalytic electron mediator across an organic liquid membrane.[148]



$MV^{2\oplus}$



$TFPB^{\ominus}$

Electrically conductive polymer films doped with 1,2-di[N-n-propylpyridinium-4]-ethane[TCNQ] $\frac{2}{5}$ and 1,2-di[N-n-propylpyridinium-4] ethylene[TCNQ] $\frac{2}{5}$ have been obtained and their use discussed.[149,150]

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