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Chemistry of bicyclic pyridines containing a ring-junction nitrogen

W. S. Hamama* and H. H. Zoorob

Department of Chemistry, Faculty of Science, Mansoura University, Egypt

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Contents

Keywords: bicyclic pyridines; ring-junction nitrogen; benzotriazole.

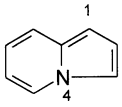
* Corresponding author. Tel.: +20-50-2242388; fax: +20-50-2246254; e-mail: sinfac@mum.mans.edu.eg

Abbreviations: AIBN, α,α′-azobisisobutyronitrile; BtH, benzotriazole; *m*CPBA, *m*-chloroperbenzoic acid; DBU, 1,9-diazabicyclo[5.4.0]-7-undecene; DDQ, 2,3-dichloro-4,5-dicyano-*p*-benzoquinone; DIEA, *N*-diisopropylethylamine; DMA, *N*,*N*-dimethylaniline; DMAD, dimethyl acetylenedicarboxylate; DMFDMA, dimethylformamide dimethyl acetal; DMSO, dimethylsulphoxide; EMME, ethyl(ethoxymethylene)malonate; IMDA, intramolecular Diels–Alder reaction; LDA, lithium diisopropylamide; MSTA, mesitylene sulphate; TBDPS, *t*-butyldiphenylsilyl; TEA, triethylamine; Tfa, trifluoroacetyl; TMA, trimethylamine; TMS, trimethylsilyl.

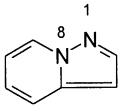
PII: S0040-4020(02)00585-9

1. Introduction

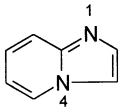
There are several fused bicyclic ring systems containing pyridine moieties. The most important are those containing a nitrogen ring-junction, where a nitrogen is common to two rings. The present review deals with some of these systems, and the following examples are illustrated:



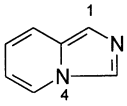
pyrrolo[1,2-a]pyridine (indolizine)



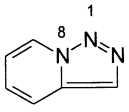
pyrazolo[1,5-a]pyridine



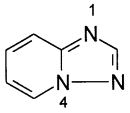
imidazo[1,2-a]pyridine



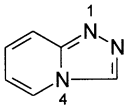
imidazo[1,5-a]pyridine



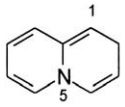
[1,2,3]triazolo[1,5-a]pyridine



[1,2,4]triazolo[1,5-a]pyridine



[1,2,4]triazolo[4,3-a]pyridine



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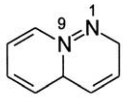

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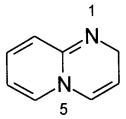

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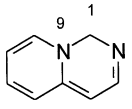

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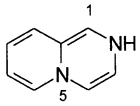

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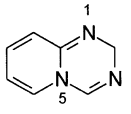
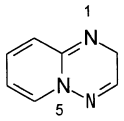
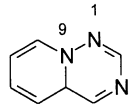


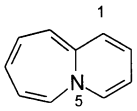
2H-pyrido[1,2-a][1,3,5]triazine



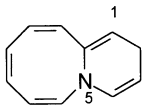
2H-pyrido[1,2-b][1,2,4]triazine



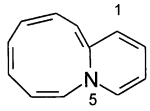
pyrido[2,1-f][1,2,4]triazine



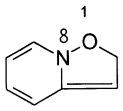
pyrido[1,2-a]azepine



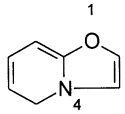
2H-pyrido[1,2-a]azocine



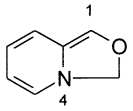
pyrido[1,2-a]azonine



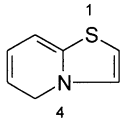
2H-isoxazolo[2,3-a]pyridine



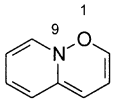
5H-oxazolo[3,2-a]pyridine



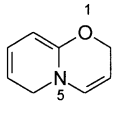
3H-oxazolo[3,4-a]pyridine



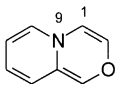
5H-thiazolo[3,2-a]pyridine



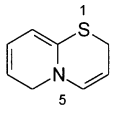
pyrido[1,2-b][1,2]oxazine



2H,6H-pyrido[2,1-b][1,3]oxazine

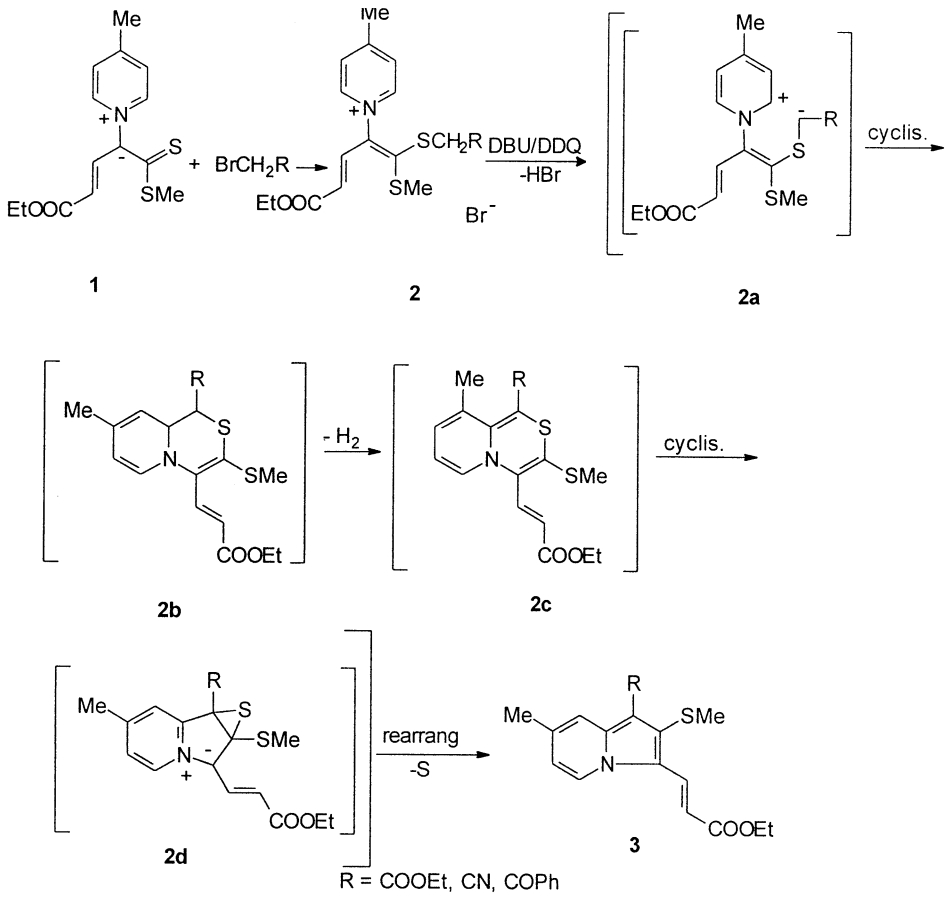


pyrido[2,1-c][1,4]oxazine



2H,6H-pyrido[2,1-b][1,3]thiazine

The vast majority of these systems do not occur naturally, but they have been the subject of many studies from the



Scheme 1.

theoretical point of view, for the preparation of potentially biologically active analogues and for some industrial uses.

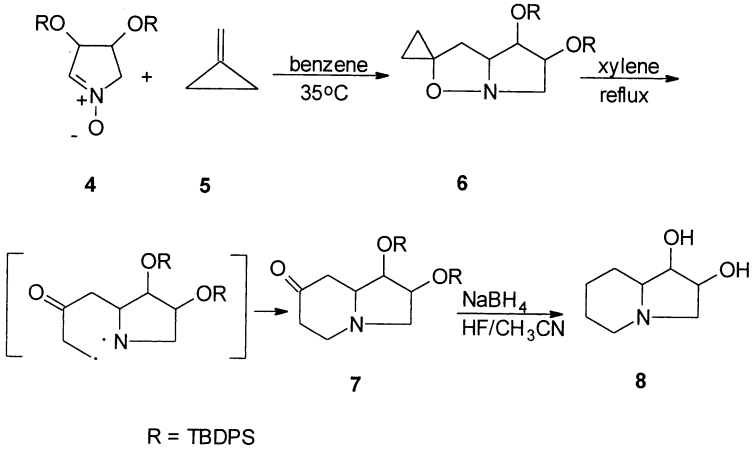
In this review, the synthesis of the title compounds is systematically arranged according to the complexity of the heterocyclic ring directly fused to a pyridine nucleus containing a nitrogen ring- junction. The literature has been searched from 1990 to 2000.

2. Synthetic approaches to bicyclic pyridines containing a nitrogen ring-junction

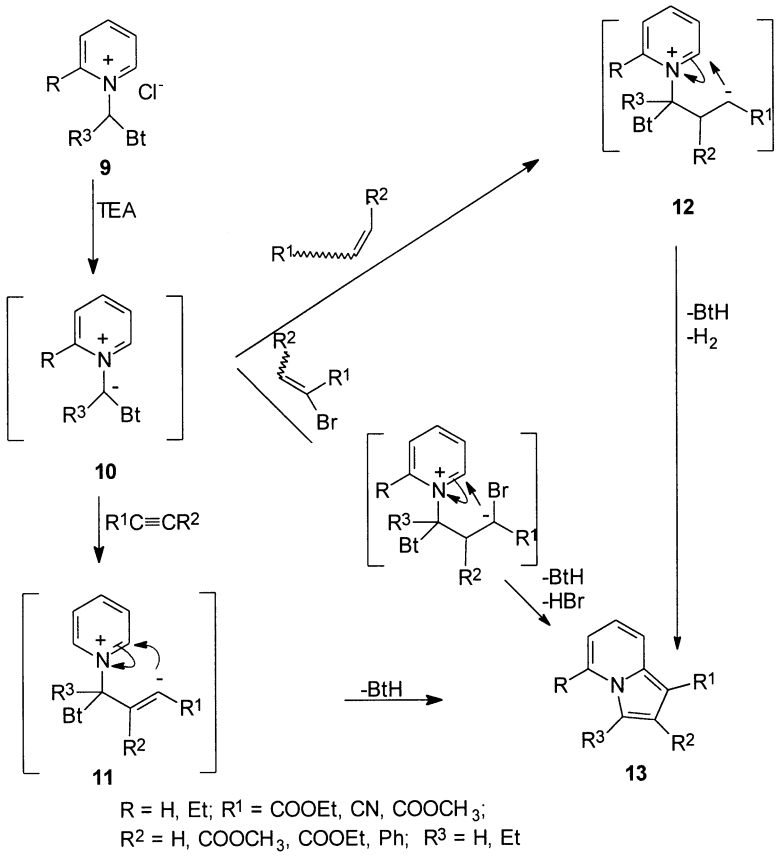
2.1. Five-membered rings

2.1.1. Azolopyridines

2.1.1.1. Pyrrolo[1,2-*a*]pyridines (indolizines). 2-Methylthio-3-vinylpyrrolo[1,2-*a*]pyridine derivatives **3** were prepared by S-alkylation of the pyridinium allylide **1** with an



Scheme 2.



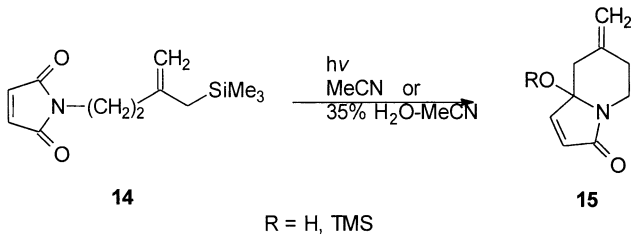
Scheme 3.

alkyl halide followed by treatment of the resulting pyridinium salt **2** with base (DBU) and then a dehydrogenating agent (DDQ) via the corresponding intermediates **2a–d** (Scheme 1).[1]

The indolizidinone **7** was obtained through cycloaddition of the nitrone **4** with methylenecyclopropane **5** followed by thermal rearrangement of the adduct **6** to the octahydropyrrolo[1,2-*a*]pyridine-7-one (indolizidinone) **7**. The ketone **7** was converted to the naturally occurring alkaloid **8** ((+)-lentiginosine) via reduction and deprotection (Scheme 2).[2,3]

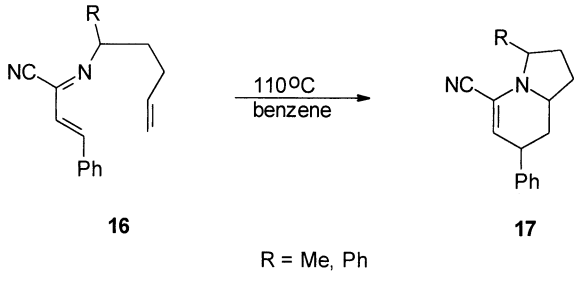
Pyrrolo[1,2-*a*]pyridine derivatives (indolizines) **13** are synthesised by 1,3-dipolar cycloadditions of pyridinium benzotriazolylmethylides **9** with ethylenes and acetylenes through the intermediates **10–12** (Scheme 3).[4]

Photoreactions of the allylsilane containing maleimide **14** in either MeCN or 35% H_2O–MeCN led to the formation of the indolizidines **15** (Scheme 4);[5] using the aqueous solvent (H_2O–MeCN) did not increase the yield appreciably.



Scheme 4.

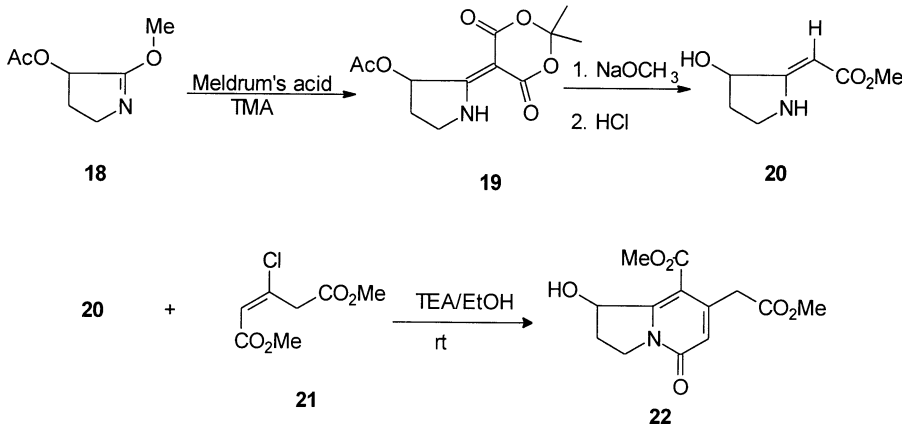
The intramolecular Diels–Alder reaction (IMDA) of the 2-cyano-1-aza-1,3-butadienes **16** by heating in benzene led to a very clean conversion to the indolizidines **17** (Scheme 5).[6,7]



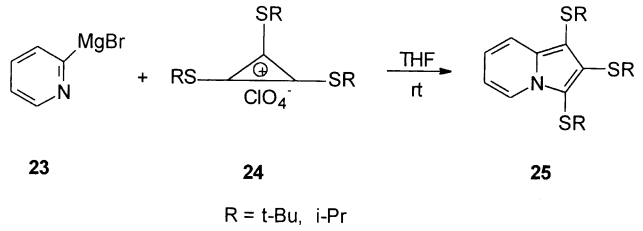
Scheme 5.

The imino ether **18** was condensed with Meldrum's acid under basic conditions using trimethylamine (TMA) to afford **19** which was converted to the enamine **20** upon treatment with sodium methoxide. Compound **20** was reacted with dimethyl 3-chloroglutaconate **21** to afford **22** (Scheme 6).[8]

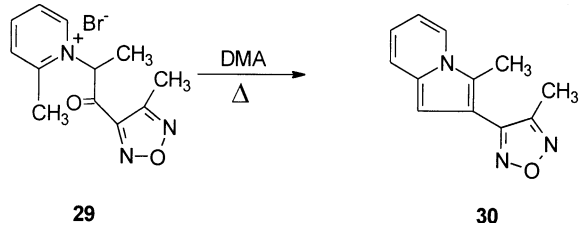
In another approach, the indolizines **25** were prepared from



Scheme 6.



Scheme 7.

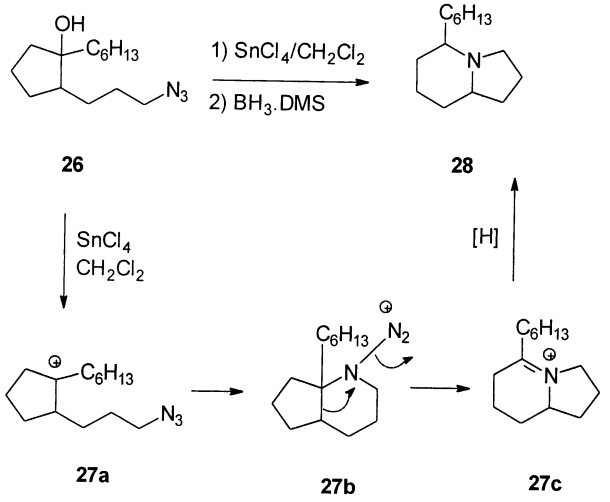


Scheme 9.

pyridylmagnesium bromide **23**, using the tris(alkylthio)-cyclopropenyl cations **24** as a three-carbon building block (Scheme 7).[9]

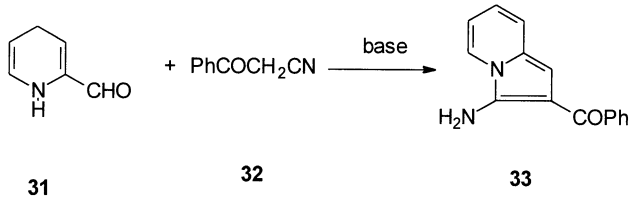
Aliphatic azides are useful in intramolecular Schmidt reactions with carbocations. Ionisation of the tertiary alcohol **26** with tin tetrachloride gave the tertiary cation **27a** which was transformed via **27b** and **c** to the 5-alkyl-indolizidine **28** (Scheme 8).[10]

Heating the *N*-[2-(4-methylfurazan-3-yl)-2-oxoethyl]-2-methyl-pyridinium bromides **29** with *N*,*N*-dimethylaniline (DMA) afforded the indolizine (pyrrolo[1,2-*a*]pyridine) derivative **30** (Scheme 9).[11]



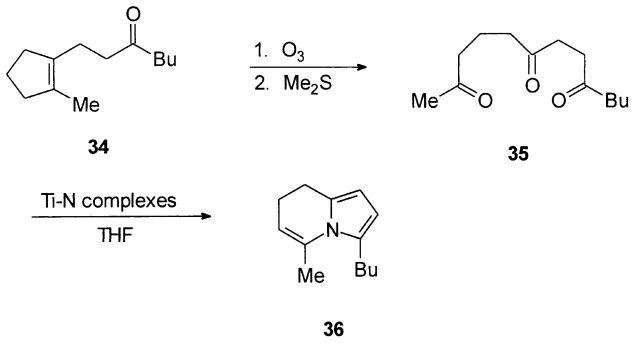
Scheme 8.

Treatment of 2-formyl-1,4-dihydropyridine **31** with 3-oxo-3-phenylpropanenitrile **32** gives the substituted 3-amino-indolizine **33** (Scheme 10).[12]

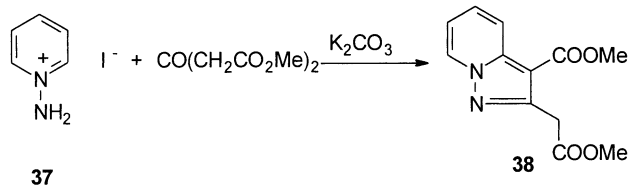


Scheme 10.

Ozonolysis of the cyclopentene derivative **34** followed by treatment with Me_2S gave the triketone **35** which reacted with Ti–N complexes (chlorotrimethylsilane in the presence of Li and $TiCl_4$ and dry air) to give the indolizine **36** (Scheme 11).[13]

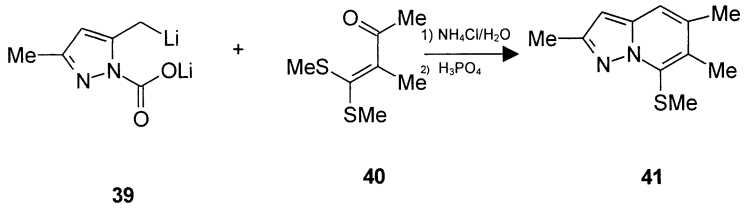


Scheme 11.



Scheme 12.

2.1.2.2. Imidazo[1,2-*a*]pyridines. Imidazo[1,2-*a*]-pyridines have been prepared from an α-haloketone with 2-aminopyridine.[17–22] As an example, the cyclocondensation of ethyl 3-bromo-2-oxo-4-phenylbutyrate **44** with 2-aminopyridine gave **45** which was converted to a 2,3-disubstituted imidazo[1,2-*a*]pyridine **46**, designed as a potential aromatase inhibitor (Scheme 15).[17]



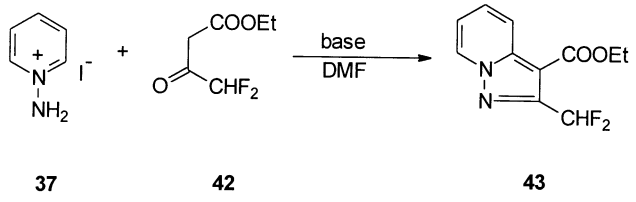
Scheme 13.

2.1.2. Diazolopyridines

2.1.2.1. Pyrazolo[1,5-*a*]pyridines. Treatment of *N*-aminopyridinium iodide **37** with acetonedi-carboxylic acid dimethyl ester in an aqueous potassium carbonate solution at room temperature afforded methyl(3-methoxycarbonyl-pyrazolo[1,5-*a*]pyridine-2-yl)acetate **38** (Scheme 12).[14]

In addition, lithium 5-lithiomethyl-3-methylpyrazole-1-carboxylate **39**, on reaction with the α-oxoketene dithio-acetal **40**, yielded pyrazolo[1,5-*a*]pyridine derivative **41** (Scheme 13).[15]

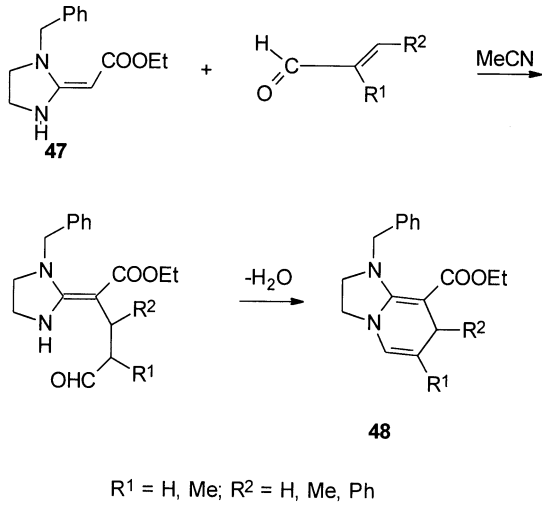
Moreover, in the presence of base the ethyl 2,2-dihydrodi-fluoro-alkanoate **42** reacted with *N*-aminopyridinum iodide **37** in DMF to give **43** (Scheme 14).[16]



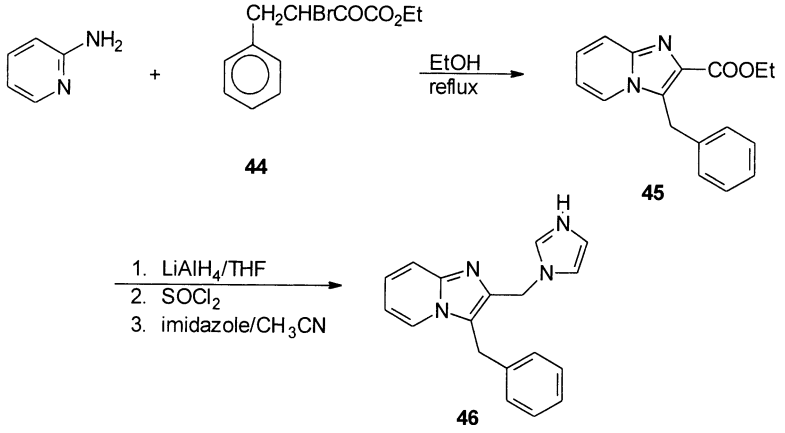
Scheme 14.

In addition, *C*-alkylation of the enamine **47** with enals followed by cyclisation afforded the tetrahydroimidazo-[1,2-*a*]pyridines **48** (Scheme 16).[23]

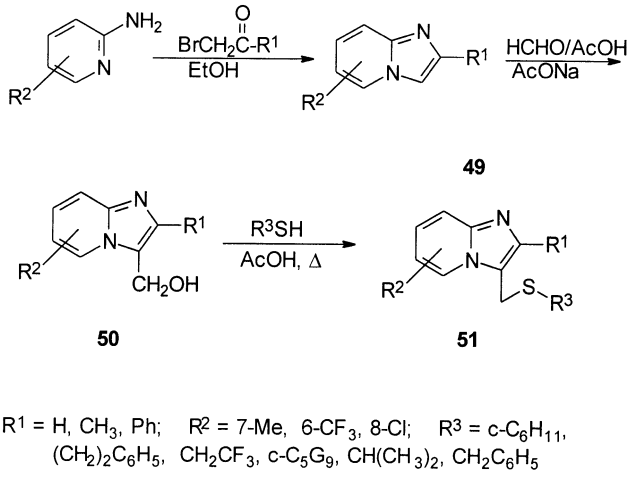
The imidazo[1,2-*a*]pyridines **51** bearing a thioether side chain at the 3-position, which are useful as antiviral agents,



Scheme 16.



Scheme 15.



Scheme 17.

were obtained through compounds **49** and **50** according to the following reaction sequences (Scheme 17).[24]

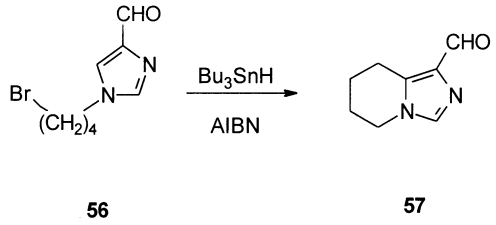
Cyclocondensation of ethyl 4,4,4-trifluoroacetoacetate with (4-chlorophenyl)acetonitrile gave the pyridone derivative **52** which was heated with a primary amine **53** and Bu_3N at 130°C to give the compound **54** which was converted to **55** by refluxing with $POCl_3$ (Scheme 18).[25]

2.1.2.3. Imidazo[1,5-*a*]pyridines. The intermediate nucleophilic *N*-alkyl radical, which was generated by the reaction of Bu_3SnH with the *N*-(ω-bromoalkyl)imidazole **56** undergoes regioselective radical cyclisation onto the azole **57** (Scheme 19).[26]

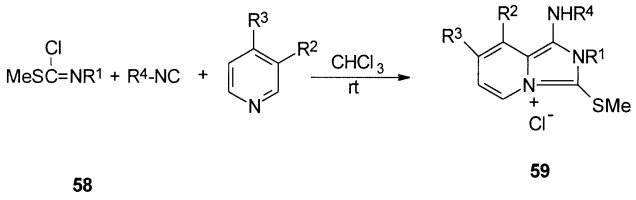
A mixture of methyl chlorothioimidates **58**, R^4NC and pyridines was reacted to give the 1-aminoimidazo[1,5-*d*]-pyridinium salts **59** (Scheme 20).[27]

2.1.3. Triazolopyridines

2.1.3.1. [1,2,3]Triazolo[1,5-*a*]pyridines. The reaction of 2-acetylpyridine **60** with hydrazines afforded the hydrazones **61**, the tautomers of which were chlorinated into **61a**. Treating **61a** with $SbCl_5$ afforded the cumulene intermediates **62**, which were cyclised into the 3-methyl[1,2,3]-triazolo[1,5-*a*]pyridinium salts **63**. The reaction of **63**



Scheme 19.



R1 = Et, CHMe2, 2,6-Me2C6H3; R2 = H, Br; R3 = H, COMe, CN; R4 = Et, i-Pr

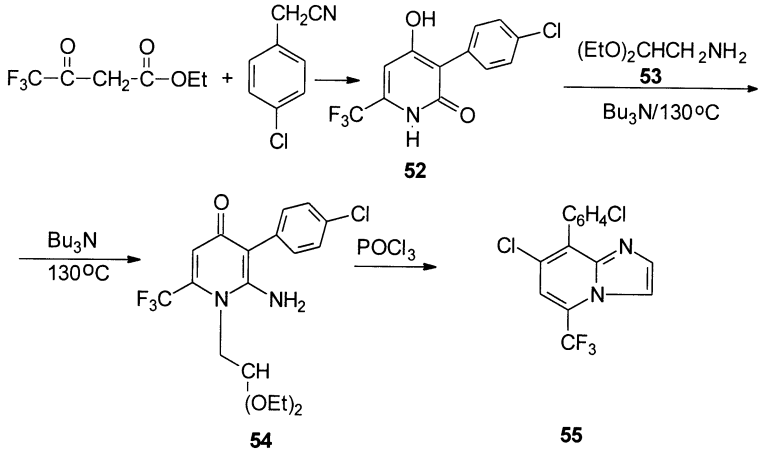
Scheme 20.

with Na_2CO_3 gave 3-methyl[1,2,3]triazolo[1,5-*a*]pyridine **64** (Scheme 21).[28]

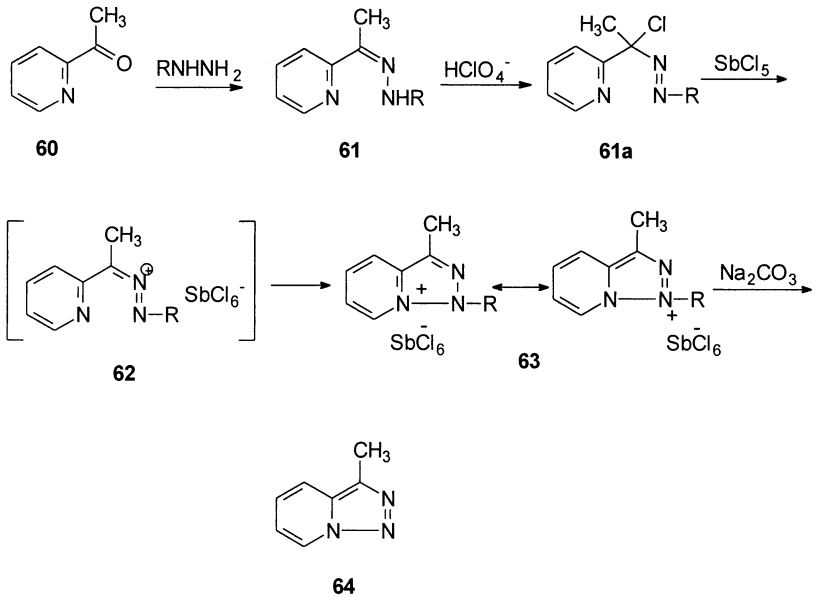
A Wittig reaction of the azidolactol **65** with $Ph_3P{=}CHCO_2Et$ proceeded via 1,3-dipolar cycloaddition of the azido function to the α,β-unsaturated ester to form the [1,2,3]triazolo[1,5-*a*]pyridine **66** (Scheme 22).[29]

2.1.3.2. [1,2,4]Triazolo[1,5-*a*]pyridines. 1,2,4-Triazolo-[1,5-*a*]pyridines have been successfully prepared in a one-pot reaction by refluxing 2-cyanoacetohydrazide, aldehydes and malononitrile in ethanol in the presence of pyridine to give **67** (Scheme 23).[30]

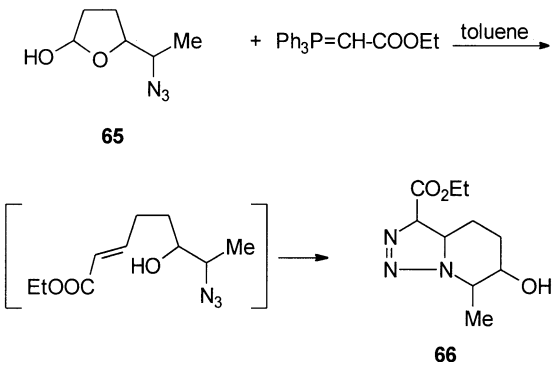
Condensation of 1-substituted ethylidenemalononitriles with tri-ethyl orthoformate in refluxing acetic anhydride yielded the dienes **68**. The reaction of **68** with hydrazine hydrate afforded the *N*-amino-2-iminopyridines **69**, and these were converted into the triazolo[1,5-*a*]pyridines **70** on treatment with DMFDMA (Scheme 24).[31]



Scheme 18.



Scheme 21.

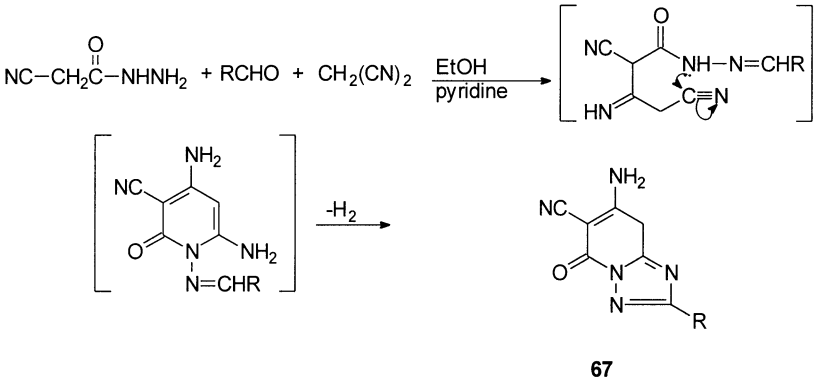


Scheme 22.

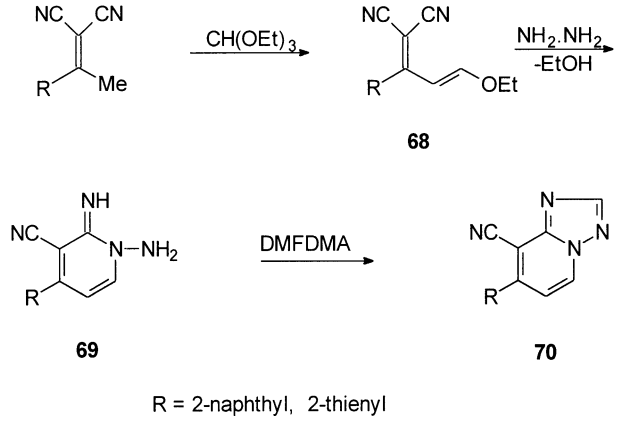
The reactions of formaldehyde and acetaldehyde with active methylenes, followed by treatment with cyanoacetic acid hydrazide, afforded the *N*-aminopyridine-2-one derivatives **71**. The reaction of **71** with aromatic aldehydes or cyclohexanone afforded **72** or **73** (Scheme 25).[32]

2.1.3.3. [1,2,4]Triazolo[4,3-*a*]pyridines. Cyclocondensation of ethyl 2-cyano-3-ethoxypropenoate with the acetamidrazones **74** in DMSO gave the [1,2,4]triazolo-[3,4-*a*]pyridines **75** via ring closure of the 6-(2-acylhydrazino)pyridine intermediates (Scheme 26).[33]

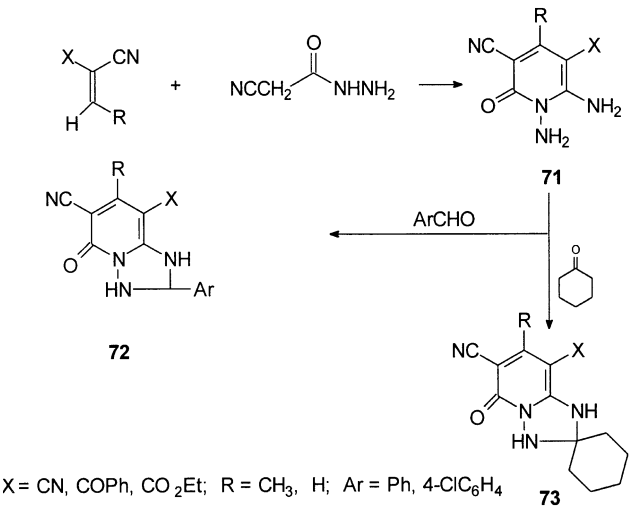
In addition, cyclisation of 3-cyano-4,6-dimethyl-2(1*H*)-pyridine thione **76** with $RC_6H_4CONHNH_2$ (R=H, 4-Cl) gave **77** (Scheme 27).[34]



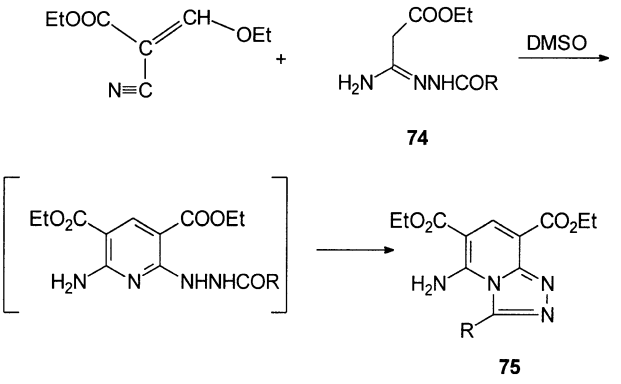
Scheme 23.



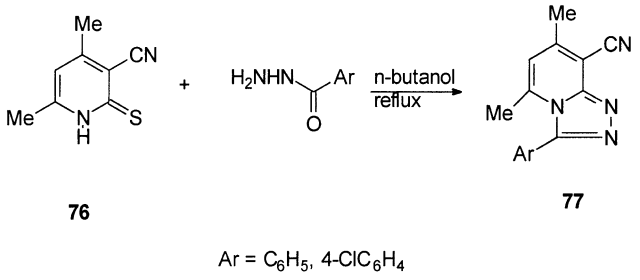
Scheme 24.



Scheme 25.



Scheme 26.

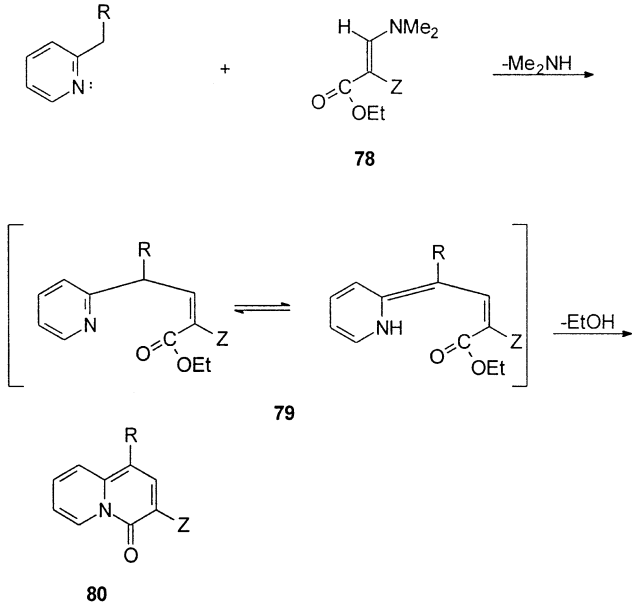


Scheme 27.

2.2. Six-membered rings

2.2.1. Synthesis of azinopyridines

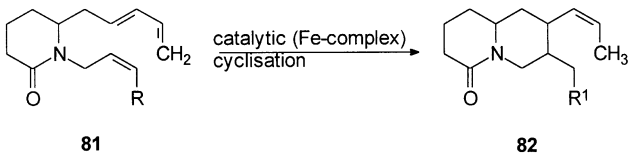
2.2.1.1. 2*H*-Pyrido[1,2-*a*]pyridines (2*H*-quinolizines). Ethyl 2-substituted-3-dimethylaminopropenoates **78** were reacted with a 2-substituted pyridine as a C- and N-binucleophile and the *N*,*N*-dimethylamino group was substituted to give the intermediates **79**, which were cyclised by heating in acetic acid to afford the 1-substituted-4*H*-quinolizine-4-one derivatives **80** (Scheme 28).[35–38]



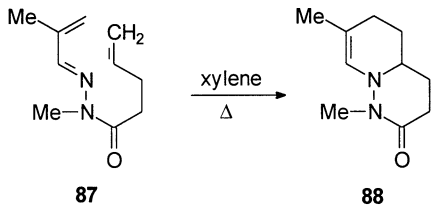
Scheme 28.

The trienes **81** in which the requisite 1,3-diene and allylic ether moieties are appended to the pre-existing ring system afford the bicyclic ring products **82** upon iron-catalysed cyclisation (Scheme 29).[39]

Oxidation of the ω-haloazidoalkene **83** to give the epoxide **84** by *m*-chloroperbenzoic acid (*m*CPBA) followed by the reduction of the azide group to the primary amine **85**, afforded the quinolizidine **86** after an intramolecular double cyclisation (Scheme 30).[40]



Scheme 29.

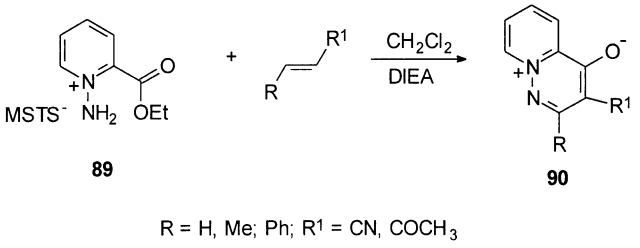


Scheme 31.

2.2.2. Diazinopyridines

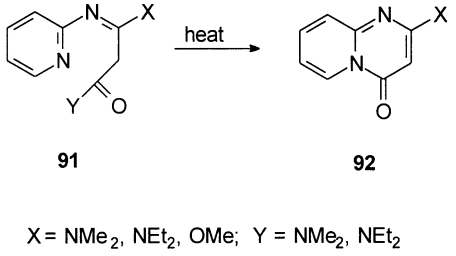
2.2.2.1. 2*H*-pyrido[1,2-*b*]pyridazines. Cyclocondensation of the α,β-unsaturated aldehyde acylhydrazone **87** via intramolecular Diels–Alder reaction at elevated temperature in the presence of xylene afforded **88** (Scheme 31).[41]

2-Ethoxycarbonylpyridinium *N*-aminides such as **89** behave as 1,3-dipoles and reacted with Michael acceptors to give the corresponding cycloadducts which subsequently gave pyrido[1,2-*b*]pyridazinium inner salts **90** (Scheme 32).[42]



Scheme 32.

2.2.2.2. Pyrido[1,2-*a*]pyrimidines. Malonic acid imide derivatives **91** underwent thermal elimination of amines to afford the 2-substituted pyrido[1,2-*a*]pyrimidines **92**, (Scheme 33).[43]



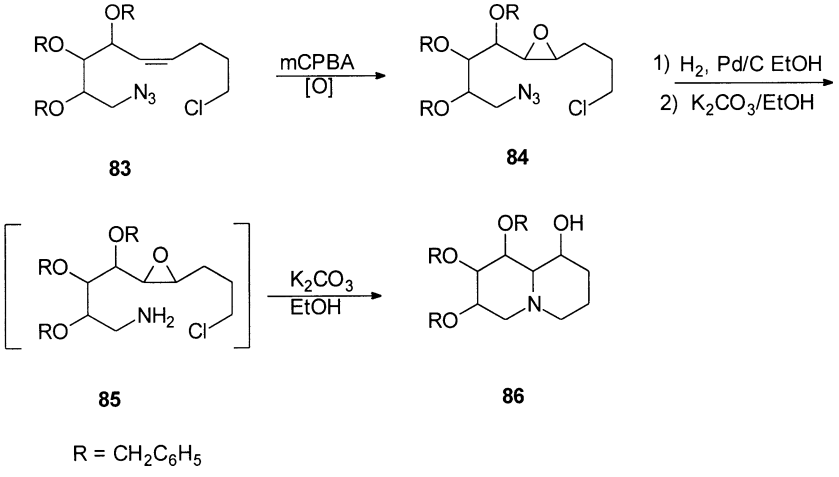
Scheme 33.

4*H*-Pyrido[1,2-*a*]pyrimidines **93** were prepared from the reaction of 2-aminopyridines with 2-alkenoates.[44–47] Methyl 2-acetylamino-3-dimethylaminopropenoate, for example, was treated with *N*-nucleophiles such as 2-aminopyridines to give **93** (Scheme 34).[44]

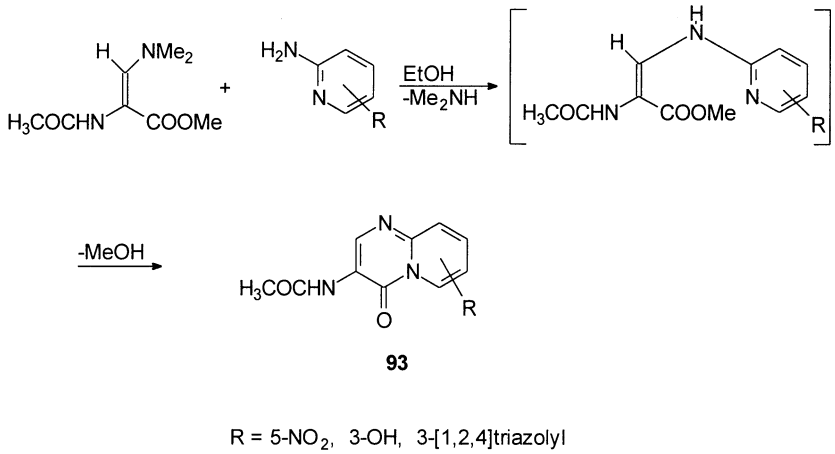
Treatment of the 5-fluoropyrimidines **94** with *n*-butyllithium followed by reaction with ethyl (ethoxymethylene)-malonate yielded the addition product **95**. The cyclisation of **95** was realised in refluxing ethanol in the presence of a catalytic amount of piperidine and acetic acid to give **96** (Scheme 35).[48]

Reaction of enones with the nitroketeneaminal **97** in refluxing ethanol yielded a Michael adduct **98** which was transformed to the bicyclic carbinolamines **99**. Its dehydration in acidic medium led to the compound **100** (Scheme 36).[49]

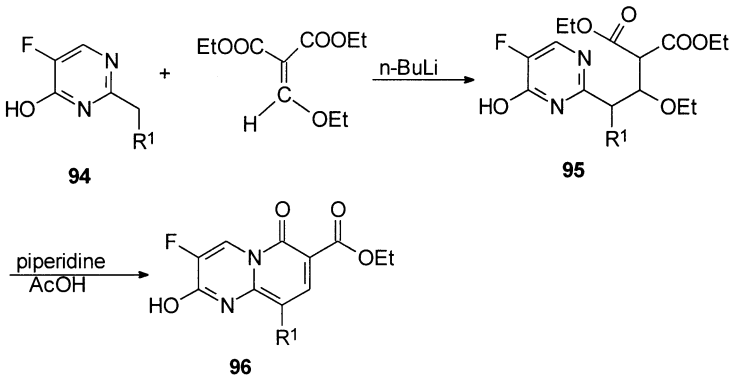
2.2.2.3. Pyrido[1,2-*c*]pyrimidines. The iminoethylidenepyridines **101** underwent cyclocondensation with



Scheme 30.



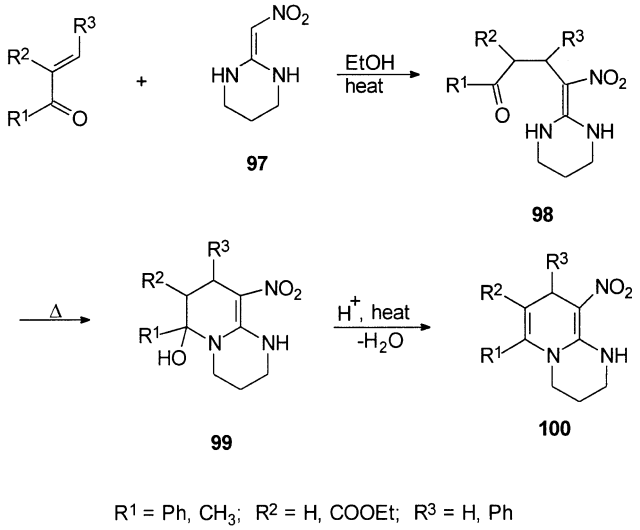
Scheme 34.



Scheme 35.

aldehydes to give the pyrido[1,2-*c*]pyrmidines **102** (Scheme 37).[50]

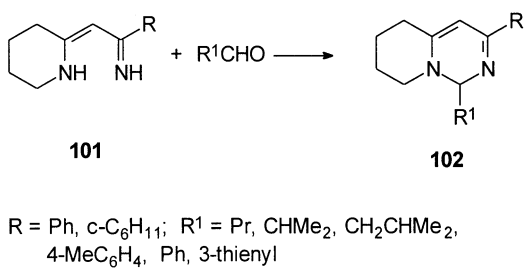
2.2.2.4. Pyrido[1,2-*a*]pyrazines. Methyl (pyrido[1,2-*a*]-pyrazin-3-yl)acetate **104** was prepared from ethyl 2(2′-pyridyl)glycinate **103** and dimethyl acetylenedicarboxylate via the formation of enamine as an intermediate (Scheme 38).[51]



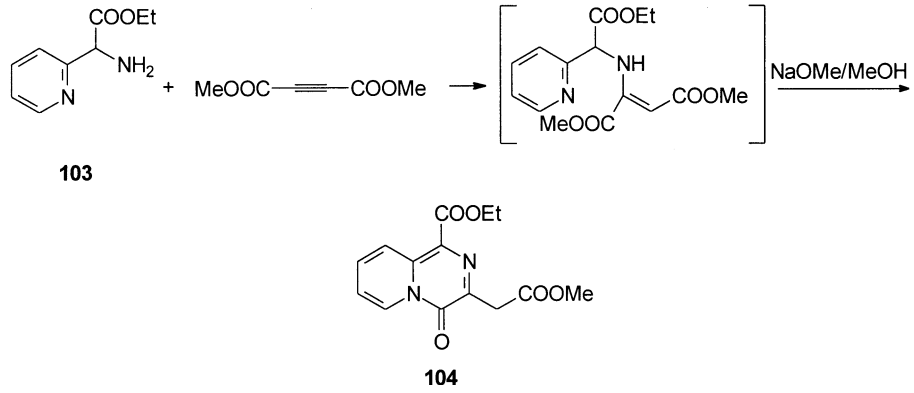
Scheme 36.

2.2.3. Triazinopyridines

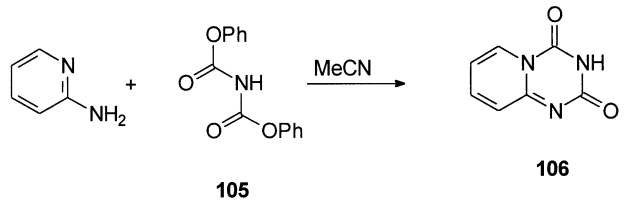
2.2.3.1. Pyrido[1,2-*a*][1,3,5]triazines. 2*H*-pyrido[1,2-*a*]-[1,3,5]triazine-2,4(3*H*)-dione **106** was obtained from the reaction of 2-aminopyridine with diphenyliminodicarboxylate **105** in acetonitrile at high temperature (Scheme 39).[52]



Scheme 37.

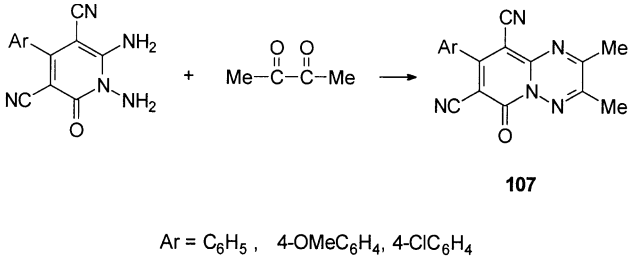


Scheme 38.



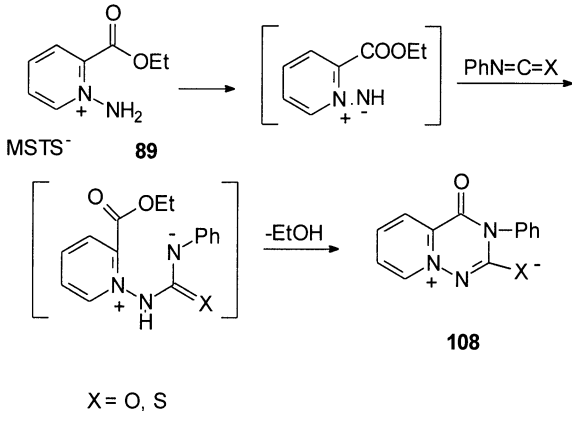
Scheme 39.

2.2.3.2. Pyrido[1,2-*b*][1,2,4]triazines. Cyclocondensation of 1,6-diaminopyridines with 1,2-dicarbonyl compounds[53,54] as MeCOCOMe afforded **107** (Scheme 40).[53]



Scheme 40.

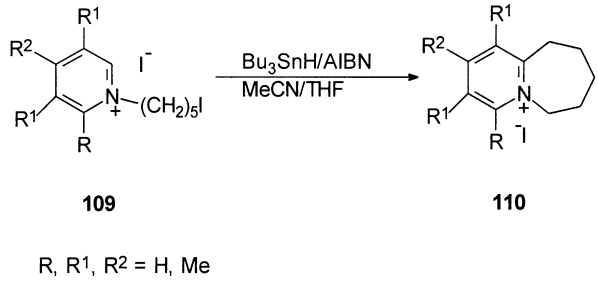
2.2.3.3. Pyrido[2,1-*f*][1,2,4]triazines. The 2-ethoxycarbonylazinium salt **89** was reacted with isocyanates and/or isothiocyanates to give the mesomeric betaines **108** in a [4+2] cyclocondensation process (Scheme 41).[42]



Scheme 41.

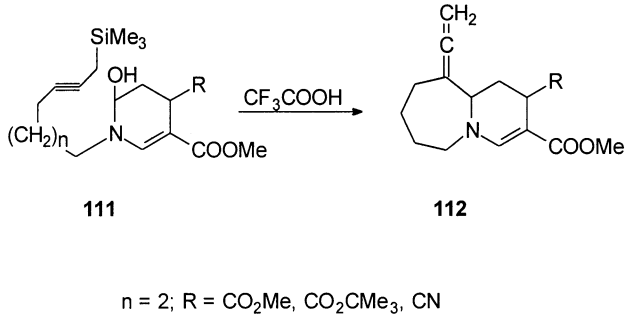
2.3. Seven-membered rings

2.3.1. Pyrido[1,2-*a*]azepines. The pyrido[1,2-*a*]azepines **110** were prepared from *N*-substituted pyridines[55–58] and treatment of the pyridinium iodides **109** with Bu_3SnH and AIBN in MeCN–THF gave **110** (Scheme 42).[55]



Scheme 42.

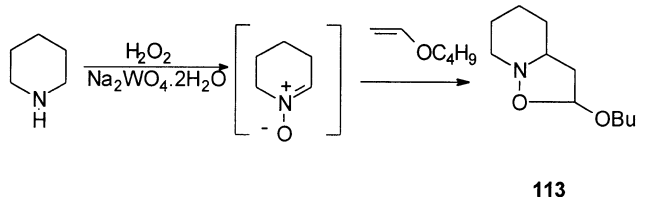
In addition, cyclisation of the compounds **111** in the presence of CF_3COOH gave the pyrido[1,2-*a*]azepines **112** (Scheme 43).[56]



Scheme 43.

2.4. Five-membered rings containing different heteroatoms

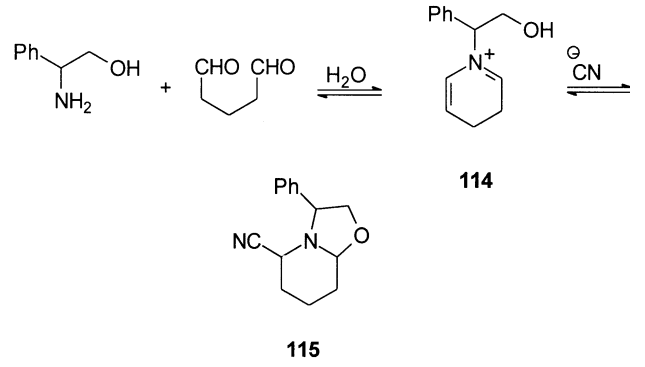
2.4.1. 2*H*-Isoxazolo[2,3-*a*]pyridines. The hexahydro(2*H*)-isoxazolo[2,3-*a*]pyridine **113** was prepared by nitrone cycloaddition[59–61] and, as an example, the oxidation of cyclic amines in the presence of alkenes afforded the



Scheme 44.

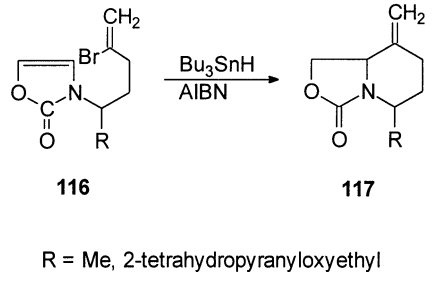
compound **113** without isolation of the nitrone (Scheme 44).[59]

2.4.2. 5*H*-Oxazolo[3,2-*a*]pyridines. The reaction of phenylglycinol with glutaraldehyde provided to 2-cyano-6-phenyltetrahydro(5*H*)oxazolo[3,2-*a*]pyridine **115** via the inter-mediate dihydropyridine unit **114** (Scheme 45).[62,63]



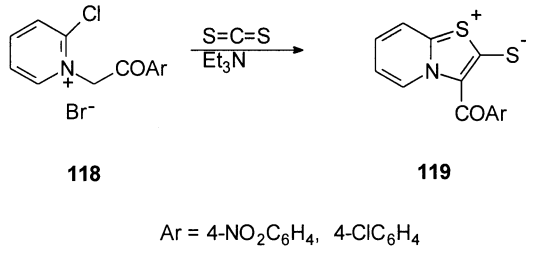
Scheme 45.

2.4.3. 3*H*-Oxazolo[3,4-*a*]pyridines. *N*-(2-Bromo-1-pentenyl)-oxazolin-2-one derivatives **116** were treated with Bu_3SnH in the presence of AIBN to afford **117** (Scheme 46).[64]

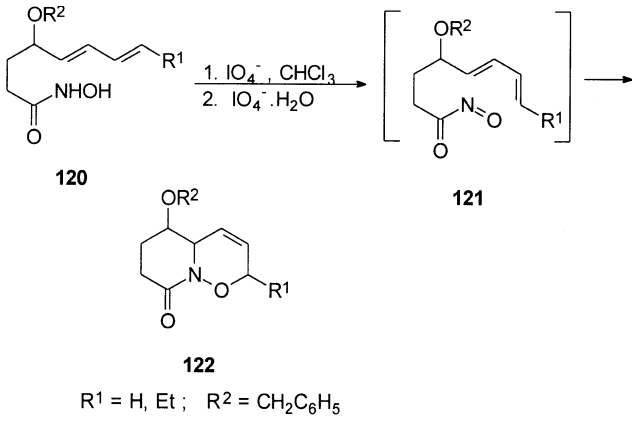


Scheme 46.

2.4.4. 5*H*-Thiazolo[3,2-*a*]pyridines. The thiazolo[3,2-*a*]-pyridinium salts **119** were prepared by cycloaddition of carbon disulphide to the 2-chloropyridinium salts **118** (Scheme 47).[65]



Scheme 47.

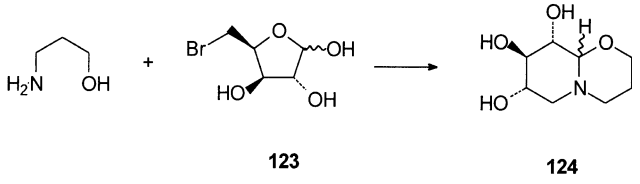


Scheme 48.

2.5. Six-membered rings containing different heteroatoms

2.5.1. Pyrido[1,2-*b*][1,2]oxazines. In an aqueous medium, intramolecular Diels–Alder cycloaddition of the acylnitroso compound **121** (generated from the hydroxamic acid **120** by periodate oxidation) gave the pyrido[1,2-*b*][1,2]oxazin-8(2*H*)-ones **122** (Scheme 48).[66,67]

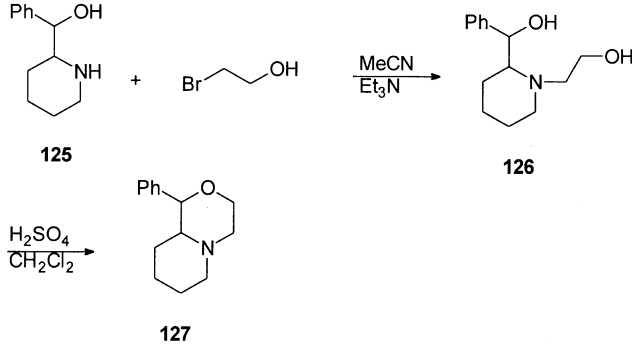
2.5.2. 2*H*,6*H*-Pyrido[2,1-*b*][1,3]oxazines. The hexahydropyrido[2,1-*b*][1,3]oxazine **124** was obtained by the reaction of 3-amino-1-propanol with 5-bromo-5-deoxy-D-xylose **123** in an aqueous medium (Scheme 49).[68]



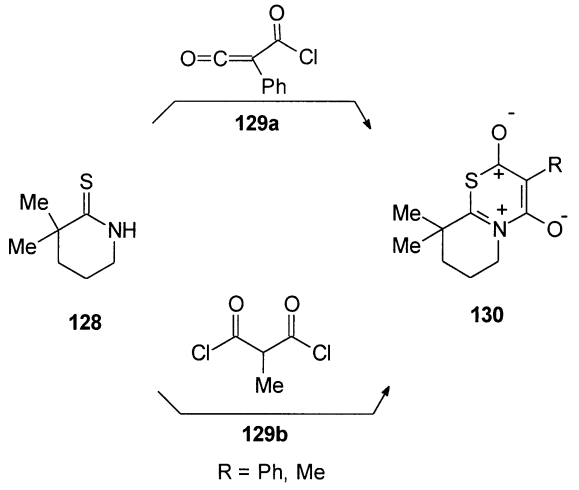
Scheme 49.

2.5.3. Pyrido[2,1-*c*][1,4]oxazines. Alkylation of phenyl-2-piperidylmethanol **125** with 2-bromoethanol and triethylamine in acetonitrile gave the aminodiol **126**, which was cyclised with sulphuric acid in dichloromethane to give octahydro-1-phenylpyrido[2,1-*c*][1,4]oxazine **127** (Scheme 50).[69]

2.5.4. 2*H*,6*H*-Pyrido[2,1-*b*][1,3]thiazines. The tetrahydropyrido[2,1-*b*][1,3]thiazinium hydroxide derivatives **130**



Scheme 50.

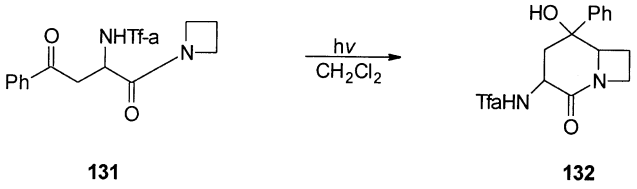


Scheme 51.

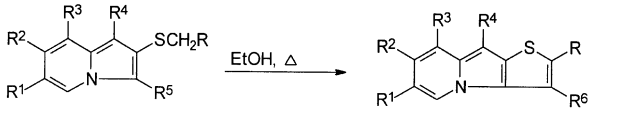
were prepared from the reaction of 3,3-dimethyl-piperidin-2-thione **128** with chlorocarbonylphenylketene **129a** or methylmalonyldichloride **129b** in CH_2Cl_2, (Scheme 51).[70]

2.6. Saturated four-membered rings

2.6.1. 1-Azabicyclo[4.2.0]octan-2-ones. Photocyclisation

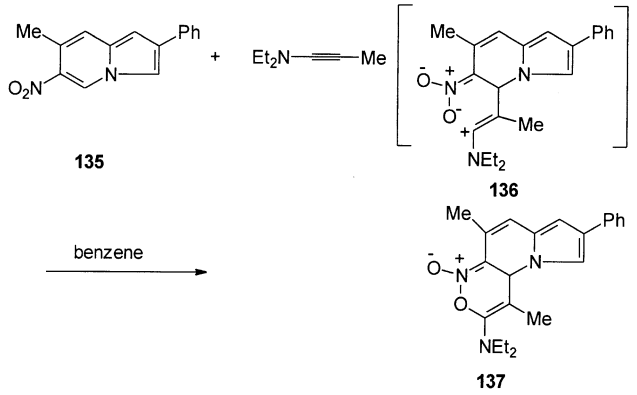


Scheme 52.

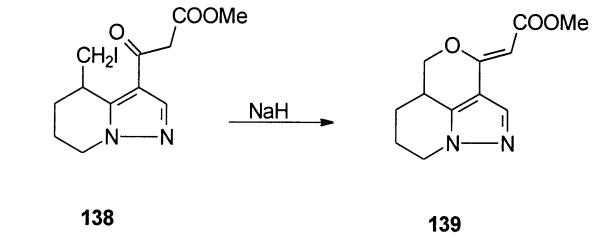


R = CO_2Et, Ac, COPh, CO(4-ClC_6H_4), $CH{=}CH_2$; R^1, R^2, R^3 = H, Me; R^4 = CN, CO_2Et; R^5 = CN, COMe; R^6 = NH_2, Me

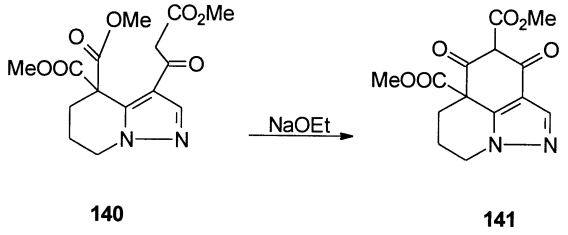
Scheme 53.



Scheme 54.



Scheme 55.



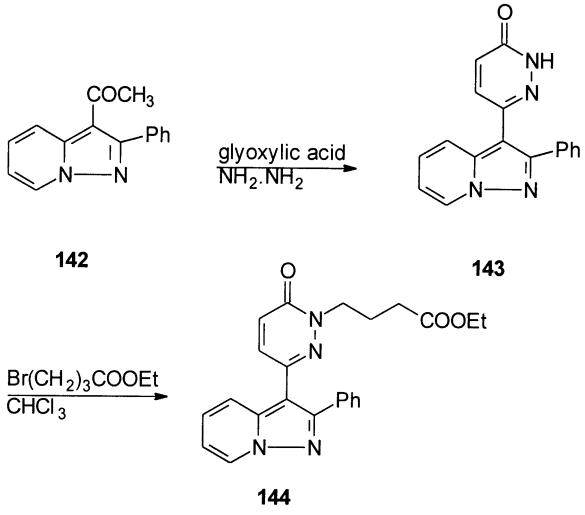
Scheme 56.

of the amide **131** via photoinduced ε-hydrogen abstraction followed by cyclisation of the corresponding 1,6-biradical to give 3-trifluoroacetylamino-5-hydroxy-5-phenyl-1-azabicyclo[4.2.0]octan-2-one **132** has been reported (Scheme 52).[71]

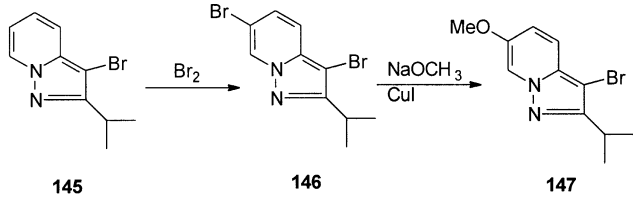
3. Reactions

3.1. Reactions of bicyclic pyridines fused to five-membered rings

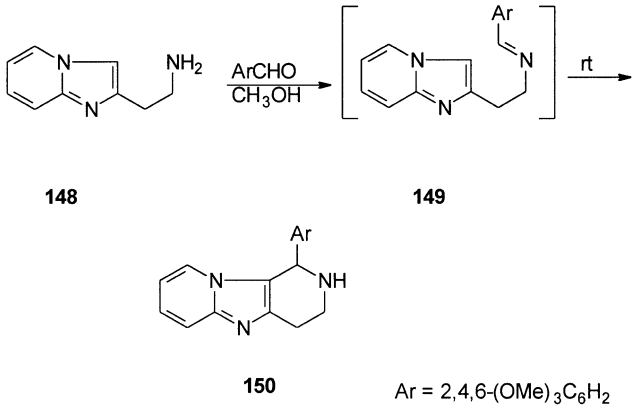
The intramolecular cyclisations of 5-alkylated indolizines



Scheme 57.



Scheme 58.



Scheme 59.

133 afforded the corresponding thieno[2,3-*b*]indolizines **134** (Scheme 53).[72–74]

In addition, 7-methyl-6-nitro-2-phenylindolizine **135** was reacted with 1-(diethylamino)-2-methylacetylene to give the cycloadduct **137** [5,9-dimethyl-8-(diethylamino)-2-phenyl-6-oxo-9a(*H*)-indolizino[6,5-*c*][1,2]isoxazine] through the intermediate cyclisation of **136** (Scheme 54).[75]

Treatment of the β-ketoester **138** with NaH resulted in *O*-alkylation to yield the tricyclic product **139** (Scheme 55).[76]

Annulation of the triester **140** via a Dieckman condensation yielded the tricyclic product **141** (Scheme 56).[76]

Condensation of the acetylpyrazolopyridine **142** with glyoxylic acid hydrate and hydrazine hydrate in aqueous ammonia the afforded the pyridazinyl compounds **143**, which were reacted with $Br(CH_2)_3COOEt$ in $CHCl_3$ to give **144** (Scheme 57).[77]

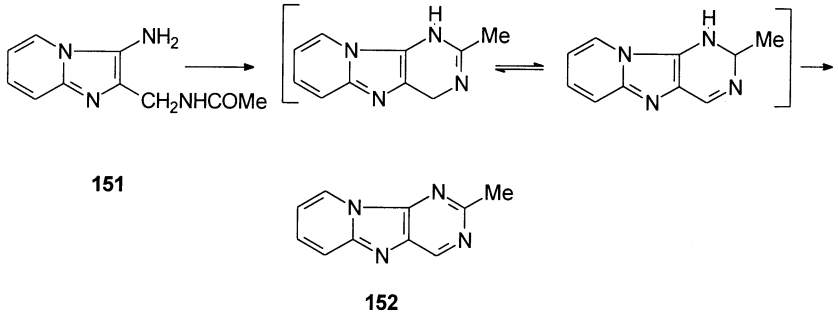
Bromination of the compound **145** gave the 6-bromo derivative **146**, which was reacted with $NaOCH_3$ in the presence of cuprous iodide to afford **147** (Scheme 58).[78]

Condensation of the amine **148** with 2,4,6-trimethoxybenzaldehyde gave a Schiff's base **149**, which was cyclised at room temperature to yield the azacarboline **150** (Scheme 59).[79]

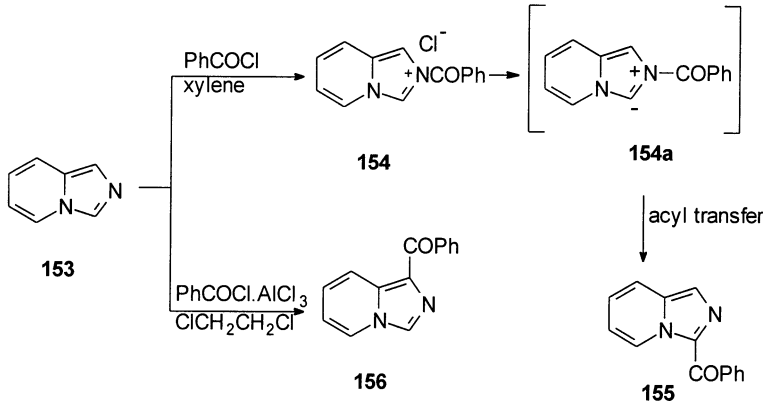
The pyrido[1,2-*e*]purine **152** was obtained by transformation of the acylated amine derivative **151** (Scheme 60).[80]

In addition, the compound **153** was benzoylated with PhCOCl in xylene to give **155** via quaternary salt **154** and a stabilised ylide **154a**, while its benzoylation under Friedel–Crafts conditions afforded **156**, (Scheme 61).[81]

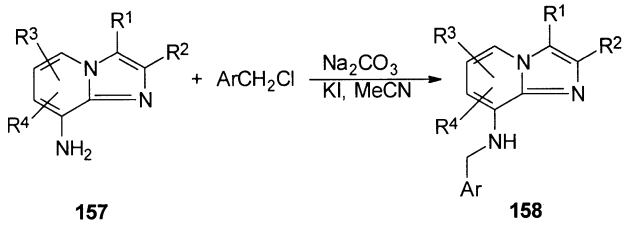
The reaction of the 8-amino derivative **157** with 2,6-dimethylbenzyl chloride in the presence of Na_2CO_3 and KI in MeCN afforded **158** (Scheme 62).[82,83]



Scheme 60.



Scheme 61.

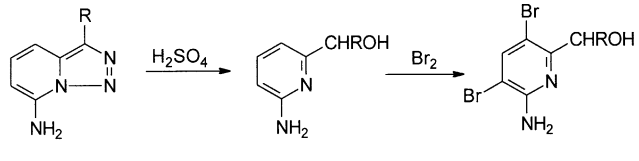


157 158

R^1 = H, alkyl, alkenyl; R^2 = alkyl, alkoxyalkyl; R^3 = H, alkoxy, alkyl; R^4 = H, alkyl, haloalkyl; Ar = Ph, thienyl, furanyl, 2,6-$(CH_3)_2C_6H_3$

Scheme 62.

The reaction between the 7-aminotriazolopyridines **159** and sulphuric acid gave hydroxyalkylpyridines **160**. Bromination of **160** gave the brominated pyridines **161** (Scheme 63).[84]

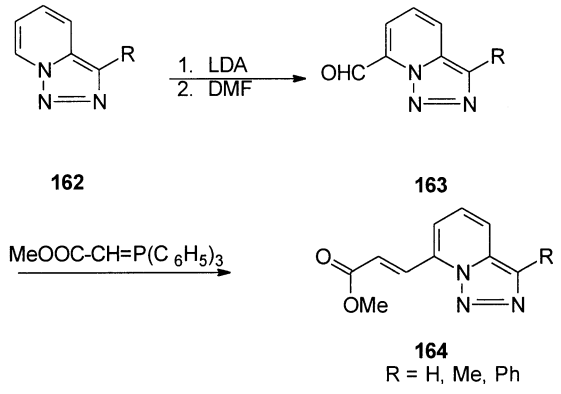


159 160 161

R = H, Me

Scheme 63.

The triazolo[1,5-*a*]pyridines **162** were lithiated by lithium diisopropylamide and then reacted with dimethylformamide to give the aldehyde derivatives **163**. These reacted with carbomethoxymethylene triphenylphosphorane to yield the esters **164** (Scheme 64).[85,86]



162 163

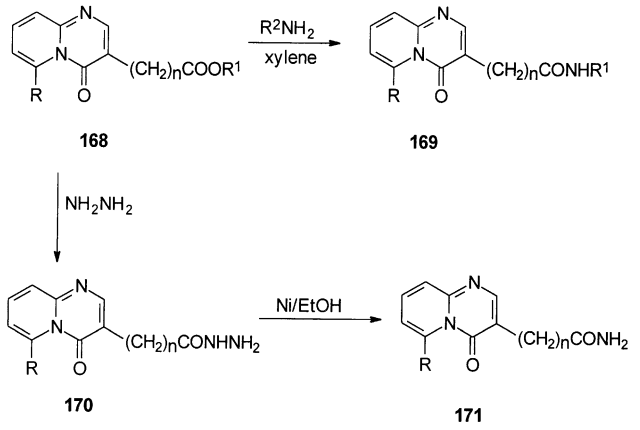
164
R = H, Me, Ph

Scheme 64.

3.2. Reactions of bicyclic pyridines fused to six-membered rings

Treatment of 3-cyano-1-ethoxycarbonyl-2-methylthio-4*H*-quinolizin-4-one **165** with 2-(aminomethyl)-5-(hydroxymethyl)pyrazine **166** in MeCN gave **167** (Scheme 65).[87]

The reaction of the compounds **168** with 2-phenylethylamine in boiling xylene gave the *N*-substituted-3-acetamide derivatives **169**, whereas the reaction of **168** with hydrazine hydrate afforded the 3-acetic hydrazides **170**, which were converted to the 3-acetamides **171** by refluxing in ethanol over Raney-Ni (Scheme 66).[88]



168 169 170 171

n = 0, 1; R = H, Me; R^1 = H, Et; R^2 = $C_6H_5CH_2CH_2$

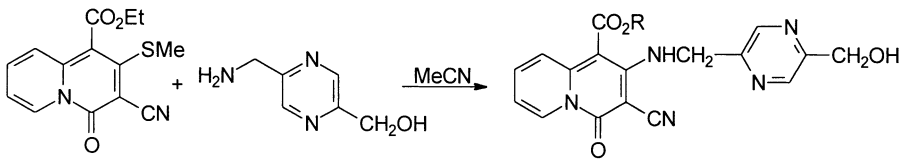
Scheme 66.

Quinolizidinylmethyl indole-3-carboxylate **174** was prepared by condensation of 3-hydroxymethylquinolizidine **172** with the acid chloride **173** (Scheme 67).[89]

The 5*H*-pyrazolo[4,3-*a*]quinolizin-5-one **176** was obtained from condensation of the compound **175** with N_2H_4 in DMSO (Scheme 68).[90]

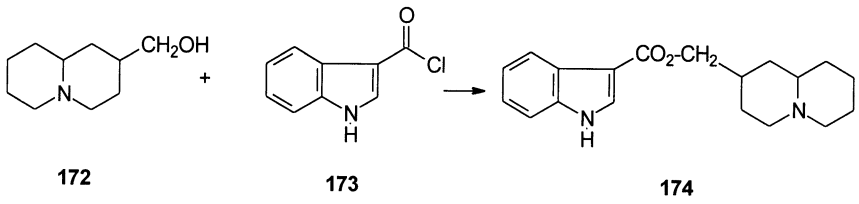
In addition, the pyrido[1,2-*b*]pyridazinium-4-olate **177** was photolysed to give the isoxazole **178** and the azirine **179** (Scheme 69).[91]

Intramolecular cycloaddition of the compound **180** under Lewis acid catalysis afforded the pyridopyrimidazepines **181** (Scheme 70).[92,93]

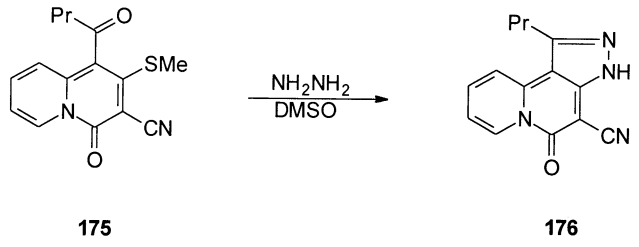


165 166 167

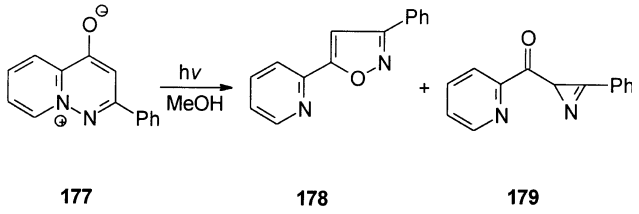
Scheme 65.



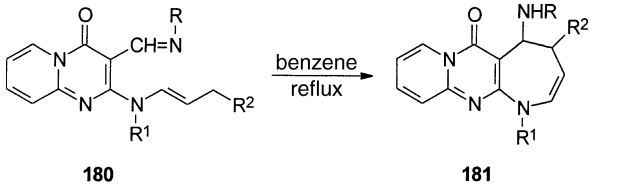
Scheme 67.



Scheme 68.



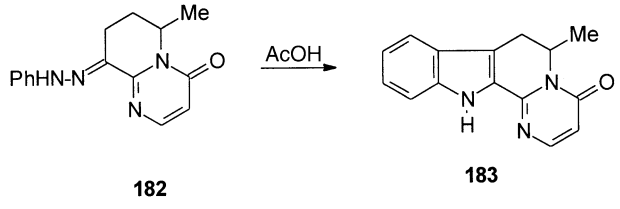
Scheme 69.



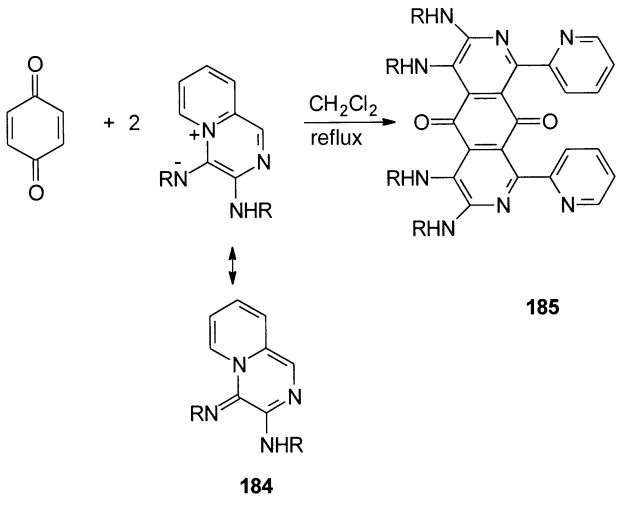
Scheme 70.

The 7,12-dihydropyrimido[1′,2′:1,2]pyrido[3,4-*b*]indol-4(6*H*)-one **183** was prepared by Fischer indolisation of the arylhydrazone **182** (Scheme 71).[94]

The compounds **184** were reacted with 1,4-benzoquinone to afford the pyrido[4,3-*g*]isoquinolines **185** (Scheme 72).[95]



Scheme 71.

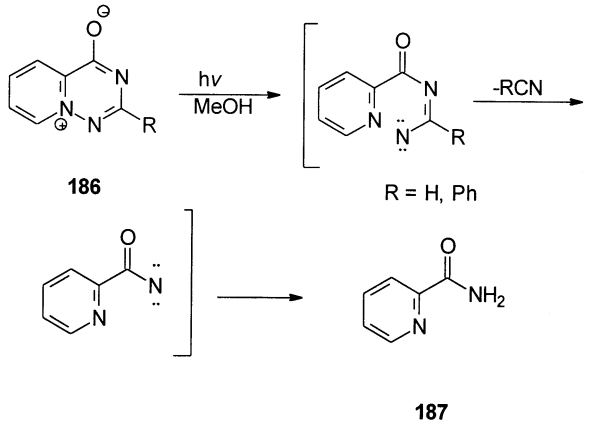


Scheme 72.

The compounds **186** were photolysed in methanol to give the acid amide **187** (Scheme 73).[96]

4. Conclusions

The present review has outlined the progress of synthetic routes to and some reactions of bicyclic pyridines containing a nitrogen ring-junction in the last ten years. The vast majority of these important compounds still require further exploration and application, especially as drugs, dyestuffs and light-screening agents in photographic emulsions.



Scheme 73.

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Biographical sketch

Wafaa Salama Hamama was born in Mansoura, Egypt. She graduated from Mansoura University where she carried out her MSc and PhD studies under the supervision of Professor H. H. Zoorob and was awarded the MSc and PhD in Chemistry from Faculty of Science, Mansoura University in 1978 and 1983, respectively. She was awarded Assistant Professor in 1988 then Professor in 2001 until now. She worked in Um-El Koura University in Saudi Arabia from 1990 to 1996. Her research focused on the development in the synthesis of heterocyclic organic compounds of different classes having pharmacological activity.

Hanafi H. Zoorob received his BSc and MSc from Faculty of Science, Cairo University. During his job as a research assistant at Chemotherapeutic Laboratory, National Research Centre, Cairo, he completed his PhD thesis in 1973 from the Faculty of Science, Ain Shams University, Cairo. In 1975 he joined the Staff members of the Chemistry Department at the Faculty of Science, Al-Mansoura University, Egypt, whereby, he was promoted to Assistant Professor in 1979 then to Professor in 1986 until now. He was awarded a postdoctoral fellowship in 1977 at Tokyo Institute of Technology (Japan) with Professor Noboru Yamazaki to work on asymmetric reduction using chirally modified reagents. In 1981 he joined Dr Robert K. Griffith's group as a postdoctoral fellow for two years at the College of Pharmacy, University of Michigan, Ann Arbor, USA. A part of Dr Griffith's programme was focussed on preparation of some histamine analogues as potential inhibitors for diamine oxidase. His research topics include study and development of new methods and synthetic approaches to organic compounds and intermediates of synthetic importance. He is currently conducting research in the synthesis of heterocyclic molecules of anticipated biological applications.