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Recent application of isocyanides in synthesis of heterocycles

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1. Introduction

The chemistry of heterocyclic compounds has attracted much attention in recent times due to its increasing importance in the field of pharmaceuticals and industrial chemicals. In fact, the development of simple, elegant and facile methodologies for the synthesis of heterocycles is one of the most important aspects in organic synthesis. Multicomponent reactions (MCRs), reactions involving at least three starting materials in a one-pot reaction, remain the most efficient method of synthesis of heterocycles.[1] Isocyanide-based multicomponent reactions (IMCRs), such as the Passerini and the Ugi reactions, are very useful for the diversity-oriented synthesis of collections of compounds. They allow a dramatic increase of structural complexity in just one step, introducing at the same time three or more diversity inputs with a high degree of atom economy.[2]

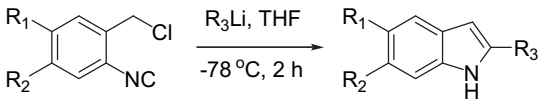
The outstanding position of IMCRs can be traced back to the exceptional reactivity of the functional group of the isocyanide. No other functional group reacts with nucleophiles and electrophiles at the same atom, leading to the so-called R-adduct. Other functional groups typically react at different atoms with nucleophiles and electrophiles. Moreover, there is virtually no restriction on the nature of the nucleophiles and electrophiles in IMCRs. Other major primary reaction pathways of isocyanides are radical reactions, R-acidity, and an intrinsically high affinity towards metallorganic reagents and their subsequent reactions.[3] Developments in isocyanide-based multicomponent reactions in applied chemistry have been extensively reviewed by Domling recently.[3] In the following sections, we wish to update some recent advances in application of isocyanide in the synthesis of heterocycles.

2. Five-member heterocycles with one heteroatom

2.1. Five-member nitrogen-containing heterocycles with one heteroatom

2.1.1. Indoles. The reaction of 2-(chloromethyl)phenyl isocyanides **1**, readily available by dehydration of the respective *N*-[2-(chloromethyl)phenyl]formamides, with organolithiums produced 2-substituted indoles **2** in satisfactory yields through the addition of organolithiums to the isocyano carbon followed by an intramolecular substitution reaction of the resulting imidoyl anion intermediates (Scheme 1).[4]

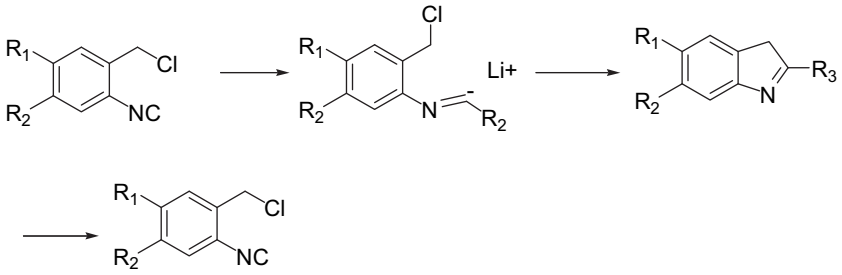
The formation of 2-substituted indoles **2** is induced by attack of the organolithium at the isocyano carbon of 2-(chloromethyl) phenyl isocyanides **1** to generate the imidoyl anion intermediate. This intermediate undergoes an intramolecular S_N2 reaction to give the indolenine intermediate, which, in all probability, tautomerised during workup and/or purification procedures to afford **2** (Scheme 2).



1 **2,** 49-74%

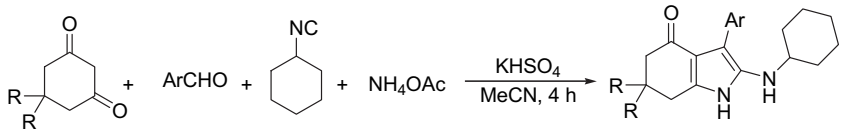
R_1 = H, Me
R_2 = H, Cl
R_3 = 3-ClC_6H_4, 4-ClC_6H_4, Ph, 3-$MeOC_6H_4$, *p*-Tol, *o*-Tol, *m*-Tol, n-Bu, 1-Naphthyl, *t*-Bu

Scheme 1.



Scheme 2.

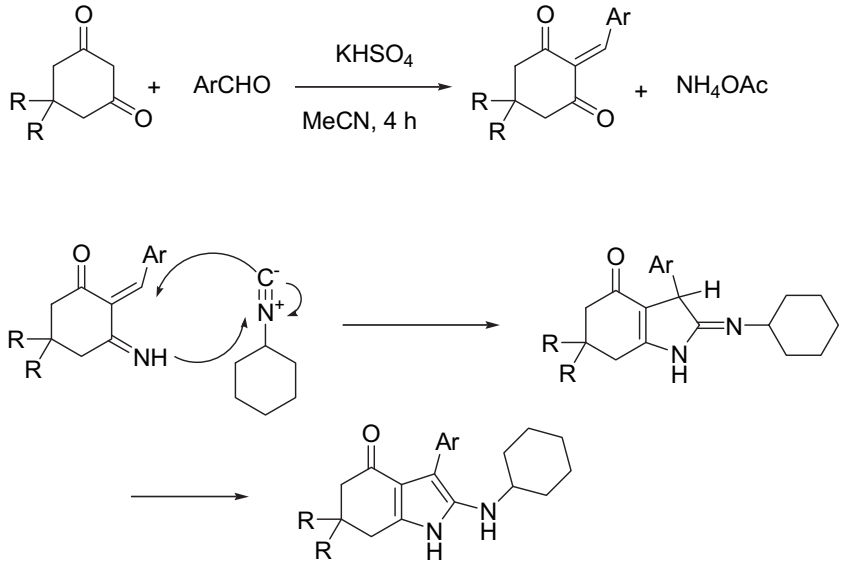
A simple and efficient synthesis of 2-(cyclohexylamino)-6,7-dihydro-3-aryl-1*H*-indole-4(5*H*)-ones **7** was achieved via a one-pot-multicomponent reaction of cyclohexyl isocyanide **5**, an aldehyde **4**, a 1,3-dicarbonyl compound **3** and ammonium acetate **6** in the presence of a catalytic amount of $KHSO_4$ in acetonitrile (Scheme 3).[5]



Scheme 3.

As shown in Scheme 4, the first step of this reaction may involve adduct formation by condensation of the 1,3-cyclohexanedione with the aromatic aldehyde, followed by attack of ammonium acetate to give the intermediate 2-benzylidene-3-imino-cyclohexanone. Reaction of cyclohexyl isocyanide with this intermediate then gives the desired product (Scheme 4).

heterodiene by standard Knoevenagel condensation of the aldehyde **9** and 3-cyanoacetyl indole **8**, followed by a [1+4] cycloaddition reaction or a Michael-type addition reaction with isocyanide **10** to afford an iminolactone, which was then isomerised to yield the 3-(2-furanyl)indoles **11** (Scheme 6).



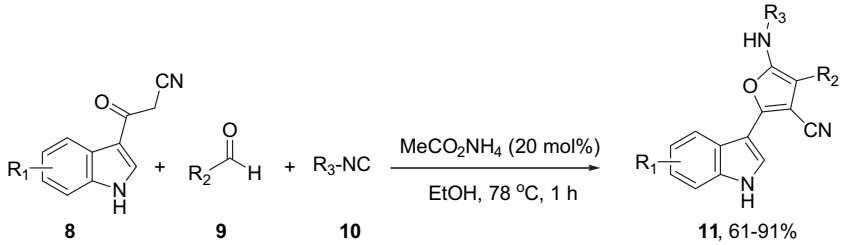
Scheme 4.

3-(2-Furanyl)indoles **11** were synthesised in a one-pot procedure by the reaction of a 3-cyanoacetyl indole **8**, aromatic aldehydes **9** and isocyanides **10** in ethanol in the presence of ammonium acetate (Scheme 5).[6]

The formation of these heterocycles can be rationalised by the initial formation of a conjugated electron-deficient

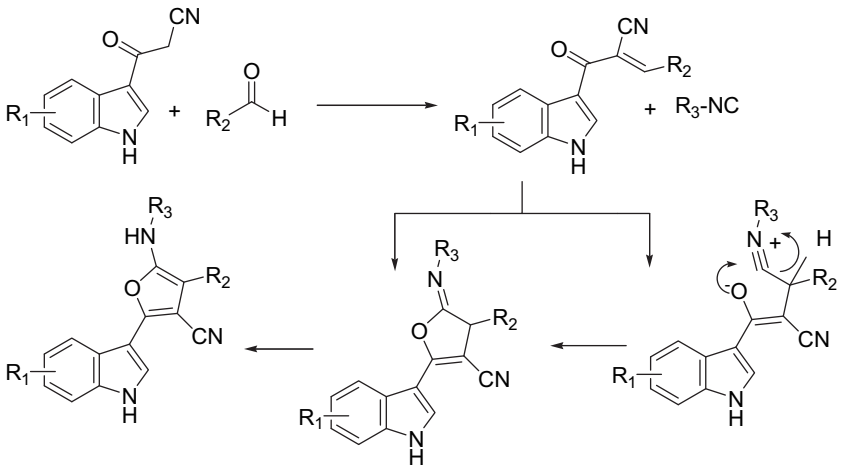
3-Oxoisoindoline-1-carboxamides **16** were efficiently prepared by the reaction of aldehydes **12**, an acid **13**, 4-methoxybenzylamine **14** and isonitriles **15** (Scheme 7).[7]

The one-pot Ugi four-component reaction (U-4CR) and intramolecular O-alkylation sequence starting from 2-aminophenols **17** in combination with α-bromoalkanoic acid **19**, aldehyde **18** and

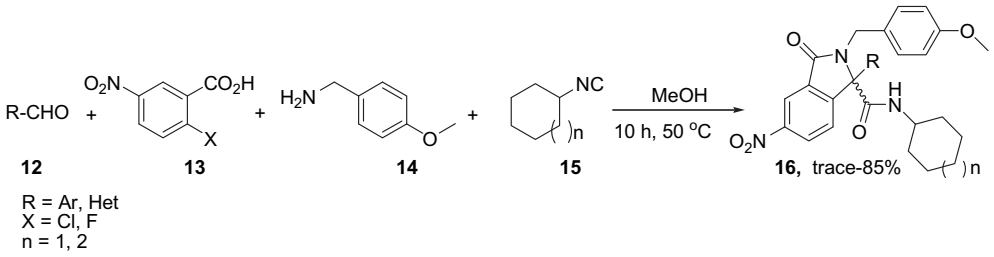


R1 = H, 1-Me,7-Me
R2 = 4-ClC6H4, 3-NO2C6H4, 4-NO2C6H4, 4-MeC6H4, 4-FC6H4, 4-BrC6H4, 2-Pyr
R3 = t-Bu, Cy

Scheme 5.



Scheme 6.



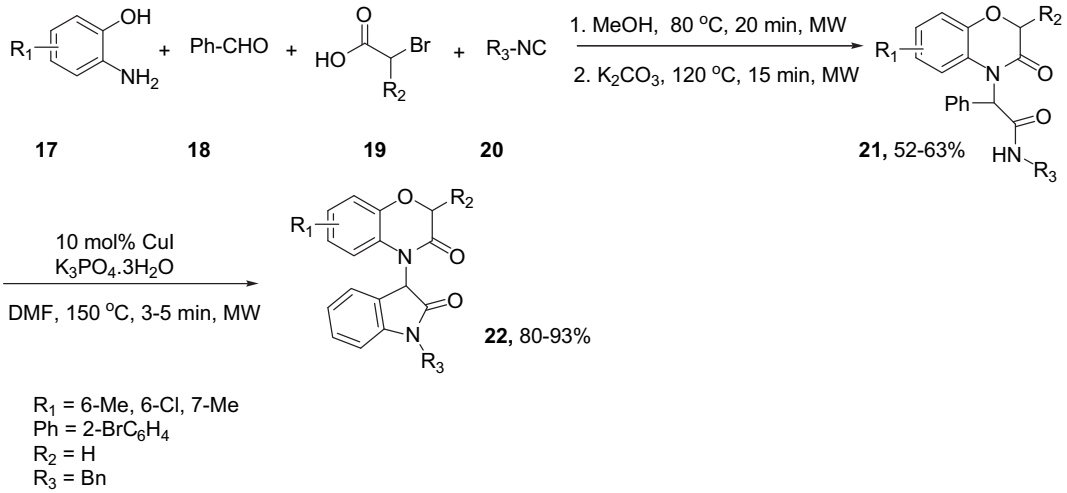
Scheme 7.

isocyanide **20** under controlled microwave heating has been established for a rapid access to highly functionalised 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines **21**. With appropriate substitutions on the 1,4-benzoxazines, a microwave-assisted Cu-catalysed intramolecular amidation was performed to furnish a novel class of heterocyclic conjugates of 1,4-benzoxazines with a 2-oxindole linked through a C–N single bond **22** (Scheme 8).[8]

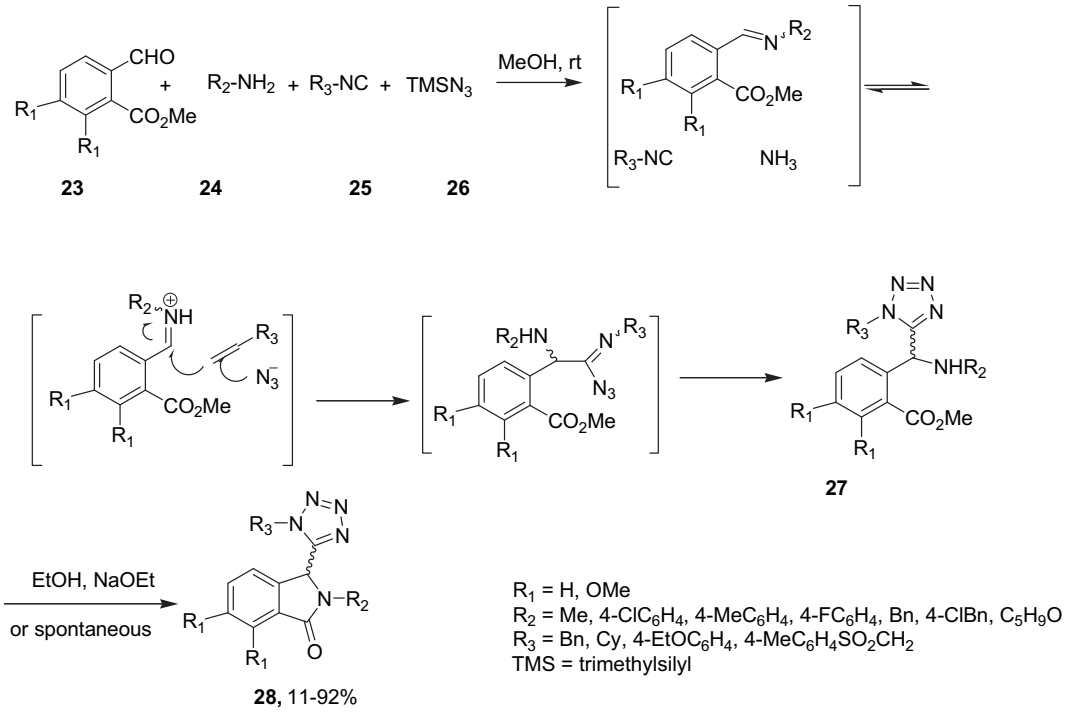
The Ugi four-component condensation between methyl *o*-formylbenzoates **23**, anilines **24**, isocyanides **25** and trimethylsilyl azide **26** afforded the expected Ugi adducts **27**, which were cyclised to the compounds **28** upon treatment with sodium ethoxide in ethanol (Scheme 9).[9]

The reaction between imines **29** and isocyanides catalysed by triflyl phosphoramide forms both 3-aminoindoles **30** and substituted indoxyls **31** (Scheme 10).[10]

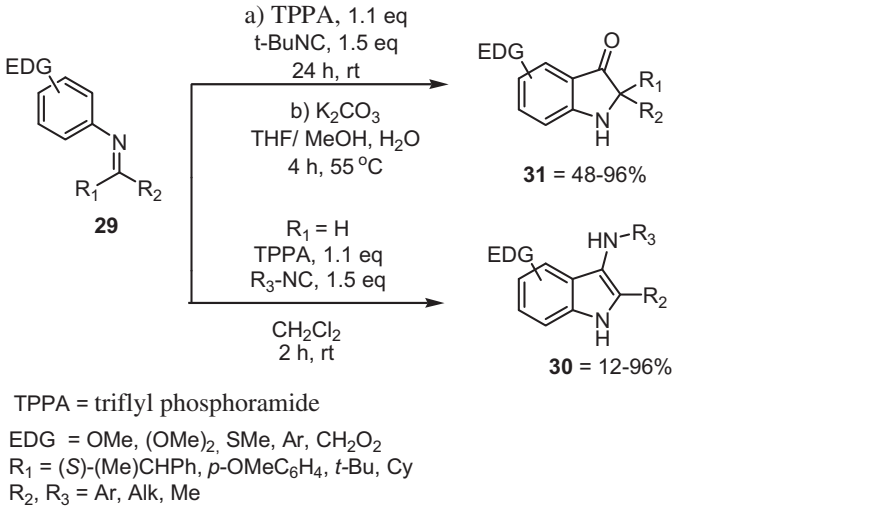
In practice, such a transformation might be accomplished by replacing the carboxylic acid component of the Ugi reaction with a Lewis acid or a strong Brénsted acid and employing an aniline



Scheme 8.



Scheme 9.



Scheme 10.

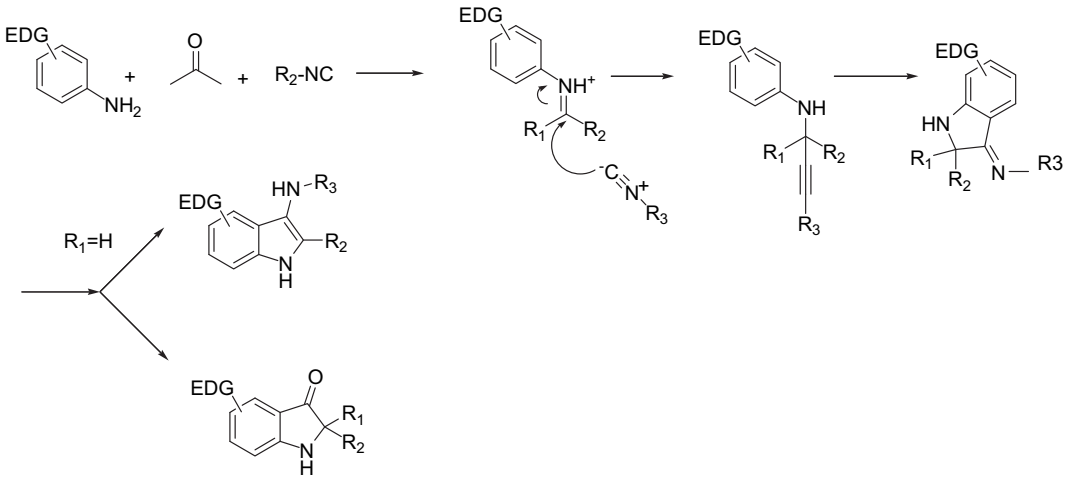
as the amine component. In the absence of a nucleophilic counterion in the reaction mixture, the α-amino nitrilium ion would be free to react selectively with the pendant nucleophilic p system. In the case of aldimines, the resultant cyclised imines could tautomerise to form 3-aminoindoles. The analogous ketimine-derived intermediates could lead to the production of indoxyls after hydrolysis of the initially formed bicyclic imine (Scheme 11).

Drug-like 2,3-dihydropyrazino[1,2-*a*]indole-1,4-diones **36** were synthesised from 1*H*-indole-2-carboxylic acids **32**, ethyl pyruvate **35**, isocyanides **34** and primary amines **33** via a one-pot, two-step procedure involving a Ugi reaction and a post-Ugi microwave-assisted cyclisation (Scheme 12).[11]

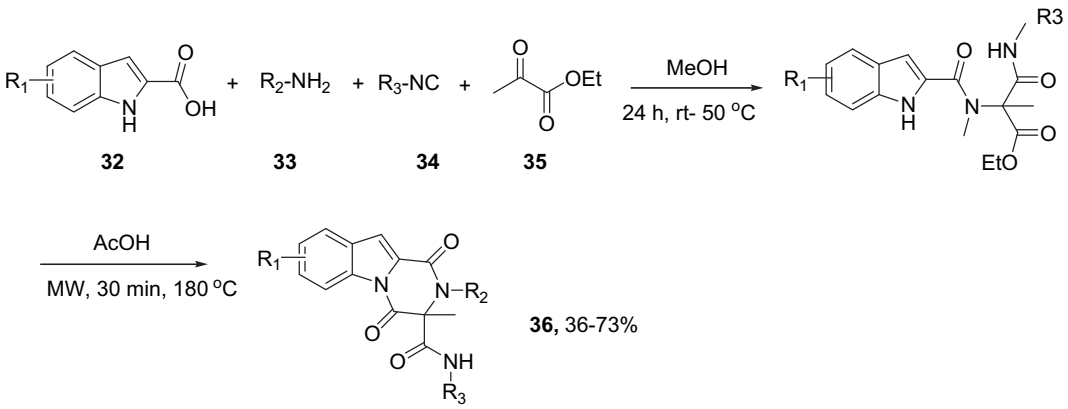
The reaction of *N*-allylamine **39**, iodinated heterocyclic phenol derivatives, such as hydroxy-pyridines and -pyrimidines **40**, isocyanides **38** and aldehydes **37** led to the synthesis of **41**, which were transformed into indole scaffolds **42** in the presence of palladium catalyst (Scheme 13).[12]

A one-pot solution-phase procedure for highly substituted indol-2-ones **47** using a combination of Ugi and Heck reactions (reaction of anilines **43**, aldehydes **44**, acrylic acids **45** and isocyanides **46**) has been reported (Scheme 14).[13]

A novel one-pot two-step multicomponent reaction of acrylic aldehydes **49**, bromoanilines **48**, acids, such as **50** and isocyanides **51** yielding polysubstituted indoles **52** and **53** has been described. The reaction was based on the combination of an Ugi

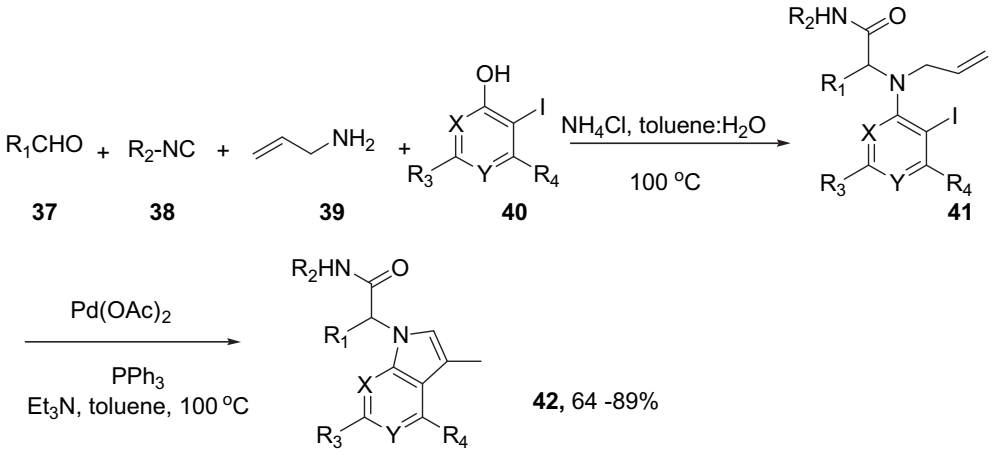


Scheme 11.



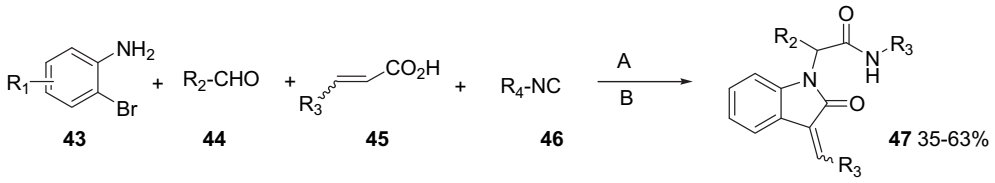
R_1 = 5-Cl, H, 6-OMe
R_2 = Bn, Ph, 4-iPrC$_6$H$_4$, 2,5-Me$_2$C$_6$H$_4$, 3,4-Me$_2$C$_6$H$_4$, 3-MeSC$_6$H$_4$, 2-MeBn, , 4-MeBn, 2,3-Me$_2$C$_6$H$_4$
R_3 = Bn, Cy, MeOCH$_2$CH$_2$, 3-FC$_6$H$_4$CH$_2$, 4-FC$_6$H$_4$CH$_2$, 4-MeC$_6$H$_4$CH$_2$, C$_5$H$_9$

Scheme 12.



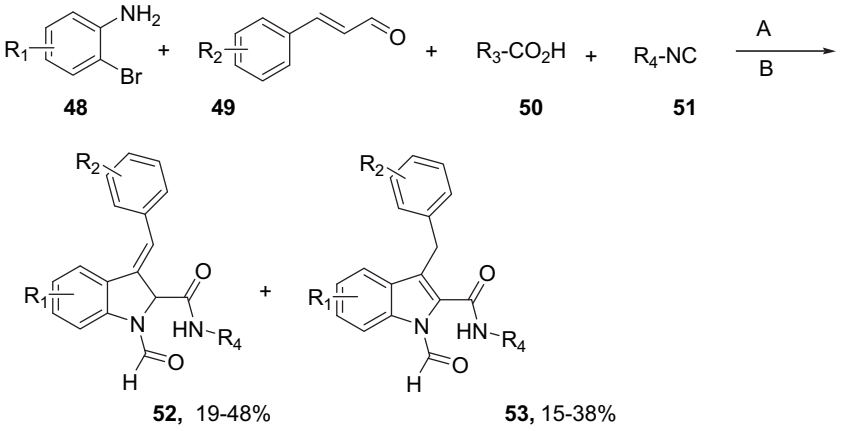
R_1 = *i*-Bu, Et
R_2 = Bn, Cy, *p*-ClBn
R_3 = Me,H, *i*-Pr
R_4 = H, Me
Y = N, CHNO$_2$
X = N, CHCl

Scheme 13.



A = trifluorethanol, 24 h, 50 °C
B = MeCN, $Pd(OAc)_2$, PPh_3, 16 -24 h, 80 °C
R_1 = H, NO_2
R_2 = H, Ph, $CH(Me)_2$
R_3 = Ph, Me, 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 2-$CF_3C_6H_4$, 2,4-$OMe_2C_6H_3$
R_4 = Bn, t-Bu, CH_2-CO_2Me

Scheme 14.



A = 2,2,2-trifluoroethanol, 1–3 d, rt
B = MeCN, $Pd(OAc)_2$, PPh_3, 16 -24 h, 80 °C
R_1 = H, 4-F
R_2 = H, 4-OMe
R_3 = H
R_4 = Bn, t-Bu, CH_2-CO_2Me,1-cyclohexen-1-yl, 4-phenyl-1-cyclohexen-1-yl

Scheme 15.

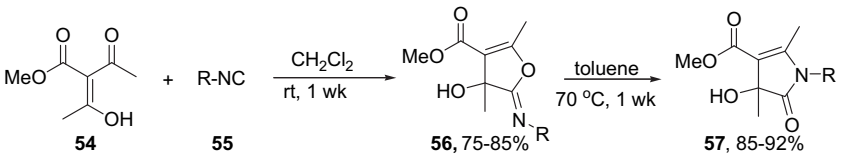
four-component reaction followed by an intramolecular Heck reaction. The simultaneous use of formic acid and cinnamaldehydes afforded the in situ generation of 1*H*-indoles. Convertible isocyanides can also be used with success in this Ugi/Heck strategy and enable the synthesis of 1*H*-indole-2-carboxylic acid building blocks (Scheme 15).[14]

2.1.2. Pyrroles. Novel 3-hydroxy-2*H*-iminolactones **56** and 3-hydroxy-2*H*-pyrrol-2-ones **57** were obtained via one-pot reactions between methyl 2-acetylacetoacetate **54** and isocyanides **55**. This reaction was performed under neutral conditions and starting materials and reagent reacted without any prior activation (Scheme 16).[15]

The proposed mechanism is shown in Scheme 17.

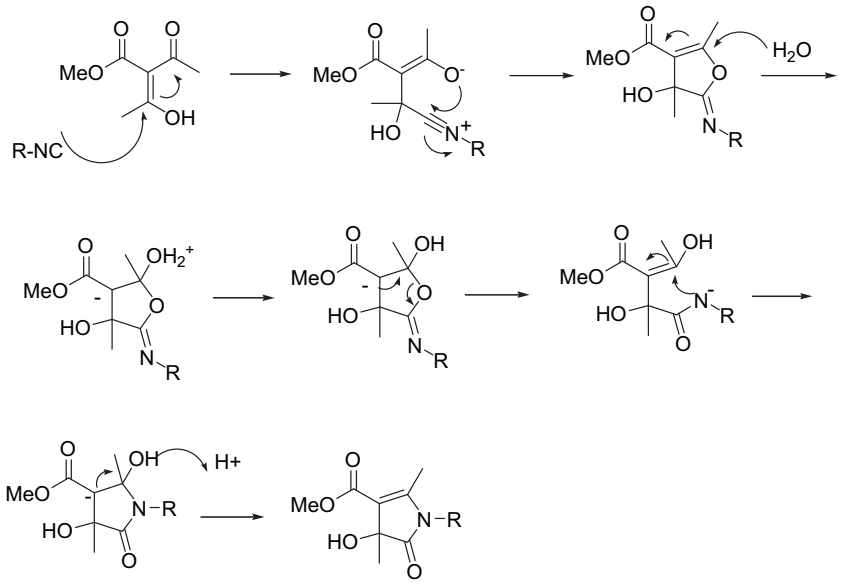
Heating a mixture of a 1,3-diaryl-2-propen-1-one **58** and an isocyanide **59** under solvent-free conditions produced 5-hydroxy-3,5-diaryl-1,5-dihydro-2*H*-pyrrol-2-ones **60** in good- to -excellent yields (Scheme 18).[16]

It is reasonable to assume that initial [4+1] cycloaddition of the α,β-unsaturated ketone and the isocyanide gives an iminolactone intermediate, which tautomerises to a 2-aminofuran. The

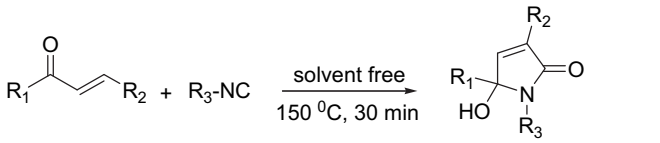


R = Cy, Bn, *t*-Bu, CH_2CO_2Et

Scheme 16.



Scheme 17.



58 **59** **60,** 85-97%

R_1 = Ph, 4-MeC_6H_4
R_2 = Ph, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 3-MeC_6H_4
R_3 =Cy, 1,1,3,3-tetramethylbutyl

Scheme 18.

readily oxidisable 2-aminofuran may combine with triplet oxygen to form a hydroperoxide, which is cyclised to an ozonide intermediate. The ozonide fragments to an open form, which cyclises rapidly to the hydroperoxide. The hydroperoxide disproportionates under the reaction conditions to afford the stable hydroxyamide (Scheme 19).

5-Hydroxy-2*H*-pyrrol-2-one derivatives **64** were synthesised from the reaction of isocyanide **61** with various aldehydes **62** and 1,3-dicarbonyl compounds **63** in the presence of piperidine as catalyst. 5-Hydroxy-2*H*-pyrrol-2-one derivatives **64** could also be achieved from the reaction of an olefin and the isocyanide (Scheme 20).[17]

The product of the reaction of alkyl(aryl) isocyanides **65** with dialkyl acetylenedicarboxylates **66** has been trapped by benzoyl chlorides **67** or **68** to yield functionalised 2,5-dihydro-1*H*-pyrroles **69** or **70**. The presence of electron-withdrawing groups at the *para* position of benzoyl chloride leads to tetrasubstituted furans (Scheme 21).[18]

A plausible rationalisation may be advanced to explain the product formation. Presumably, the zwitterionic intermediate formed from isocyanides and dialkyl acetylenedicarboxylates is attacked by benzoyl chloride to furnish a new intermediate, which is converted into another intermediate. This intermediate can lose chloride ion to generate the stabilized cation, which absorbs H_2O (presumably from moisture). This intermediate is converted into **69** via the chain opening (Scheme 22). When X=NO_2 or Cl, however, Cl^+ ion is eliminated. Nucleophilic attack of H_2O on this intermediate leads to 70 (Scheme 22).

[4+1] Cycloaddition of α,β-unsaturated imidoyl cyanides (2-cyano-1-azadienes) **74** synthesised from the reaction of α,β-unsaturated aldehydes, **71**, amines **72** and TMSCN **73** with isocyanides in the presence of a catalytic amount of $AlCl_3$ afforded polysubstituted 2-amino-5-cyanopyrroles **75** in good- to -excellent yields (Scheme 23).[19]

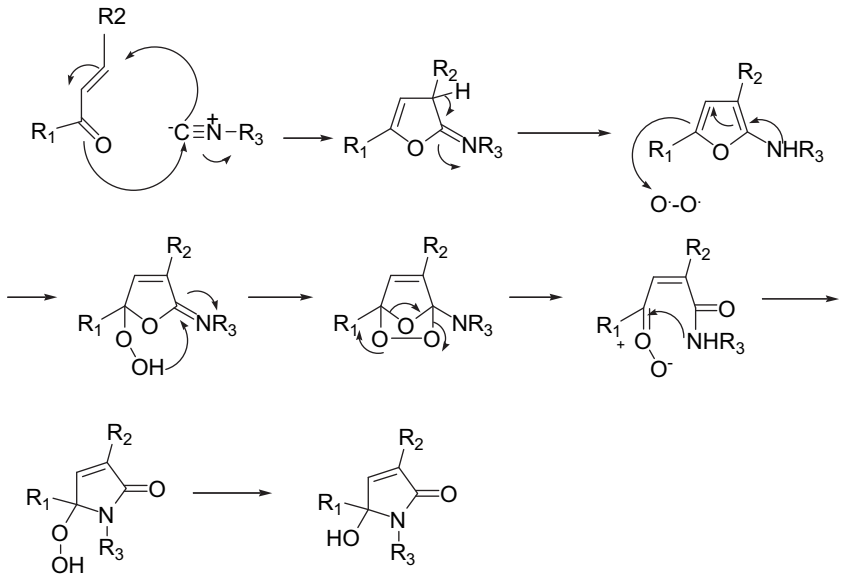
2.1.3. Lactams. Reaction of amines **76**, levulinic acid or 4-acetylbutyric acid **78** and isocyanides **77** led to the synthesis of 4-aminoquinoline γ- and δ-lactams, **79** (Scheme 24).[20]

Various aldehydes **80** and isocyanides **81** behaved similarly with allylamine **39** and chloroacetic acid **82** to give the corresponding Ugi-xanthate adducts **83**, which underwent 5-*exo*-*trig* cyclisations to furnish pyrrolidinones **84** in good yields (Scheme 25).[21]

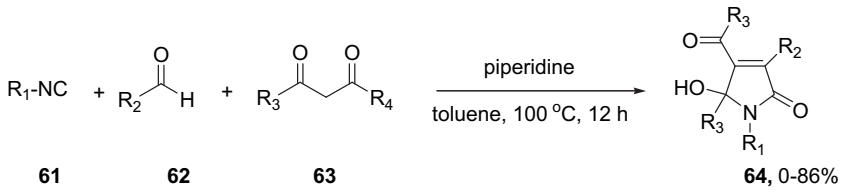
2.1.4. Prolines. Reaction of 2-substituted cyclic imines **85**, carboxylic acids **86** and isocyanides **87** at room temperature led to the synthesis of the corresponding substituted proline and homoproline derivatives **88** (Scheme 26).[22]

2.2. Five-member oxygen-containing heterocycles with one heteroatom

2.2.1. Furans. Water was reported as novel reaction medium for the synthesis of highly functionalised 2-aminofuran derivatives **92** via the coupling of aldehydes **89** with dimethyl acetylenedicarboxylate **90** and cyclohexyl isocyanide **91** (Scheme 27).[23]

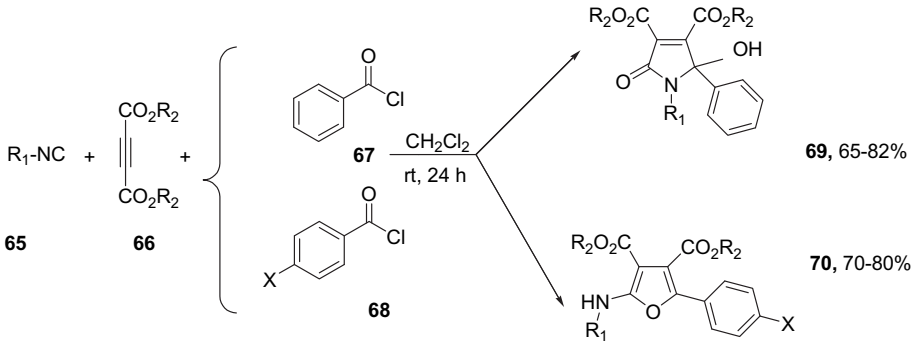


Scheme 19.



R_1 = Cy
R_2 = Ph, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-MeC_6H_4, 2-ClC_6H_4, 3-BrC_6H_4 , Et, i-Pr, n-Pr, $Me(CH_2)_4CH_2$, $(CH_3)_2CH$, n-Hex
R_3 = Me, Ph, CN, OEt,
R_4 = Me, OEt, OMe, Ph

Scheme 20.

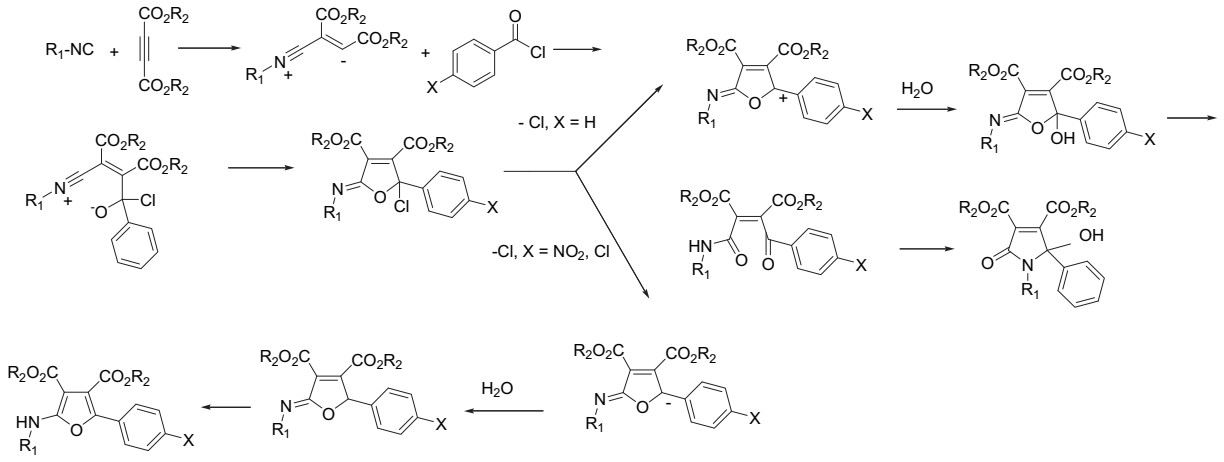


R_1 = Cy, 2,6-di-MeC_6H_3, 1,1,3,3-tetramethylbutyl, *t*-Bu
R_2 = Me, Et, *t*-Bu
X = Cl, NO_2

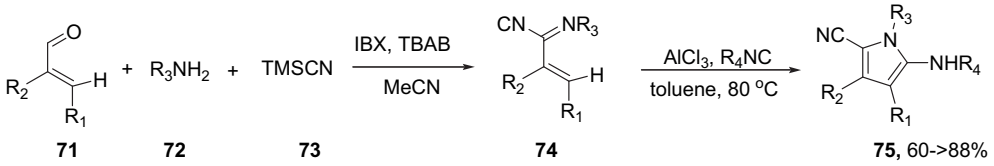
Scheme 21.

The regioselective three-component condensation reaction of 2-hydroxy-1,4-naphthoquinone **93** with isocyanides **95** in the presence of a variety of aldehydes **94** offered an easy one-pot access to linear naphtho[2,3-*b*]furan-4,9-dione derivatives **96** (Scheme 28).[24]

The reaction between alkyl(aryl) isocyanides **97** and dibenzoylacetylenes **98** in the presence of ethyl bromopyruvate **99** leads to the synthesis of functionalised 5-imino-2,5-dihydro-furans **100** (Scheme 29).[25]

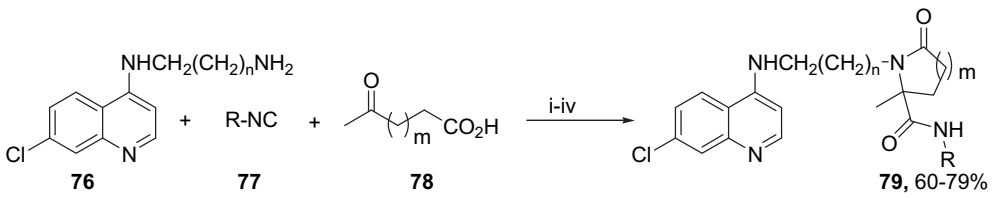


Scheme 22.



R_1 = Me, Ph
R_2 = H, Me
R_3 = CH_2-CH_2Ph, C_3H_4, CH_2-CH_2(4-NO_2)C_6H_4
R_4 = *t*-Bu, Bn, Cy, 2,6-di-MeC_6H_3

Scheme 23.



m = 1, 2
n = 1, 2, 3, 5
R = Cy, *t*-Bu
(i) MeOH, rt, 12–18 h; (ii) 1 h; (iii) filter, wash; (iv) 3% NH_3/MeOH.

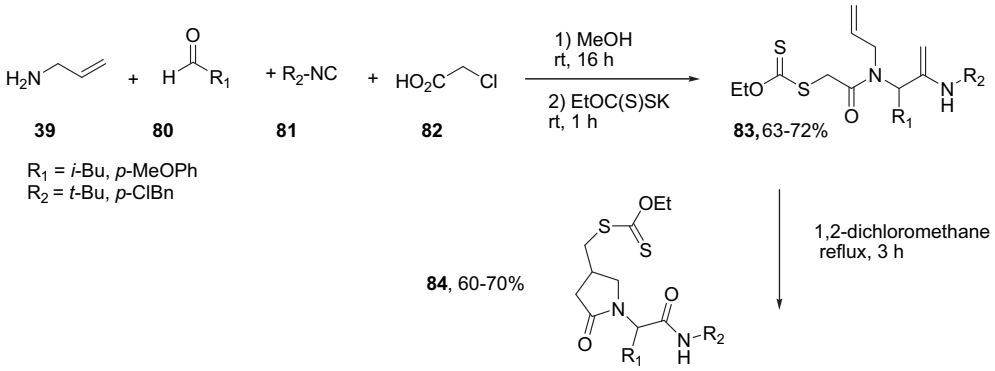
Scheme 24.

Mechanistically, it is conceivable that the reaction involves the initial formation of a 1,3-dipolar intermediate between **97** and **98**, which reacts with **99**. Cyclisation of this zwitterionic intermediate leads to **100** (Scheme 30).

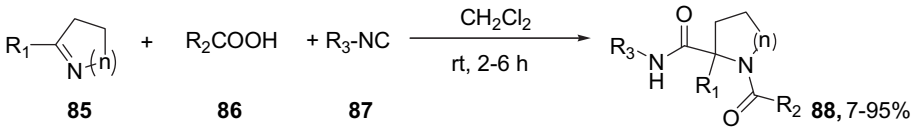
A new and efficient method for preparing electron-poor imides **105** and fully substituted furans **105** from triphenylphosphine, 1,1,3,3-tetramethylbutyl isocyanide **101**, dialkyl acetylenedicarboxylates **102** and benzoic acid **103** in neutral conditions has been reported (Scheme 31).[26]

The one-pot, three-component condensation reactions of 3-hydroxy-1*H*-phenalene-1-one **106** with various aldehydes **107** in the presence of isocyanides **108** proceeded rapidly in refluxing toluene and were completed after 20 h to afford 9-(alkyl or arylamino)-7*H*-phenaleno[1,2-*b*]furan-7-ones **109**, in good yields (Scheme 32).[27]

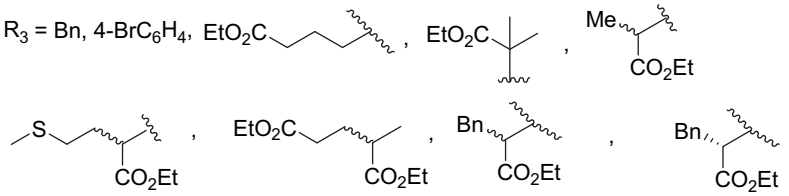
The mechanism envisages an initial acid–base reaction of activated CH-acid **106** with **108** to give an ion-pair complex. The conjugate base of the CH-acid is now sufficiently active for nucleophilic attack on **107** to produce an intermediate. The intermediate can lose a molecule of water to afford the Knoevenagel condensation adduct. This is presumably followed by a [4+1] cycloaddition reaction or Michael-type conjugate addition of isocyanide with concomitant cyclisation to give an iminolactone intermediate. The subsequent isomerization of the iminolactone leads to the formation of **109** (Scheme 33).



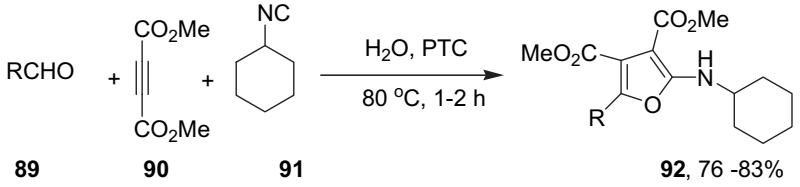
Scheme 25.



n = 1, 2
R_1 = Me, Bn, Bu, Ph, *t*-Bu, Cyclopentyl, *i*-Pr
R_2 = Me, Ph, CF_3, CCl_3, $CHCl_2$, CH_2Cl

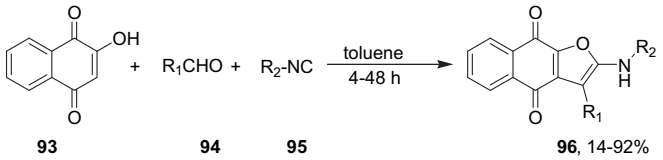


Scheme 26.



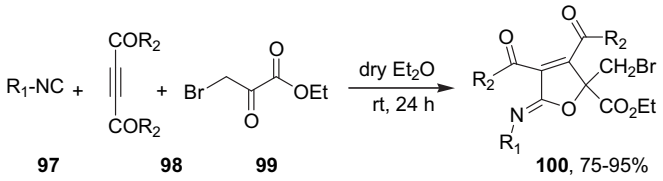
R = Ph, 4-ClC_6H_4, 2-ClC_6H_4, 2-$NO_2C_6H_4$, 3-BrC_6H_4, Cy, C_4H_3S, C_4H_3O, C_9H_{19}
PTC = benzyltriethylammonium chloride

Scheme 27.



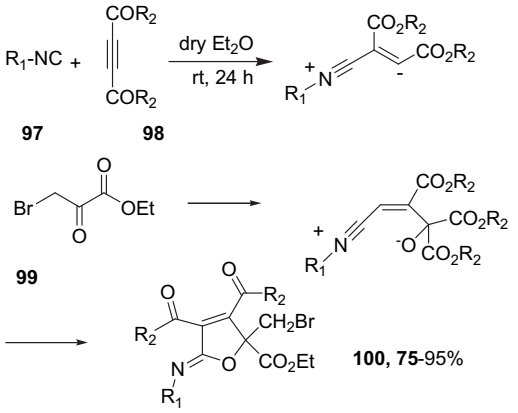
R_1 = Ar, Alk, Het
R_2 = Cy, *t*-Bu, 2,6-di-MeC_6H_3, $C_{10}H_7$, 1,1,3,3-tetramethylbutyl

Scheme 28.



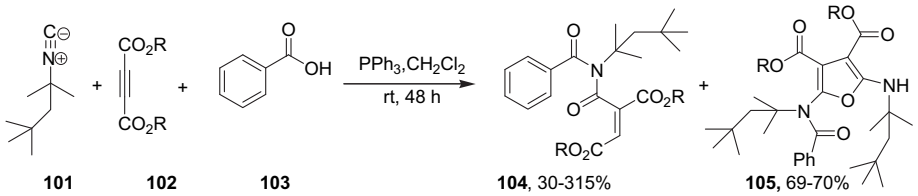
R_1 = Cy, *t*-Bu, Benz, 2,6-di-MeC_6H_3, 1,1,3,3-tetramethylbutyl, CH_2CO_2Et
R_2 = Ph, *p*-Tol

Scheme 29.

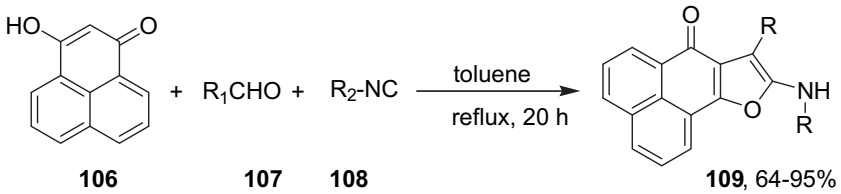


R_1 = Cy, *t*-Bu, Benz, 2,6-di-MeC_6H_3, 1,1,3,3-tetramethylbutyl, CH_2CO_2Et
R_2 = Ph, *p*-Tol

Scheme 30.

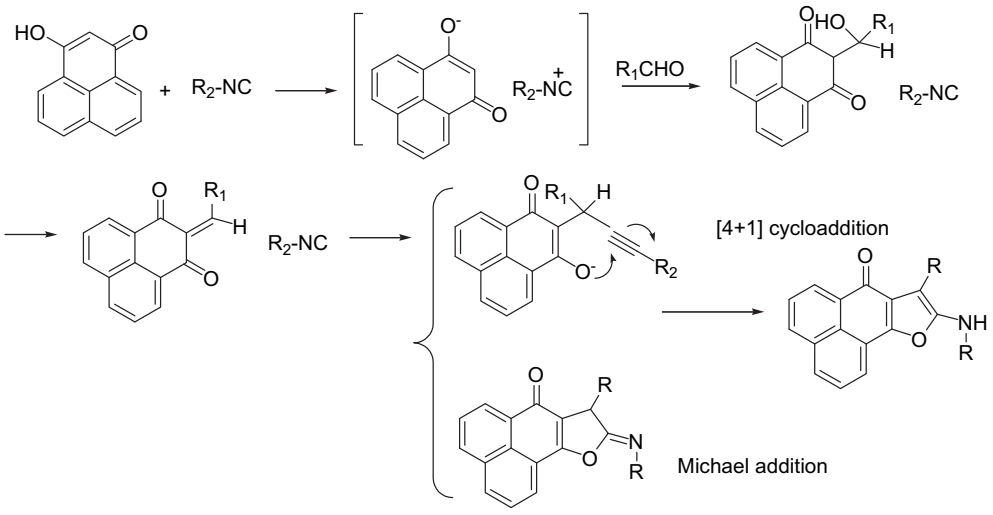


Scheme 31.



R_1 = Ar, Alk, Het
R_2 = Cy, *t*-Bu, 2,6-di-MeC_6H_3, $C_{10}H_7$, 1,1,3,3-tetramethylbutyl

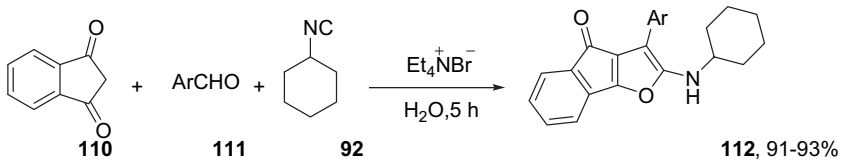
Scheme 32.



Scheme 33.

1,3-Indandione **110**, aldehydes **111**, and cyclohexyl isocyanide **92** underwent smooth coupling-cyclisation in water to produce the corresponding 2-(cyclohexylamino)-3-aryl-indeno[1,2-*b*] furan-4-ones **112** in good yields. Water was used as a solvent to avoid the use of other highly toxic and environmentally unfavourable solvents for this synthesis (Scheme 34).[28]

Although the mechanism of this reaction has not been established, a plausible rationalisation can be advanced to explain the product formation (Scheme 30). On the basis of the well-established chemistry of isocyanides, it is reasonable to assume that the zwitterionic intermediate produced by the reaction between the **130** and **131** adds to **132** or **133** resulting in the formation of new



Ar = Ph, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-BrC_6H_4

Scheme 34.

The first step involves the condensation reaction of 1,3-indandione with an aromatic aldehyde followed by a nucleophilic Michael addition of cyclohexyl isocyanide to this intermediate, which after an intramolecular rearrangement affords the desired heterocyclic product (Scheme 35).

Heating a mixture of an anthranilic acid **113**, a salicylaldehyde **114** and an isocyanide **115** in water afforded 2-[[2-(alkylimino)-1-benzofuran-3-yliden]amino]benzoic acids **116** in high yield (Scheme 36).[29]

The reaction of alkyl isocyanides **117** with dialkyl acetylenedicarboxylates **103** in the presence of pyridine-containing carbonyl compounds **118** or **119** led to the stable products **120** or **121** in excellent yields (Scheme 37).[30]

Reaction of dimethyl acetylenedicarboxylate **122** and isocyanides **123** with vicinal tricarbonyl systems **124**, **125** and **126** produced highly substituted furan or pyran derivatives **127**, **128** and **129** (Scheme 38).[31]

The zwitterion formed from an alkyl or aryl isocyanide **130** and a dialkyl acetylenedicarboxylate **131** reacted with acetic anhydride **132** or phthalic anhydride **133** to form 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylates or benzo-fused spirolactones **134** or **135** in relatively good yields at room temperature without using a catalyst (Scheme 39).[32]

intermediate, which undergoes cyclisation to deliver **134** or **135** (Scheme 40).

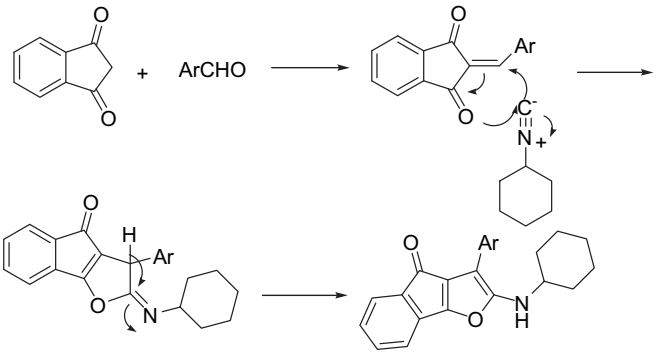
Reaction of an isocyanide with an iminium ion intermediate **138**, formed by the reaction between an electron-poor 2-hydroxybenzaldehyde derivative **137** and a secondary amine **136** in the presence of silica gel proceeds smoothly at room temperature to afford benzo[*b*]furan derivatives **139** in high yields (Scheme 41).[33]

Synthesis of highly functionalised 2-aminofuran derivatives **141** via the coupling of aldehydes **140** with dimethyl acetylenedicarboxylate **125** and cyclohexyl isocyanide **92** by microwave-assisted, continuous-flow organic synthesis has been developed (Scheme 42).[34]

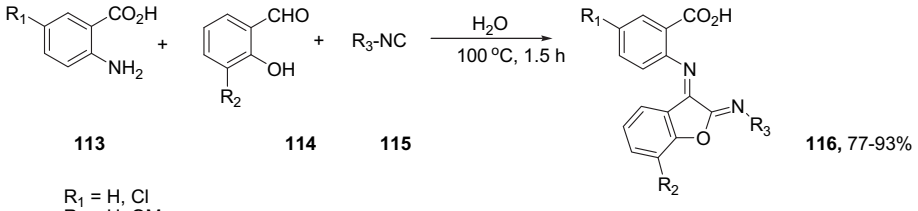
2.2.2. Lactones. The reaction between alkyl isocyanides **142** and phenanthraquinone **144** or aceanthraquinone **145** in the presence of dialkyl acetylenedicarboxylates **143** was found to afford γ-dispiroiminolactones **146** and **147** in high yields (Scheme 43).[35]

The formation of the products **146** or **147** could be rationalised as shown in Scheme 44.

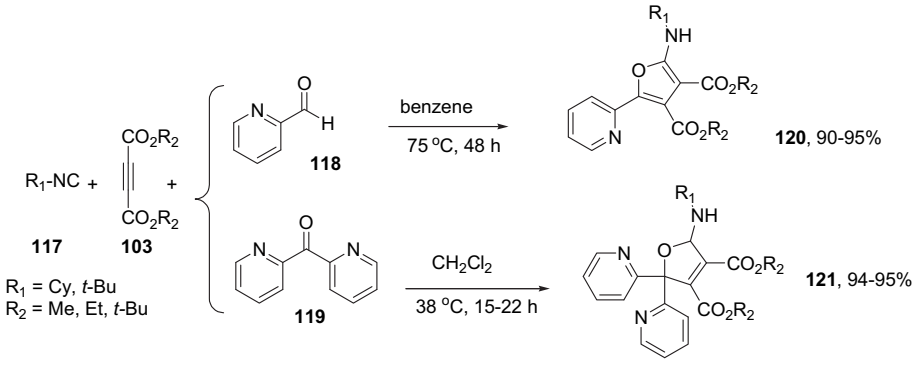
A three-component condensation reaction between an isocyanide **148**, an electron-deficient acetylenic ester **149** and 2-bromo-1-(4-bromophenyl)-ethanone **150** efficiently provided fully



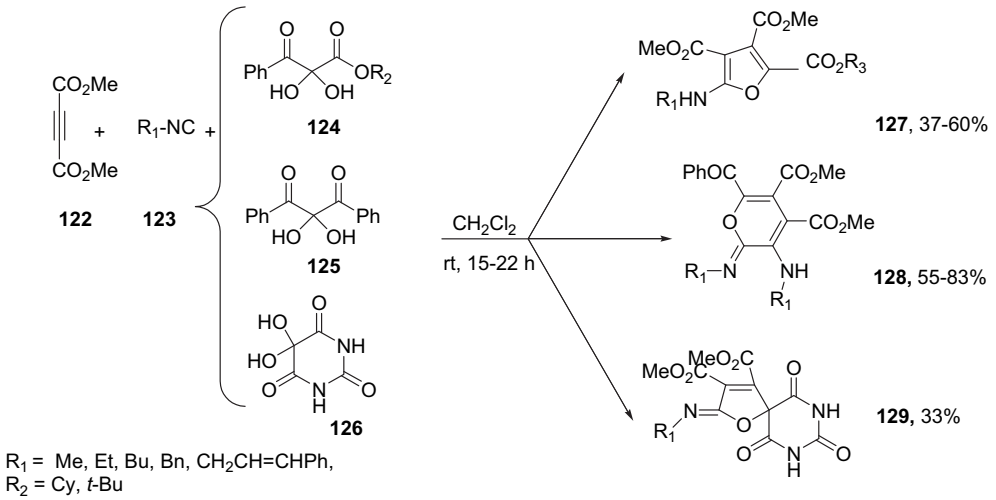
Scheme 35.



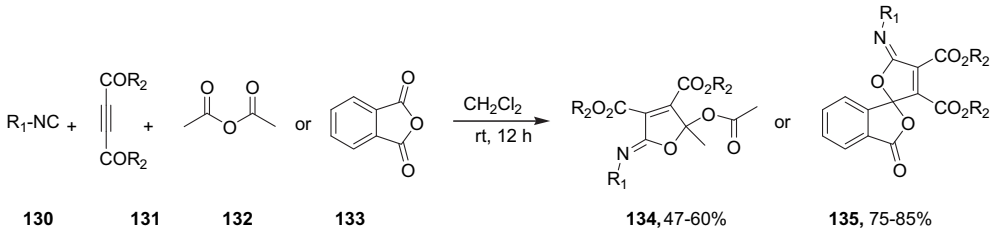
Scheme 36.



Scheme 37.



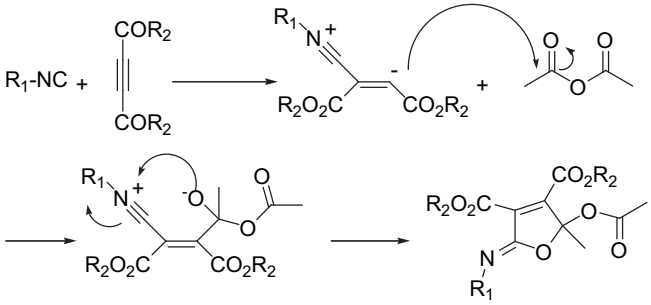
Scheme 38.



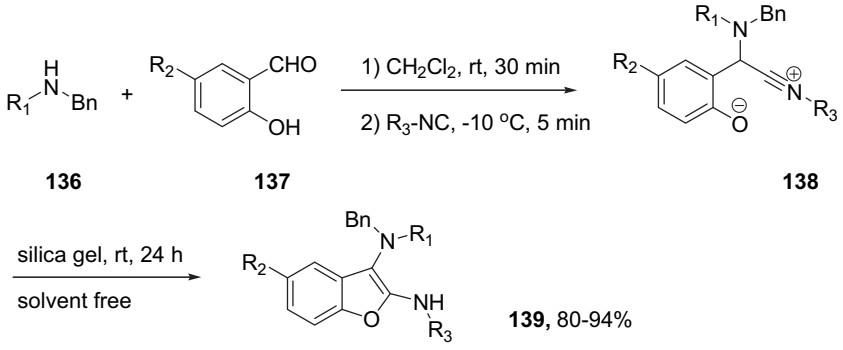
130 **131** **132** **133** **134,** 47-60% **135,** 75-85%

R_1 = Cy, t-Bu, 2,6-di-MeC_6H_3, 1,1,3,3-tetramethylbutyl
R_2 = Et, Me, t-Bu

Scheme 39.



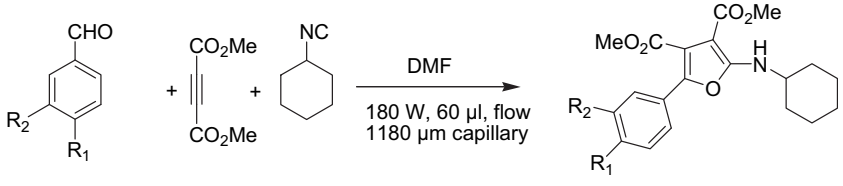
Scheme 40.



136 **137** **138** **139,** 80-94%

R_1 = Bn, Me
R_2 = NO_2, Br
R_3 = *t*-Bu, Cy, 1,1,3,3-tetramethylbutyl, Bn, 2,6-di-MeC_6H_3

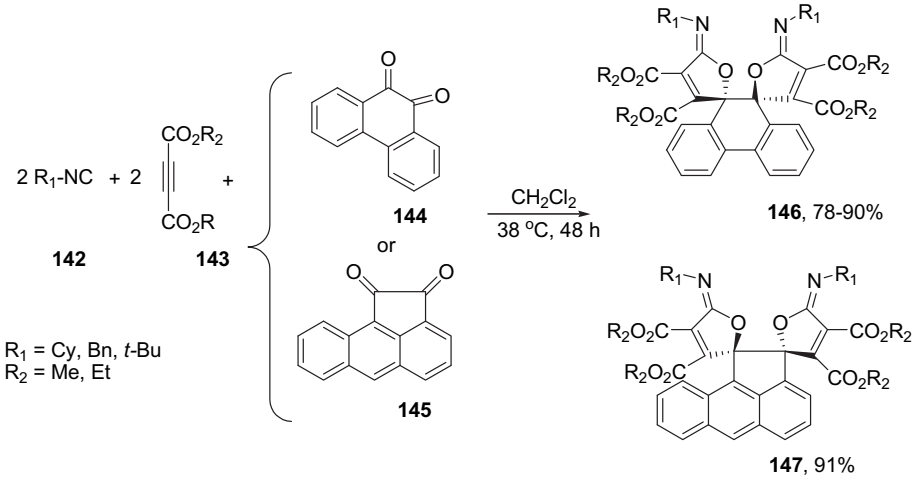
Scheme 41.



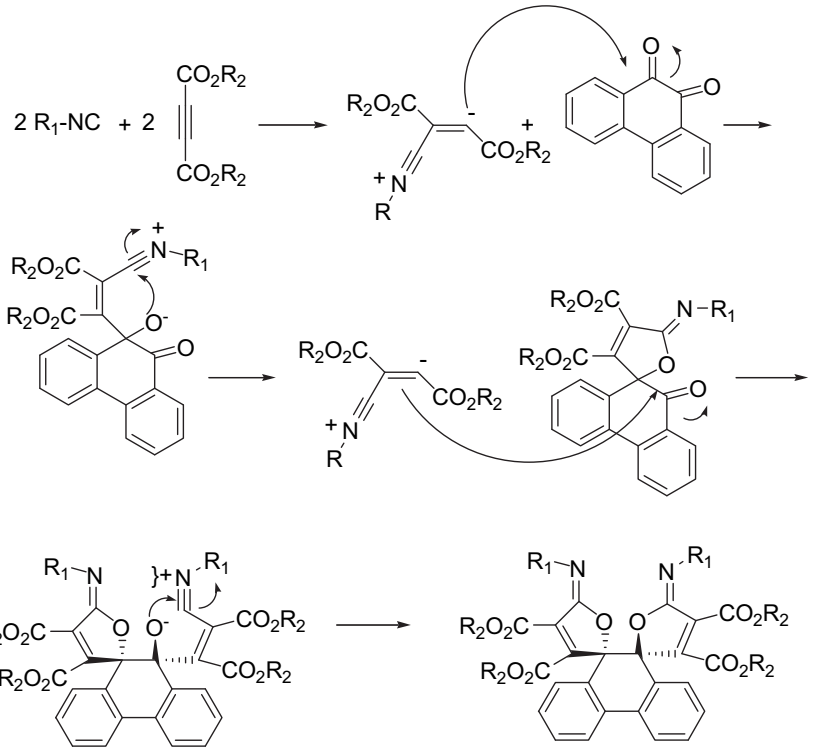
140 **125** **92** **141**, 39 -83%

R_1 = H, NO_2, Cl, OMe, F, CO_2Me, CF_3
R_2 = H, NO_2

Scheme 42.



Scheme 43.



Scheme 44.

substituted iminolactones **151** in high yields in a one-pot condensation reaction without any activation or modification (Scheme 45).[36]

Reaction of *tert*-butyl isocyanide **154** with dialkyl acetylenedicarboxylates **152** in the presence of 2-acetylbutyrolactone **153** led to the formation of dialkyl (*E*)-2-[(*tert*-butylamino)[2-oxo-4,5-dihydro-3(2*H*)-furanylidene]methyl]-2-butenedioates **155** (Scheme 46).[37]

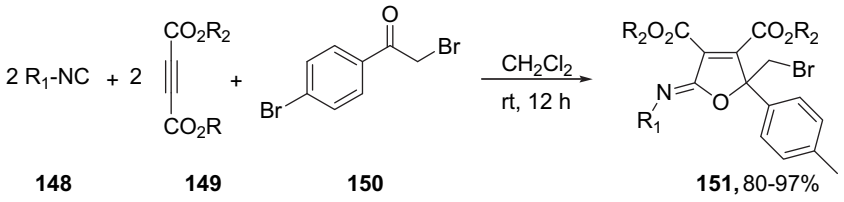
The highly reactive 1:1 adduct produced from the reaction between dialkyl acetylenedicarboxylates **157** and alkyl isocyanides **156** was trapped by benzoyl cyanide derivatives **158** to afford dialkyl 5-alkylimino-2-cyano-2-aryl-2,5-dihydro-3,4-furandicarboxylates **159** in fairly good yields (Scheme 47).[38]

3. Six-member heterocycles with one heteroatom

3.1. Six-member heterocycled with one nitrogen-containing heterocycles with one heteroatom

3.1.1. Quinolines. Treatment of 2-(pyrrol-1-yl)-benzaldehydes **160** with secondary amine hydrochloride/NaI/TMSCl/Et_3N in the presence of an isocyano compound **161** formed 4-alkyl(or aryl)amino-5-dialkylaminopyrrolo[1,2-*a*]quinolines **162** (Scheme 48).[39]

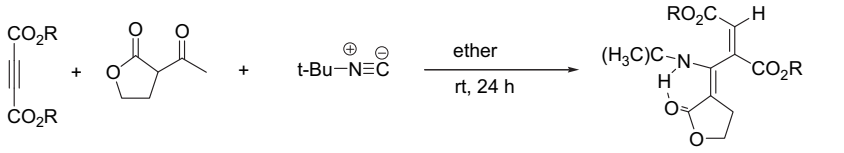
Intramolecular radical cyclisation of *o*-ethynylaryl isocyanides **163** mediated by ditelluride, under visible-light irradiation, afforded the corresponding bistellurated quinolines **164** (Scheme 49).[40]



148 **149** **150** **151,** 80-97%

R_1 = Cy, *t*-Bu
R_2 = Me, Et

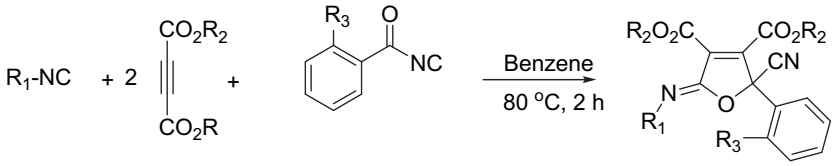
Scheme 45.



152 **153** **154** **155,** 62-67%

R = Me, Et, t-Bu

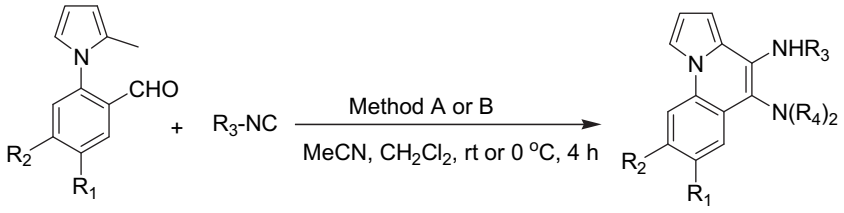
Scheme 46.



156 **157** **158** **159,** 62-91%

R_1 = Cy, *t*-Bu
R_2 = Me, Et
R_3 = H, Cl

Scheme 47.



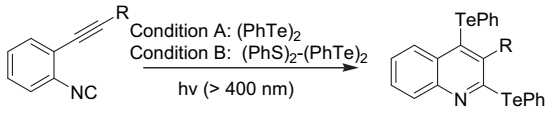
160 **161** **162**, 32-70%

Method A = $(R_4)_2NH^+H_2Cl^-$, NaI, Me_3SiCl, Et_3N
Method B = $(R_4)_2NH$, NaI, Me_3SiCl, Et_3N, $(Et)_3N^+HCl^-$

R_1 = H, OMe, Cl
R_2 = H, OMe
R_3= Ph, *t*-Bu, *o*-Tol
Amine = $HNMe_2$, $HNEt_2$, Pyrrolidine, Piperidine, Morpholine

Scheme 48.

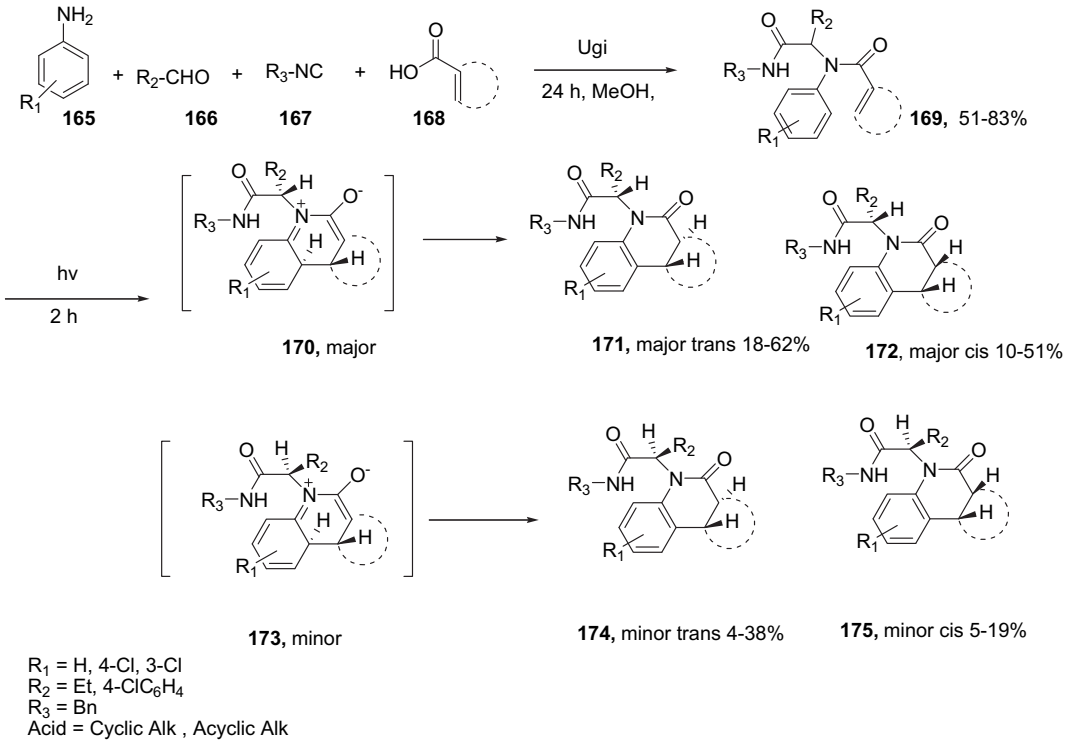
The Ugi reaction of **169**, **170**, **171** and **172** proceeds to give the adducts **173**, which were subjected to irradiation in protic and aprotic solvents using an immersion well reactor equipped with a quartz Pen-Ray 5.5 W, low-pressure, cold-cathode mercury lamp. The existence of a racemic chiral centre in the initial Ugi products **174** and **177** could potentially lead to the formation of four diastereomers of substituted 3,4-dihydroquinolin-2(1*H*)-ones (**175**, **176**, **178** and **179**) as racemic mixtures (Scheme 50).[41]



163 **164**, Condition A: 28-82%, Condition B: 30-88%

R = Ph, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-ClC_6H_4, 4-CNC_6H_4, 4-$NO_2C_6H_4$, Bn, *n*-Bu, C_6H_9

Scheme 49.



165 **166** **167** **168** **169,** 51-83%

170, major **171,** major trans 18-62% **172**, major cis 10-51%

173, minor **174,** minor trans 4-38% **175,** minor cis 5-19%

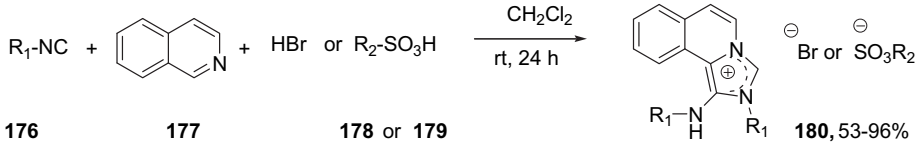
R_1 = H, 4-Cl, 3-Cl
R_2 = Et, 4-ClC_6H_4
R_3 = Bn
Acid = Cyclic Alk , Acyclic Alk

Scheme 50.

3.1.2. Isoquinolines. 1-Aminoimidazo[5,1-*a*]isoquinolinium salts **180** were synthesised from the reaction of various isocyanides **176** with isoquinoline **177** in the presence of HBr **178** or various sulfonic acids **179** (Scheme 51).[42]

of 2-formylbenzoic acid **185** and 2-aminopyridines **187** with isocyanides **186** has been developed (Scheme 53).[43]

A possible mechanism for this three-component reaction has been postulated. The reaction proceeds via an iminium species,



176 **177** **178** or **179** **180,** 53-96%

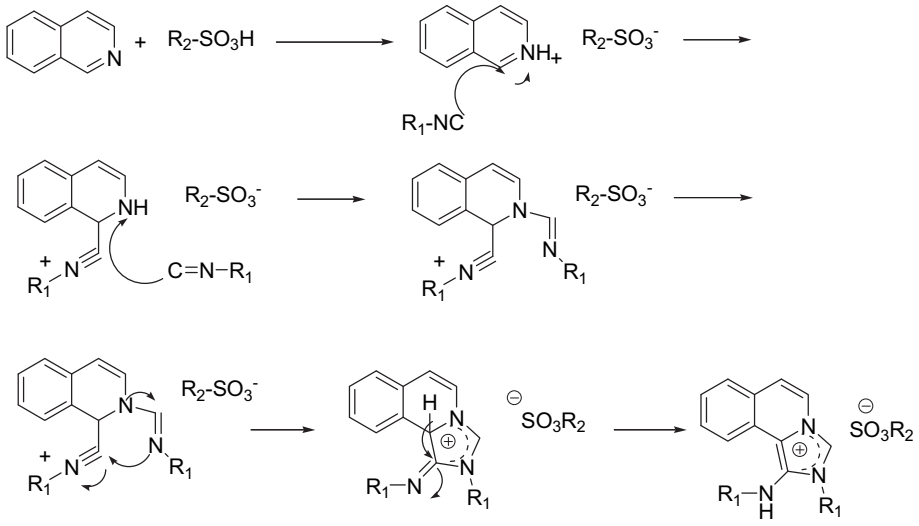
R_1 = Cy, *t*-Bu, 2,6-di-MeC_6H_3, 1,1,3,3-tetramethylbutyl
Sulfonic acid = *p*-Toluenesulfonic acid, Phenylsulfonic acid, Methanesulfonic acid, (-)-Camphorsulfonic acid

Scheme 51.

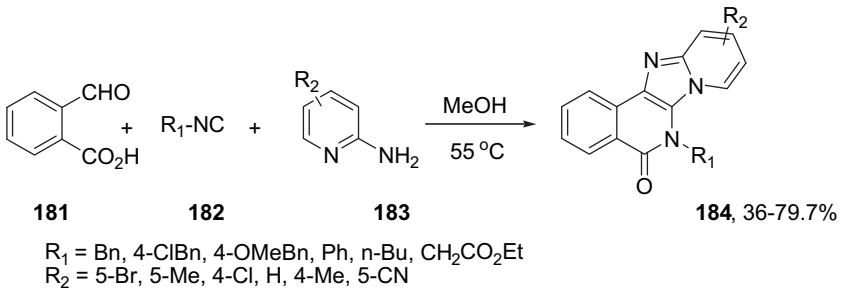
The first reaction step is protonation of isoquinoline with the sulfonic acid and the second is nucleophilic addition of isocyanide to the activated NH^+=CHα bond of isoquinolinium sulfonate (Scheme 52).

A convenient and efficient synthetic route for the solution-phase combinatorial synthesis of a library of diverse 6*H*-pyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-ones **188** from reaction

which is attacked by the isocyanide to give nitrilium ion, the pyridine nitrogen of the nitrilium ion being in a favourable position for a 5-*exo*-dig cyclisation, and this is followed by addition of the carboxylic acid oxygen to the imino carbon giving the assumed internal ester intermediate; the resulting internal ester rearranges by an acyl transfer to generate the lactam (Scheme 54).



Scheme 52.



181 **182** **183** **184**, 36-79.7%

R_1 = Bn, 4-ClBn, 4-OMeBn, Ph, n-Bu, CH_2CO_2Et
R_2 = 5-Br, 5-Me, 4-Cl, H, 4-Me, 5-CN

Scheme 53.

An unexpected three-component condensation reaction between an isocyanide **186**, isoquinoline **181** and a strong CH-acid **185** efficiently provided 1,2-dihydroisoquinoline derivatives **187** in a one-pot reaction in water at 70 °C without using catalyst (Scheme 55).[44]

3.1.3. Pyridines. 3-Aminoimidazo[1,2-*a*]pyridines **191** have been synthesised in good- to -excellent yields from a three-component reaction of aldehydes **188**, 2-aminopyridines **189** and isocyanides **190** in the presence of the ionic liquid, 1-butyl-3-methylimidazolium bromide [bmim]Br (Scheme 56).[45]

The reaction of 5-benzenesulfonyl-3,4-dihydro-1*H*-pyridin-2-one derivatives **192** with isocyanides **193** provided new class of compounds, pyrrolo[3,4-b]pyridin-2-ones **194** in good yields and regioselectivity (Scheme 57).[46]

Isocyanodihydropyridones **195** reacted with aldehydes **196** and amines **197** to afford dihydrooxazolopyridines **198** in high yield (Scheme 58).[47]

The novel application of zinc chloride, a cheap catalyst, has been reported for the one-pot preparation of imidazo[1,2-*a*]pyridines **202** from the reaction of aldehydes **199**, 2-aminopyridine **200** and isocyanides **201** using either conventional heating or microwave irradiation (Scheme 59).[48]

3.2. Six-member oxygen-containing heterocycles with one heteroatom

3.2.1. Chromenes. The reaction between 2,6-dimethylphenyl isocyanide **203**, 1,3-cyclohexanediones **204** and acetylenic esters **205** provided a simple one-pot entry into the synthesis of polyfunctional 4*H*-chromene derivatives **206**. A dynamic ^{1}H NMR study of the compounds **206** confirmed a restricted rotation around the aryl–nitrogen single bond (Scheme 60).[49]

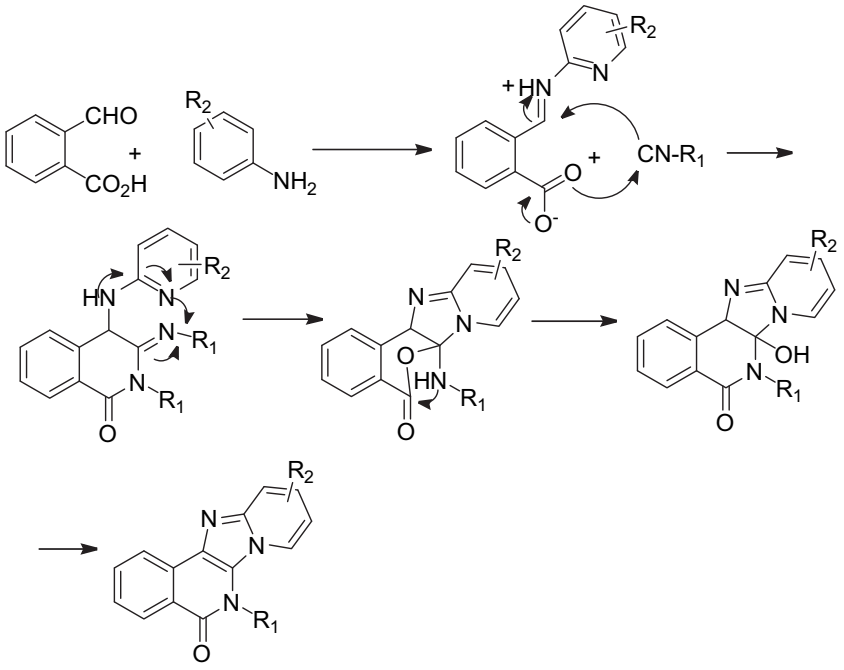
It is assumed that the compounds **206** result from an initial addition of the aryl isocyanide to the acetylenic ester and subsequent protonation of the 1:1 adduct by the 1,3-cyclohexanedione. The positively charged ion might then be attacked by the enolate anion of the 1,3-dicarbonyl compounds in a Michael addition process to afford the keteneimine intermediate. Under the reaction conditions, the keteneimine intermediate could be isomerised for the generation of fused heterocyclic compound **206** (Scheme 61).

3.2.2. Pyrans. Functionalised 5-oxo-4,5-dihydroindeno[1,2-*b*]pyrans **210** were synthesised from the reaction of alkyl(aryl) isocyanides **207**, dialkyl acetylenedicarboxylates **208** and indan-1,3-dione **209**. In the case of 2,6-dimethylphenyl isocyanide, in addition to the desired product **210**, methyl 2-[(2,6-dimethylphenyl)imino]-3-(2-methoxy-2-oxoethyl)-4-oxo-3,4-dihydro-2*H*-indeno[1,2-*b*]furan-3-carboxylate was obtained in 25% yield (Scheme 62).[50]

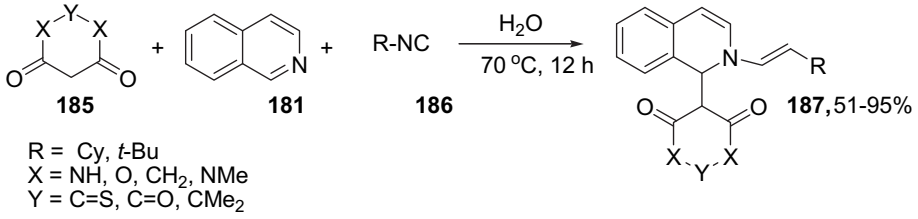
The proposed mechanism is shown in Scheme 63.

An unexpected four-component (3+1) reaction of cyclo alkyl isocyanide **211** with alkylidene-substituted Meldrum's acids **212** in CH_2Cl_2 at room temperature produced imino-furopyranones **213** in good yields (Scheme 64).[51]

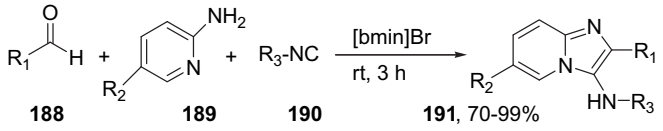
It is reasonable to assume that the furo-pyran **213** results from an initial [4+1] cycloaddition reaction of the electron-deficient heterodiene moiety of **217** with cyclohexyl isocyanide to produce



Scheme 54.

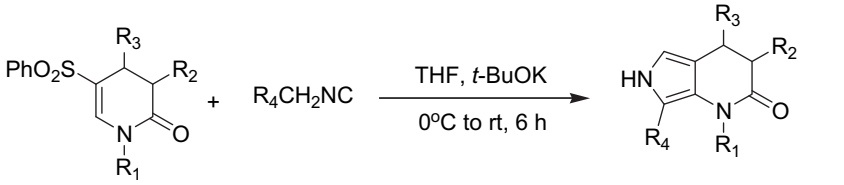


Scheme 55.



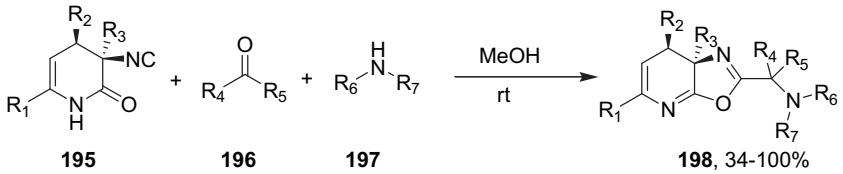
R_1 = 4-Pyr, Ph, 4-MePh, 4-ClPh, 3-NO_2Ph
R_2 = Me, Br
R_3 = *t*-Bu, Cy, 2,6-di-MeC_6H_3

Scheme 56.



R_1 = Bn, Bu$CH_2C_4H_3O$
R_2 = H, Me, Ph
R_3 = H, Me, Ph, *t*-Bu
R_4 = Tos, CO_2Et

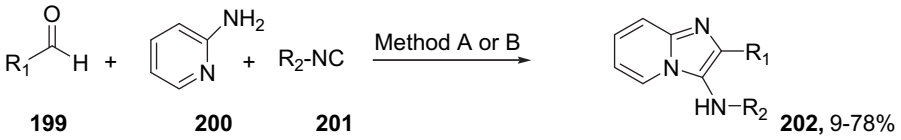
Scheme 57.



195 **196** **197** **198**, 34-100%

R_1 = Ph, *i*-Pr
R_2 = Ph, 4-OMePh, 4-ClPh, Cyclohexen-1-yl
R_3 = Ph, 4-ClPh
R_4 = Ph, *i*-Pr, *t*-Bu, Me, Cy, H
R_5 = H, Me
R_6 = Bn, nBu, Ph, 4-NO_2Bn
R_7 = H, -$(CH_2)_2$-O-$(CH_2)_2$-

Scheme 58.

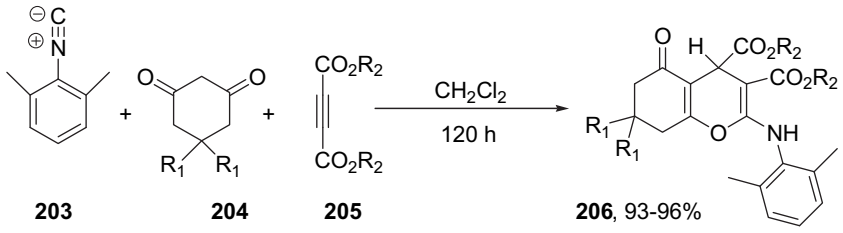


199 **200** **201** **202,** 9-78%

Mthod A = $ZnCl_2$, 5 h reflux
Method B = $ZnCl_2$, MW, 1 h,

R_1 = Ar, Het
R_2= *t*-Bu,Cy, 2,6-$(Me)_2C_6H_3$, $C_6H_{11}NO$

Scheme 59.



203 **204** **205** **206**, 93-96%

R_1 = H, Me
R_2 = Me, Et

Scheme 60.

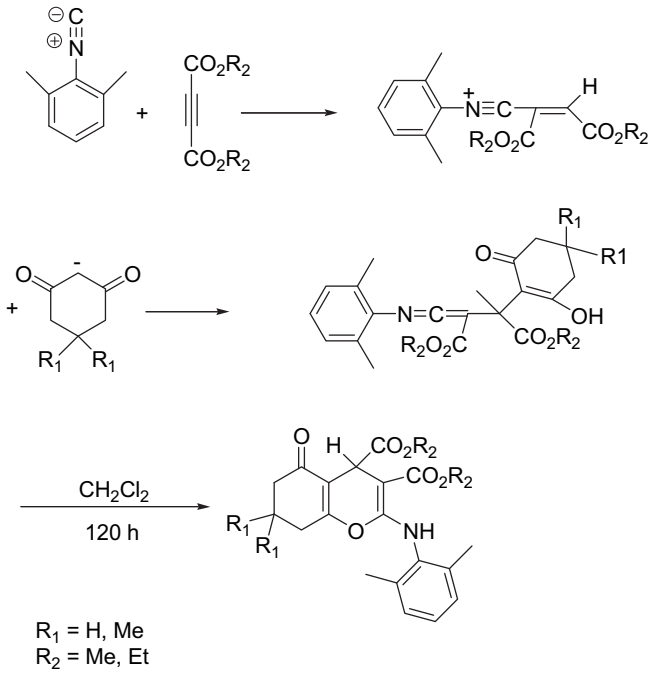
an iminolactone intermediate. Nucleophilic attack of a second isocyanide on the imine carbon of the iminolactone intermediate followed by cleavage of the five-membered ring and subsequent cyclisation gives a di-imino pyran intermediate. Addition of a third isocyanide to the carbonyl of this intermediate gives an unstable intermediate that easily loses an acetone molecule and cyclises to give **213** (Scheme 65).

Chemoselective reaction of isocyanides **214** with dialkyl acetylenedicarboxylates **215** in the presence of relatively strong cyclic CH-acids, such as 4-hydroxy-6-methyl-2*H*-pyran-2-one or 4-hydroxycoumarin **216** led to a facile synthesis of highly functionalised dialkyl 2-(alkylamino)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3,4-dicarboxylates or dialkyl 7-methyl-2-(alkylamino)-5-oxo-4H,5*H*-pyrano-[4,3-*b*]pyran-3,4-dicarboxylates **217**, respectively, in good yields (Scheme 66).[52]

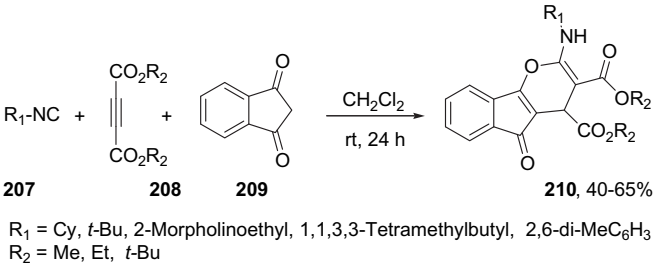
A three-component reaction of an isocyanide **218**, a dialkyl acetylenedicarboxylate **219** and tetronic acid **220** in dichloromethane at room temperature afforded 4*H*-furo[3,4-*b*]pyran derivatives **221** (Scheme 67).[53]

The formation of these heterocycles can be rationalised by an initial Michael-type vinylisonitrilium cation. The positively charged ion might then be attacked by the anion of the tetronic acid, leading to the keteneimine. Such an addition product may isomerise under the reaction conditions employed to produce the fused heterocyclic system **221** (Scheme 68).

An isocyanide-catalysed reaction between tetracyanoethylene **222** and various activated CH-acid compounds **223** provided the corresponding pyran-annulated heterocyclic ring systems **225**, in high yield, in which the isocyanide **224** functions as only a catalyst, but not a reagent, and the product **226** was not observed (Scheme 69).[54]



Scheme 61.



Scheme 62.

The proposed mechanism involves a condensation reaction of **227** and **228** followed by cyclisation to yield **230** (Scheme 70).

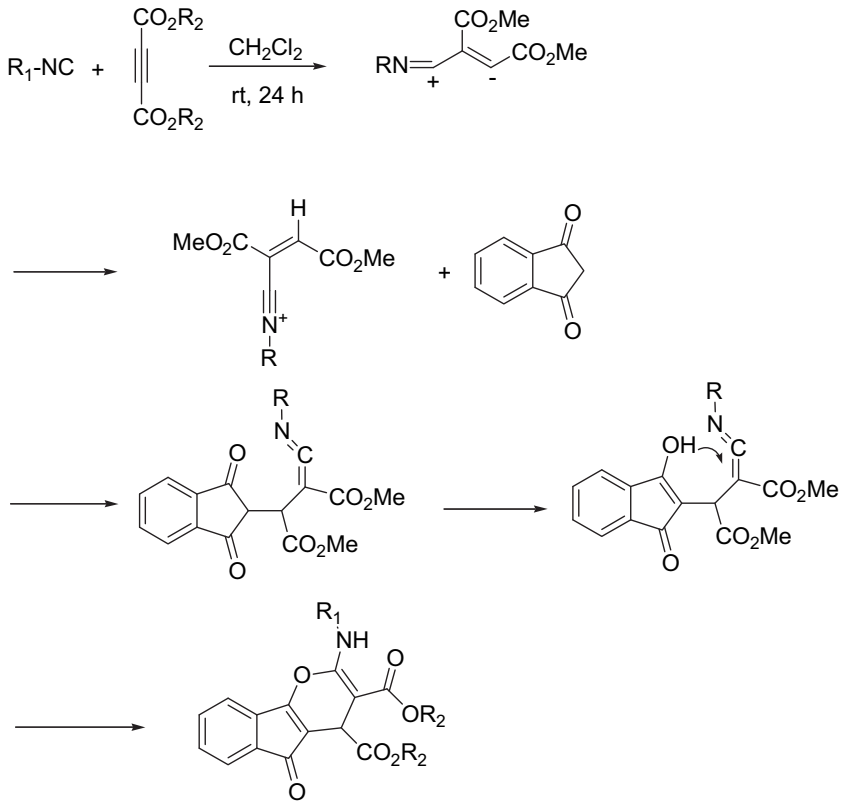
The reaction between alkyl or aryl isocyanides **227** and electron-deficient acetylenic esters **228** with 3-hydroxy-1*H*-phenalene-1-one **229** produced a vinylisonitrilium cation, which undergoes an addition reaction with the conjugate base of the 3-hydroxy-1*H*-phenalene-1-one to produce biologically interesting dialkyl 10-(alkyl or arylamino)-7-oxo-7*H*,8*H*-naphtho[1,8-*gh*] chromene-8,9-dicarboxylates **230** in moderate- to -fairly good yields (Scheme 71).[55]

3.2.3. Coumarins. A three-component reaction of substituted 2-hydroxybenzaldehydes **231**, Meldrum's acid **232** and isocyanides **233** in dichloromethane gave novel 3,4-dihydrocoumarin derivatives **234** without using any catalysts and activation (Scheme 72). Changing the solvent to MeCN provided the 3-carboxylic acid coumarin derivatives.[56]

The reaction may be rationalised as by the initial formation of a conjugated electron-deficient heterodyne by standard Knoevenagel condensation of the **231** and **232**. It is known that acylated Meldrum's acid is readily transformed into β-ketoesters by alcoholysis, and so it is reasonable to assume that the intramolecular reaction of the heterodyne with the hydroxyl group of 2-hydroxybenzaldehydes and subsequent loss of acetone forms the 2-oxo-2*H*-chromene-3-carboxylic acid. This is followed by a Michael reaction with **233** to afford a new intermediate. Then, hydrolysis of this intermediate then affords a further intermediate, which decarboxylates under the reaction conditions to afford the product (Scheme 73).

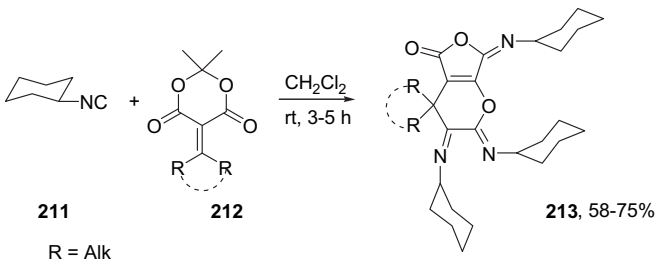
A four-component reaction between a 2-hydroxybenzaldehyde **235**, Meldrum's acid **236**, an isocyanide **237** and an aromatic or an aliphatic alcohol **238** efficiently provided 3,4-dihydrocoumarin derivatives **239** in good- to -excellent yields without using any catalyst or activation. The reaction can be carried out as a simple one-pot protocol at room temperature (Scheme 74).[57]

Mechanistically, the reaction may be rationalised by the initial formation of a conjugated electron-deficient heterodyne by standard Knoevenagel condensation of **235** and **236**, followed by a [4+1] cycloaddition reaction or a Michael-type addition reaction with **242** to afford an iminolactone intermediate. It is well known that acylated Meldrum's acid is readily transformed into β-ketoesters by alcoholysis, and so it is reasonable to assume that the intramolecular reaction of the iminolactone with the hydroxy group of 2-hydroxybenzaldehyde and subsequent loss of acetone



R_1 = Cy, *t*-Bu, 2-Morpholinoethyl, 1,1,3,3-Tetramethylbutyl, 2,6-di-MeC_6H_3
R_2 = Me, Et, *t*-Bu

Scheme 63.



Scheme 64.

leads to formation of a new intermediate. Nucleophilic attack of alcohol on the activated carbonyl moiety of this intermediate then yields the product (Scheme 75).

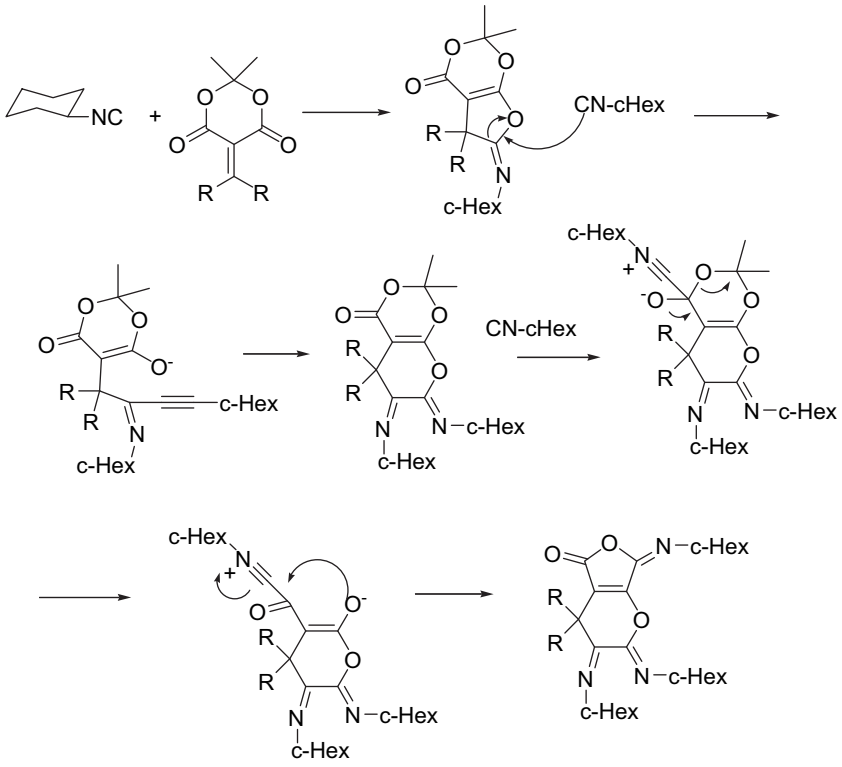
4. Five-member heterocycles with two heteroatoms

4.1. Five-member nitrogen-containing heterocycles with two or more heteroatoms

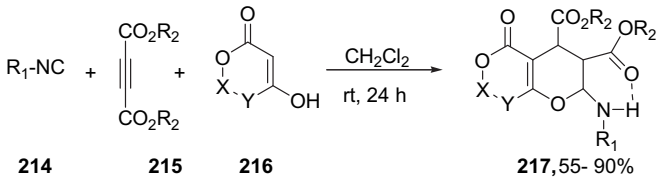
4.1.1. Thiazoles. A one-pot synthesis of 3-amino-benzo[*d*]imidazo [2,1-*b*]thiazoles **243** by the reaction of 2-aminobenzothiazole **240**, aldehydes **241** and isocyanide **242** in the presence of NH_4Cl has been reported (Scheme 76).[58]

A probable mechanism, which accounts for the observed results involves a (nonconcerted) [4+1] cycloaddition between the protonated Schiff base (which bears both the electrophile and nucleophile) and the isocyanide (which behaves as a vinylidene carbenoid). A subsequent prototropic shift gives the final aromatic fused 3-amino-benzo[*d*]imidazo-[2,1-*b*]thiazoles (Scheme 77).

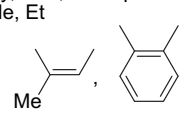
Novel 5-aminothiazoles **249** has been synthesised based on the cyclisation of diamide adducts **248**, prepared using the Ugi reaction of carboxylic acids **244**, aldehydes **245**, isocyanide **246** and 2,4-dimethoxybenzylamine **247** in the presence of Lawesson's reagent. The Walborsky reagent (1,1,3,3-tetramethylbutyl isocyanide **246**) was used as an isonitrile component, facilitating subsequent deprotection of the *N*-alkyl group to yield free 5-aminothiazoles,



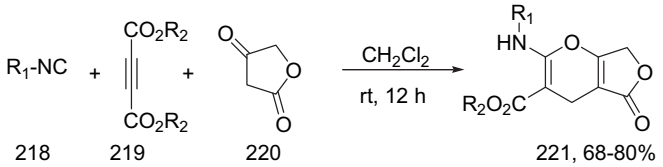
Scheme 65.



R_1 = Cy, *t*-Bu, 2-Morpholinoethyl, 1,1,3,3-tetramethylbutyl
R_2 = Me, Et

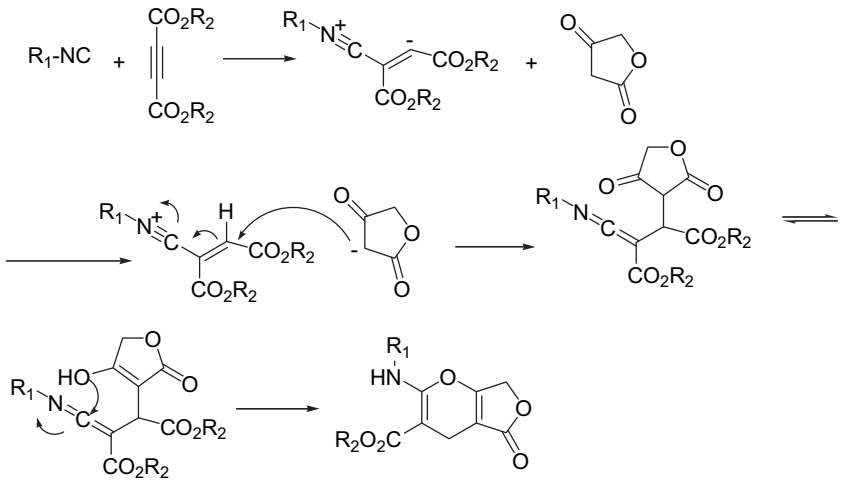
X-Y = 

Scheme 66.

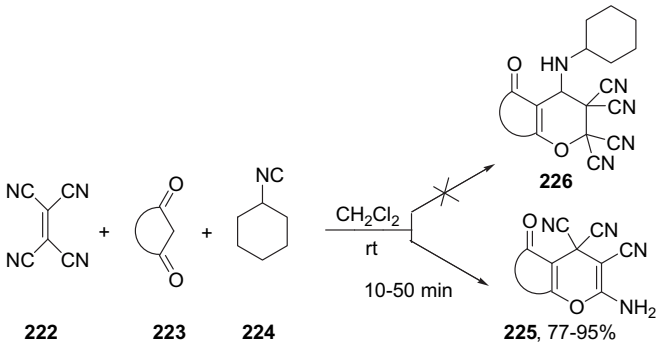


R_1 =Cy, t-Bu, 1,1,3,3-tetramethylbutyl, 2,6-di-MeC_6H_3
R_2 = Me, Et, t-Bu

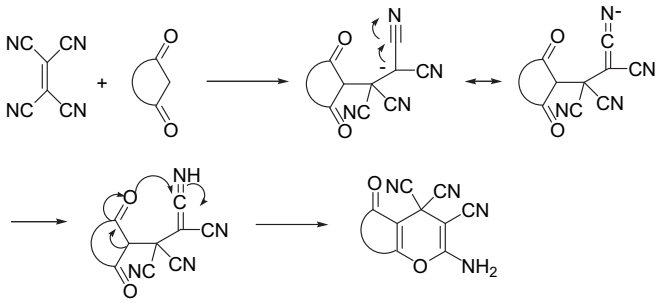
Scheme 67.



Scheme 68.



Scheme 69.



Scheme 70.

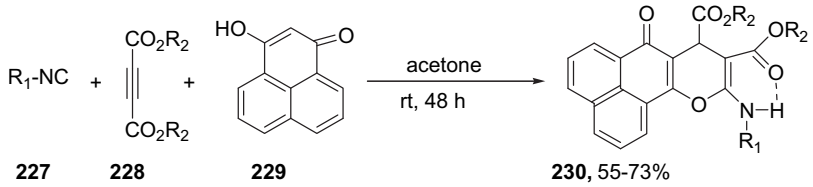
which were prepared with a variety of substituents at the 2- and 4-positions (Scheme 78).[59]

4.1.2. Pyrazoles. A three-component reaction of isocyanides **250**, dialkyl acetylenedicarboxylates **251** and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one **252** led to the synthesis of fully substituted pyrano[2,3-*c*]pyrazole derivatives **253** (Scheme 79).[60]

The formation of these pyranopyrazoles **253** can be rationalised by an initial Michael-type vinylisonitrilium cation. The positively charged ion might then be attacked by the anion of the phenyl-1*H*-pyrazol-5(4*H*)-one to give the keteneimine. Such an addition product may isomerise under the reaction conditions employed to produce the fused heterocyclic derivatives **253** (Scheme 80).

4.1.3. Oxazoles. A one-pot synthesis of 2,5-disubstituted oxazoles **256**, starting from benzyl halides **254** and acyl chlorides has been reported. The in situ formation of isocyanides **255**, followed by the addition of an acyl chloride in the presence of a base, provided the desired oxazoles in good yields (Scheme 81).[61]

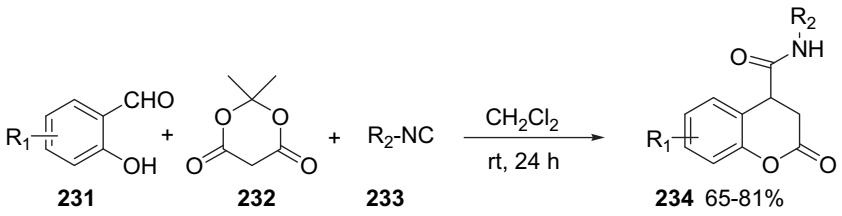
A multipurpose mesofluidic flow reactor capable of producing gram quantities of material has been used for the synthesis of 4,5-disubstituted oxazoles **259** from the reaction of isocyanoacetate **258** with an acyl chloride **257** (Scheme 82).[62]



227 **228** **229** **230,** 55-73%

R_1 = Cy, *t*-Bu, 1,1,3,3-tetramethylbutyl, 2,6-di-MeC_6H_3, Bn, t-Oct
R_2 = Me, Et

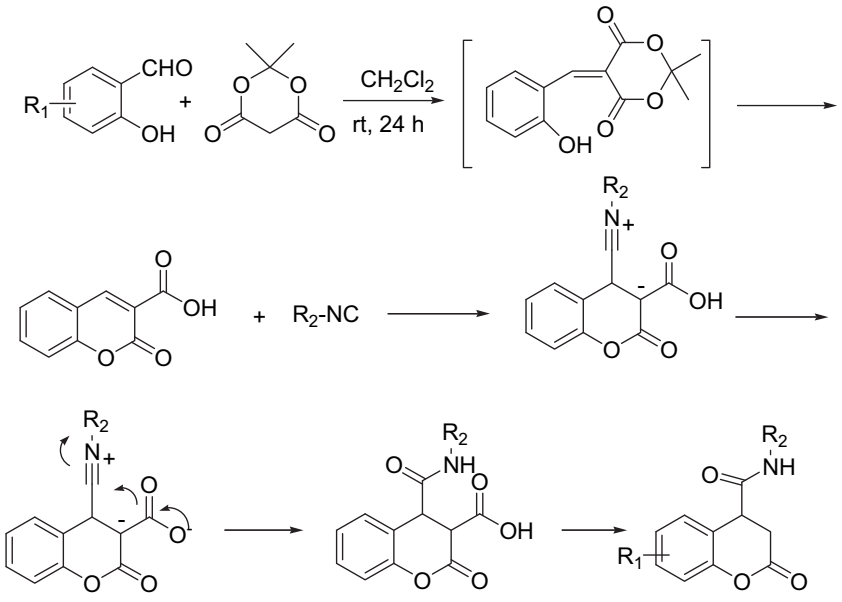
Scheme 71.



231 **232** **233** **234** 65-81%

R_1 = H, 5-Br, 3-OMe, 4-OMe
R_2 = Bn, Cyl, *t*-Bu, 2,6-di-MeC_6H_3, 4-Me$C_6H_4CH_2SO_2$

Scheme 72.

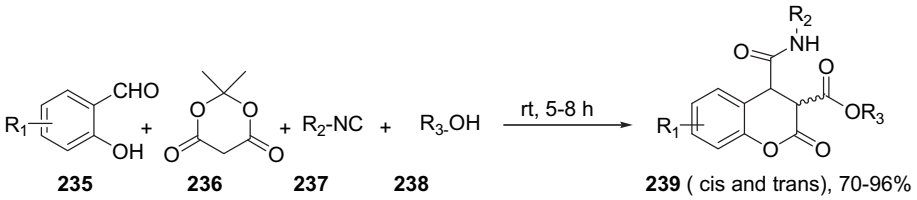


R_1 = H, 5-Br, 3-OMe, 4-OMe
R_2 = Bn, Cyl, *t*-Bu, 2,6-di-MeC_6H_3, 4-Me$C_6H_4CH_2SO_2$

Scheme 73.

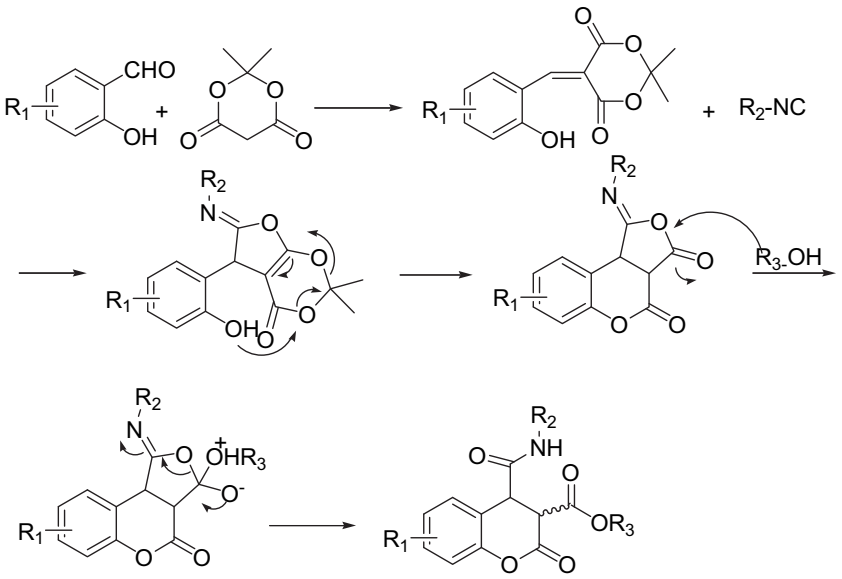
4.1.4. Oxadiazoles. The reaction of 4-substituted benzoic acid derivatives **260** with (*N*-isocyanimino) triphenylphosphorane **261** proceeded smoothly at room temperature to afford the corresponding 2-aryl-1,3,4-oxadiazoles **262** via an intramolecular aza-Wittig reaction in excellent yields under neutral conditions (Scheme 83).[63]

The mechanism of the reaction between the 4-substituted benzoic acid derivatives and (*N*-isocyanimino)-triphenylphosphorane has not been established experimentally. On the basis of the well-established chemistry of isocyanides, however, it is reasonable to assume that the protonation of **261** by **260** followed by quenching of the cationic centre by the conjugate base of the carboxylic acid can generate the iminophosphorane. An intramolecular aza-Wittig reaction of the iminophosphorane would lead to formation of the 2-aryl-1,3,4-oxadiazoles **262** and triphenylphosphine oxide (Scheme 84).

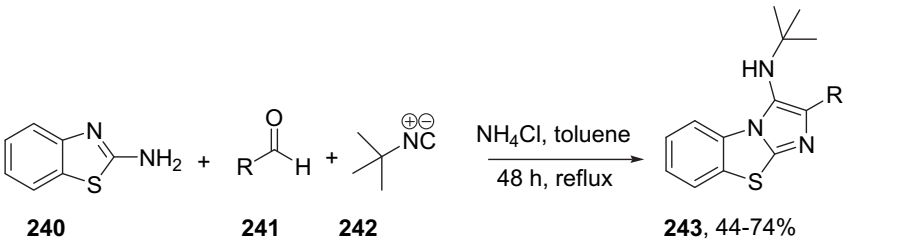


R_1 = H, 5-Br, 3-OMe, 4-OMe
R_2 = Benz, Cy, *t*-Bu, 2,6-di-MeC_6H_3, 4-$MeC_6H_4CH_2SO_2$
R_3 = Et, Me, Cycloheptyl, 4-ClBenz, 4-FBenz, Heptayl

Scheme 74.



Scheme 75.

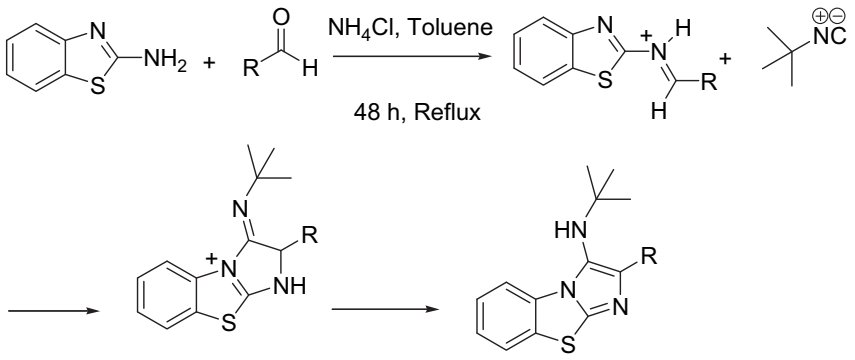


R = 2-Thienyl, 3-Thienyl, i-Pr, n-Hex, n-Oct, 2-Pyr, Bn, Ph, 4-NO_2Ph, 4-NO_2Ph, 4-MePh, 4-OHPh, 4-ClPh, 4-OMePh, 3,4-$OCH_2OC_6H_3$, 2,4-di-ClC_6H_3, 4-OH-3-OMePh

Scheme 76.

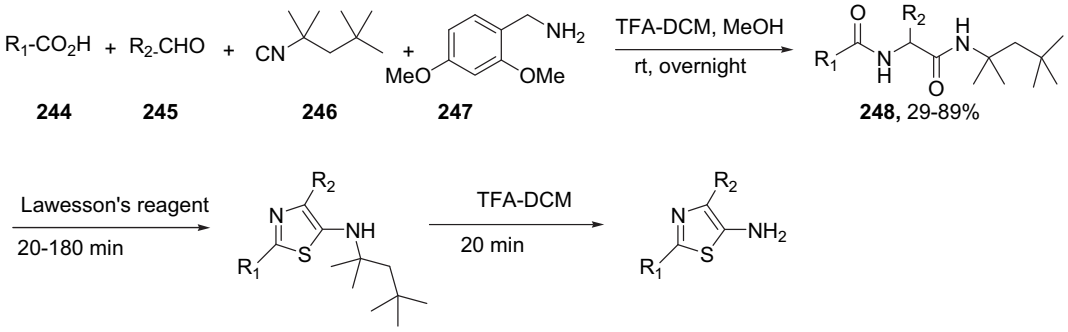
4.1.5. Benzoxazoles, thiazoles and imidazoles. A novel two-step synthesis procedure for the preparation of highly substituted benzoxazoles and benzothiazoles **268** has been described. The reaction of amines **263**, carbonyls **264**, acids **265** and isocyanides **266** gave **267**, which underwent copper-catalysed cyclisation to **268** (Scheme 85).[64]

A Ugi–Smiles reaction of **269**, **270**, **271** and **272** gave a mixture, which was treated with 1 equiv of *p*-toluenesulfonic acid (PTSA) followed by the addition of palladium on carbon (10% Pd/C). The expected secondary anilines were isolated in fair- to -good yields. The products were not isolated, but directly converted into benzotriazoles **273** on treatment with sodium nitrite and acetic acid. Two different benzimidazole families **274** and **275** have been prepared from these *o*-phenylenediamines either under treatment with CS_2 or by adding aldehydes under oxidative conditions (Scheme 86).[65]



R = 2-Thienyl, 3-Thienyl, i-Pr, n-Hex, n-Oct, 2-Pyr, Bn, Ph, 4-NO_2Ph, 4-NO_2Ph, 4-MePh, 4-OHPh, 4-ClPh, 4-OMePh, 3,4-$OCH_2OC_6H_3$, 2,4-di-ClC_6H_3, 4-OH-3-OMePh

Scheme 77.

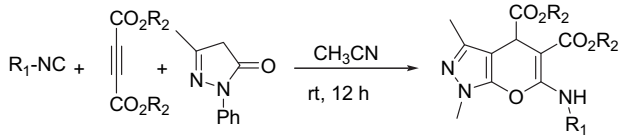


244 **245** **246** **247** **248,** 29-89%

249, 30-69%

R_1 = Ph, Me, C_5H_5S, C_5H_4N, 4-$OMeC_6H_4$, 4-FC_6H_4, *i*-Pr, Benzthiazole
R_2 = Ph, 4-$OMeC_6H_4$, 4-FC_6H_4, 3,4-di-ClC_6H_3, C_4H_3S, C_4H_3O

Scheme 78.



250 **251** **252** **253**, 58-79%

R_1 = Cy, *t*-Bu, Bn, 2,6-di-MeC_6H_3, 1,1,3,3-tetramethylbutyl, EtOC(O)Me
R_2 = *t*-Bu, Me, Et

Scheme 79.

5. Six-member heterocycles with two heteroatoms

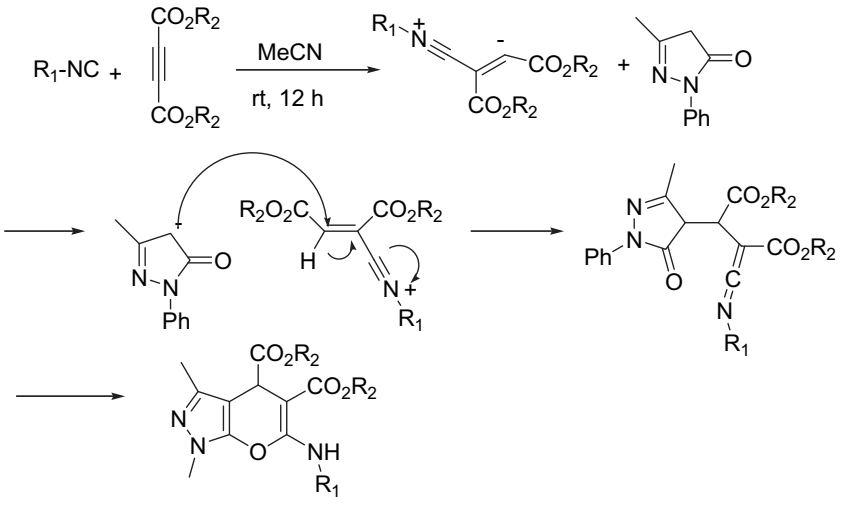
5.1. Six-member nitrogen-containing heterocycles with two or more heteroatoms

5.1.1. Quinazolines. Reaction of **276** with isocyanates and isothiocyanates gave **277**, which hydrolysed to form the corresponding 2,3-disubstituted 3*H*-quinazolin-4-ones and 3*H*-quinazolin-4-thiones **278** (Scheme 87).[66]

Aliphatic isocyanides reacted with *o*-aminobenzophenones **279** in dichloromethane under Lewis acid catalysis at ambient temperature to give, unexpectedly, 4-aryl-4-hydroxy-3,4-dihydroquinazolines **280** in good- to -excellent yields (Scheme 88).[67]

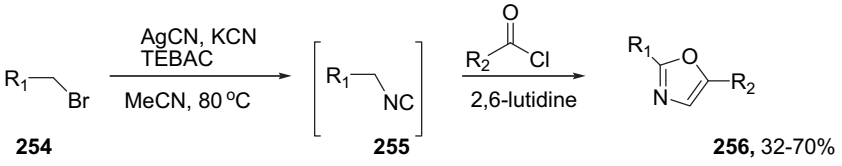
5.1.2. Quinoxalines. The reaction of 2-fluoroanilines **281**, aldehydes **282**, 1*H*-imidazole-4-carboxylic acid or 1*H*-pyrazole-3-carboxylic acid **283** and isocyanides **284** gave the products **285**, which can be transformed into compound **286** via two methods, namely using microwave irradiation in the presence of K_2CO_3 or classical stirring conditions at room temperature (Scheme 89).[68]

The three-component condensation reaction of *o*-phenylenediamine **287**, aromatic aldehydes **289** and cyclohexyl isocyanide



R_1 = Cy, *t*-Bu, Bn, 2,6-di-MeC_6H_3, 1,1,3,3-tetramethylbutyl, EtOC(O)Me
R_2 = *t*-Bu, Me, Et

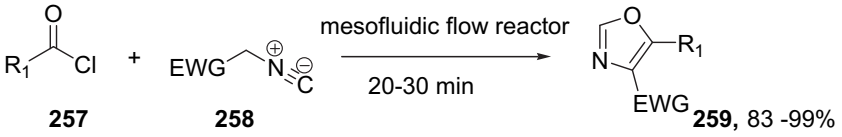
Scheme 80.



254 **255** **256,** 32-70%

R_1 = Ph, 4-OMePh, 4-ClPh, 2-BrPh, t-BuPh
R_2 = *t*-Bu, *i*-Pr, Ph, 4-FPh, n-Pr
TEBAC = Triethylbenzylammonium chloride

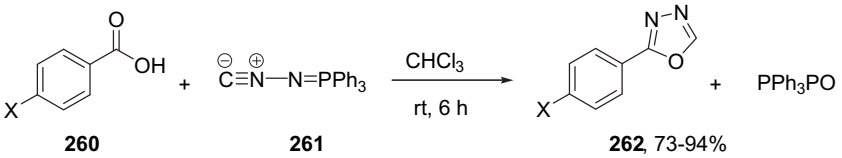
Scheme 81.



257 **258** **259,** 83 -99%

R_1 = Ar, Het
EWG = CO_2Et

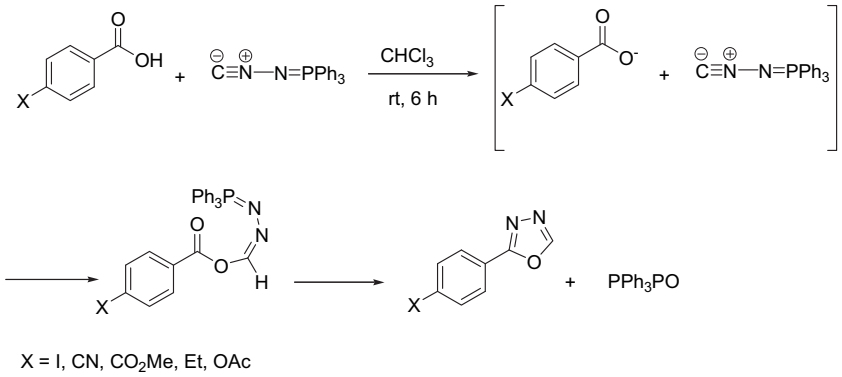
Scheme 82.



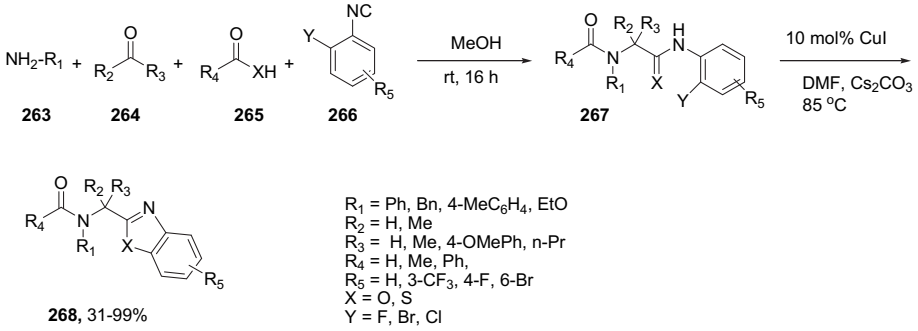
260 **261** **262**, 73-94%

X = I, CN, CO_2Me, Et, OAc

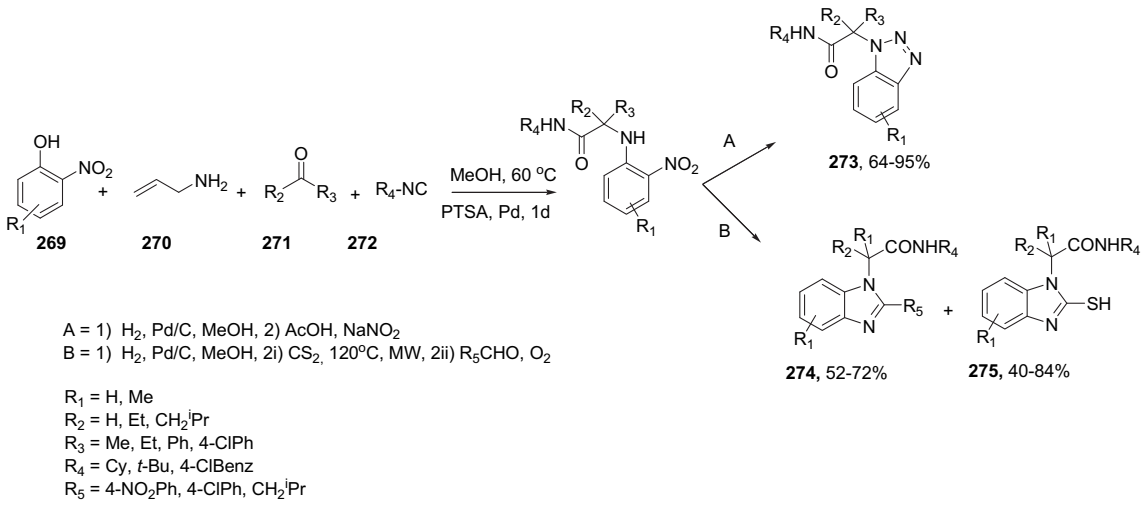
Scheme 83.



Scheme 84.



Scheme 85.

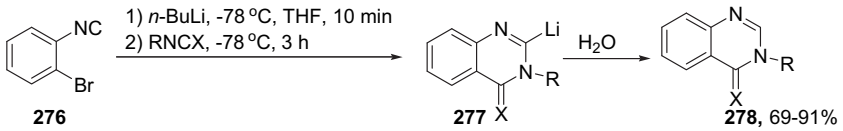


Scheme 86.

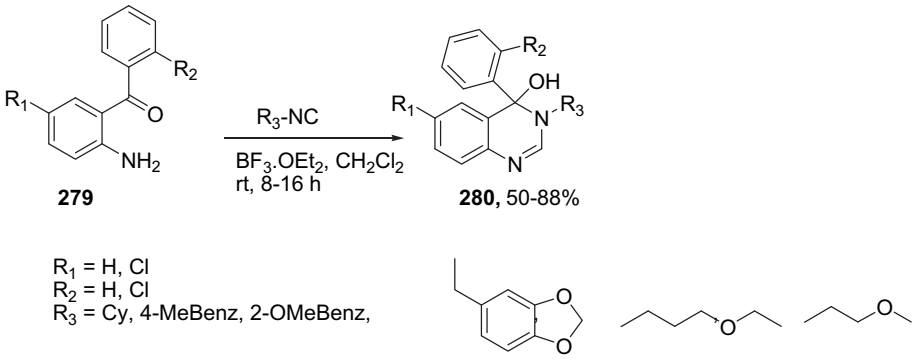
288 catalysed by ferric perchlorate affords the corresponding *N*-cyclohexyl-3-aryl-quinoxaline-2-amines **295** in good yields (Scheme 90).[69]

The first step may involve the reaction of **288** with **287** followed by attack of **289** on the resulting intermediate. Following rearrangement and catalytic oxidation by ferric perchlorate, the product **290** is obtained (Scheme 91).

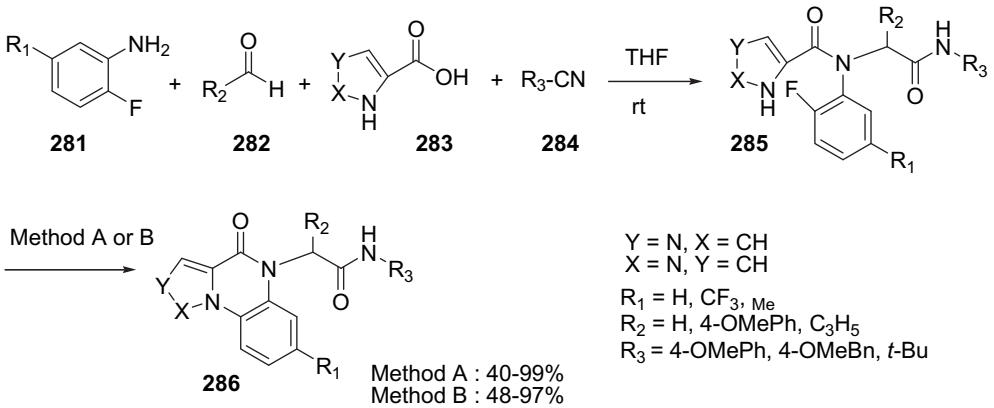
The reaction of *o*-phenylenediamines **291**, ketones **292** and isocyanides **293**, in the presence of a catalytic amount of cerium(IV) ammonium nitrate (CAN) at room temperature, provided a variety



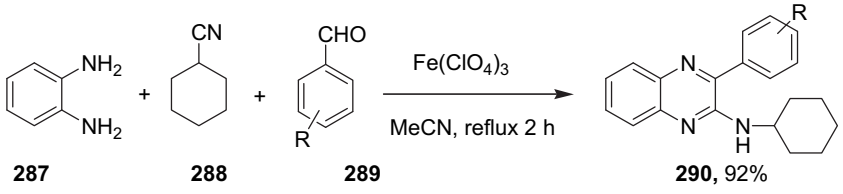
Scheme 87.



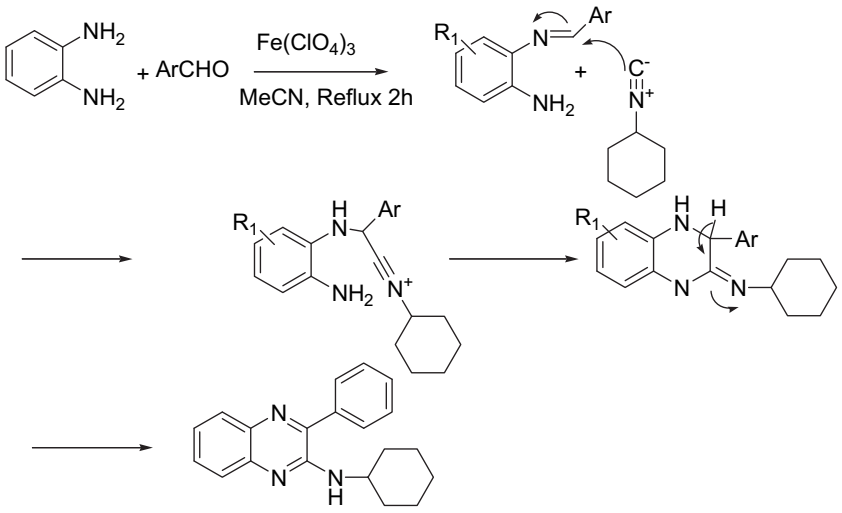
Scheme 88.



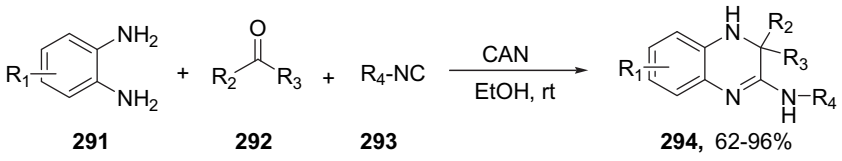
Scheme 89.



Scheme 90.



Scheme 91.



R_1 = 4-NO_2, 2-NO_2, H, 4-Me, C_5H_4CO
Ketone = Acetone, 2-Butanone, Cyclopentanone, 4-Methylacetophenone
R_4 = Cy, *t*-Bu, 1,1,3,3-tetramethylbutyl, 2,6-di-MeC_6H_3, Bn

Scheme 92.

of highly substituted 3,4-dihydroquinoxalin-2-amine derivatives **294** (Scheme 92).[70]

Reaction of anilines **295**, carbonyl compounds **296**, 2-fluorophenyl isocyanide **297**and azidotrimethylsilane **298** yielded fused tetrazolo[1,5-*a*]quinoxalines **299**, which led to products **300** in the presence of Cs_2CO_3 (Scheme 93).[71]

Highly substituted 3,4-dihydroquinoxalin-2-amine derivatives **304** were synthesised from a three-component condensation reaction of *o*-phenylenediamines **301**, diverse carbonyl compounds **302** and isocyanides **303** in good- to -excellent yields in the presence of a catalytic amount of *p*-toluenesulfonic acid (Scheme 94).[72]

The formation of the secondary amides **309** originally has been achieved via a Ugi reaction of **305**, **306**, **307** and **308**. Following a ring-closing reaction by a classical intramolecular *N*-aryl amidation of secondary amides using the catalytic system tris(dibenzylideneacetone) di-palladium $Pd_2(dba)_3$, tri-*o*-tolylphosphine as a ligand and a carbonate base (caesium carbonate with the use of aliphatic isocyanides or potassium carbonate with the use of benzylic isocyanides), synthesis of **310** was achieved (Scheme 95).[73]

5.1.3. Pyrimidines. The three-component condensation of aldehydes **312**, *N*,*N*′-dimethylbarbituric acid **311** and alkyl or aryl isocyanides **313** afforded the corresponding furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **314** in high yields in 1-butyl-3-methylimidazolium bromide as an ionic liquid solvent at room temperature within several minutes (Scheme 96).[74]

Reaction of alkyl isocyanides **317**, dialkyl acetylenedicarboxylates **316** and *N*,*N*′-dimethylurea **315** in 1 M aq glucose provided novel 2,6-dioxohexahydropyrimidines **318** (Scheme 97).[75]

Presumably, the zwitterionic intermediate formed from **317** and **316** is protonated by *N*,*N*′-dimethylurea **315** to furnish an intermediate, which then adds to the anion to produce the keteneimine. This intermediate undergoes cyclisation and dehydration to **318** (Scheme 98).

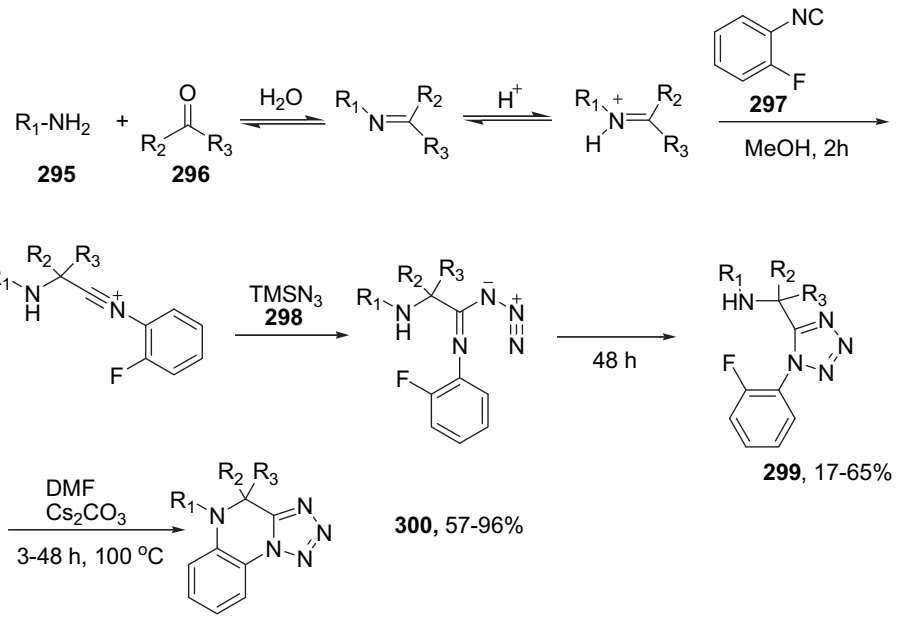
A [4+1]-cycloaddition reaction was used for the synthesis of imidazo[1,2-*c*]pyrimidines **322** from the reaction of aldehydes **319**, amidines **320** and isocyanides **321** (Scheme 61). This reaction can be performed in a two-step procedure including the reaction of **319** and **320** in the presence of *p*-toluenesulfonic acid to form the corresponding imine following the reaction with **321** with stirring for 16 h. This procedure was only successful for highly electron-deficient pyridine carbaldehydes (Scheme 99).[76]

The proposed mechanism is shown in Scheme 100.

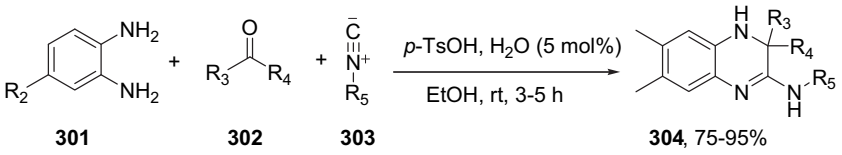
A one-pot, three-component synthesis of 2-amino-4*H*-pyrido[1,2-*a*]pyrimidine-3,4-dicarboxylates, 2-amino-4*H*-pyrimido[1,2-*a*]pyrimidine-3,4-dicarboxylates and 2-amino-4*H*-pyrazino[1,2-*a*]pyrimidine-3,4-dicarboxylates **326** from the reaction of isocyanides **323**, dialkyl acetylenedicarboxylates **324** and *N*-(2-heteroaryl)-amides **325** has been reported (Scheme 101).[77]

A three-component reaction of isocyanides **327**, dialkyl acetylenedicarboxylates **328** and *N*-(2-pyridyl)amides **329** led to synthesis of the corresponding 4*H*-pyrido[1,2-*a*]pyrimidines **330** (Scheme 102).[78]

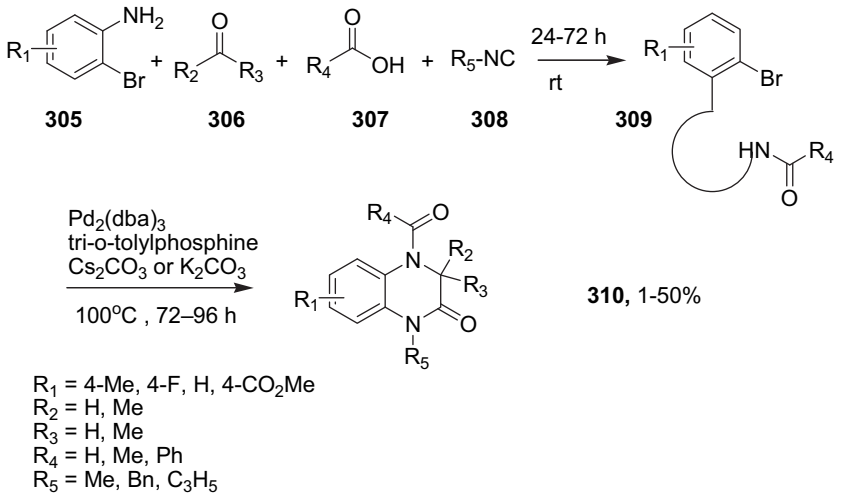
It is reasonable to assume that **330** result from the initial addition of the **327** to **328** and subsequent protonation of the 1:1 zwitterionic adduct by **329**, followed by conjugate addition of the formed anion to the α,β-unsaturated nitrilium ion to form a ketenimine intermediate. The ketenimine may undergo intramolecular



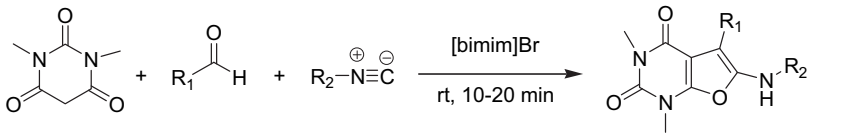
Scheme 93.



Scheme 94.



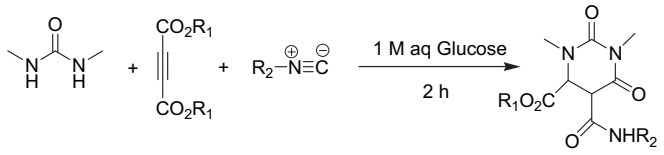
Scheme 95.



311 **312** **313** **314,** 40-90%

R_1 = Ph, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 2-$NO_2C_6H_4$
R_2 = *t*-Bu, Cy, 2,6-di-MeC_6H_3
[bimim]Br = 1-butyl-3-methylimidazolium bromide

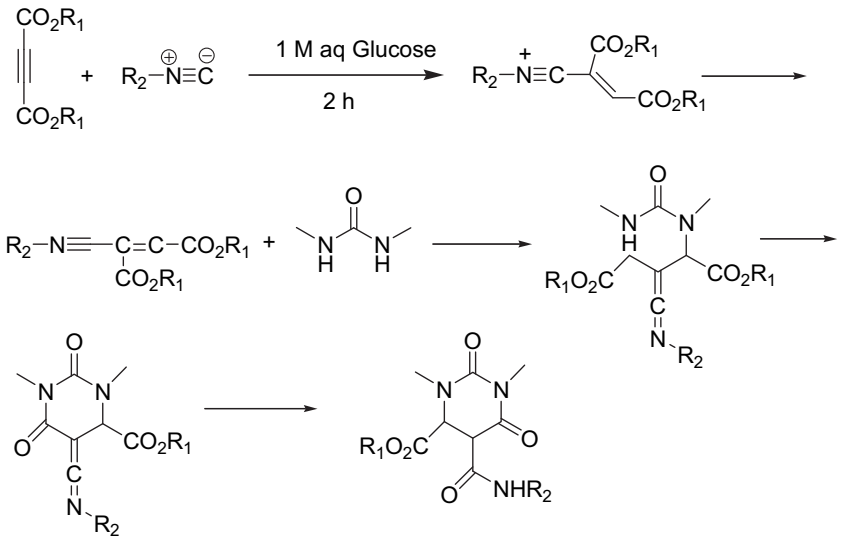
Scheme 96.



315 **316** **317** **318,** 85-98%

R_1 = Me, Et
R_2 = Bu, Cy, 2,6-di-MeC_6H_3, 1,1,3,3-tetramethylbutyl, 2-morpholinoethyl

Scheme 97.



R_1 = Me, Et
R_2 = Bu, Cy, 2,6-di-MeC_6H_3, 1,1,3,3-tetramethylbutyl, 2-morpholinoethyl

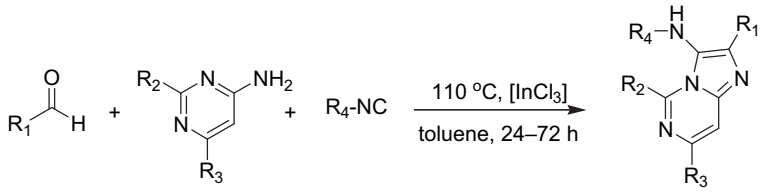
Scheme 98.

cyclisation to a bicyclic zwitterion. Intramolecular nucleophilic addition of the nitrogen to the adjacent carbonyl group would yield a tricyclic system. Subsequent ring opening produces the fused heterocyclic system **330** (Scheme 103).

1,4-Bis(furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dion-5-yl)benzene derivatives **334** were achieved via a one-pot three-component reaction of isocyanides **331**, *N*,*N*′-dimethylbarbituric acid **332** and terephthalaldehyde **333** in DMF at room temperature for 30 min (Scheme 104).[79]

5.1.4. Oxazines. A high-yielding and rapid method for the synthesis of 3-aryl-4*H*-benzo[1,4]oxazin-2-ylamine **338** via one-pot, three-component reaction of an aromatic aldehydes **337**, isocyanides **336** and *o*-aminophenols **335** using *p*-toluenesulfonic acid as a catalyst has been reported (Scheme 105).[80]

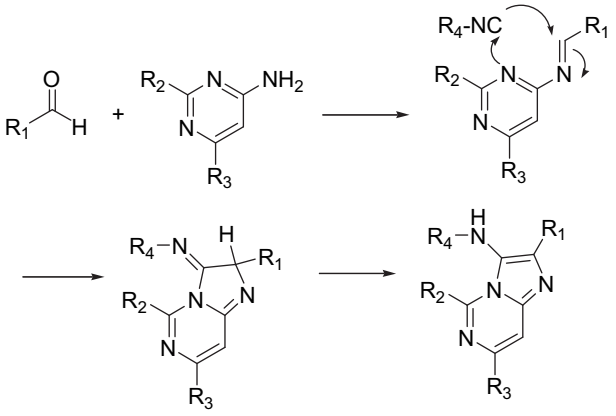
The first step may involve reaction of the aromatic aldehyde with the *o*-aminophenol followed by isocyanide attack on the resulting intermediate to give the desired product (Scheme 106).



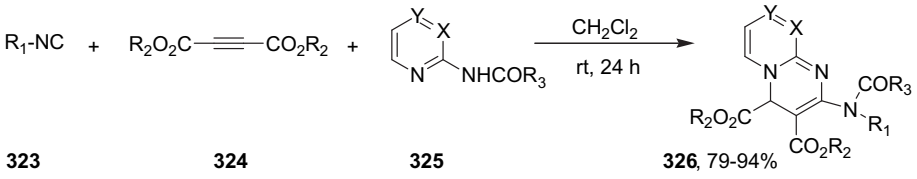
319 **320** **321** **322**, 21-42%

R_1 = Ph, 3-C_5H_4N, 3-C_5H_4N, C_5H_5, 3,4-di-ClPh
R_2 = H, Me
R_3 = H, Me, OMe
R_4 = Et, C_5H_{11}, Ph, C_5H_9, 3-FPh, 4-OMePh, Benz, 4-OMeBenz, 4-ClBenz, 4-OMeBenz

Scheme 99.



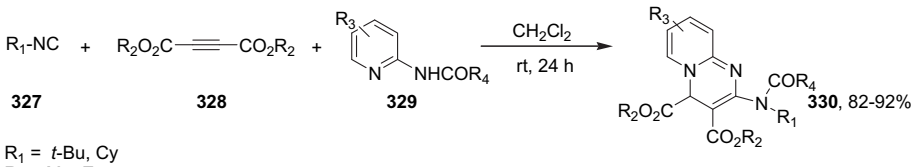
Scheme 100.



323 **324** **325** **326**, 79-94%

R_1 = *t*-Bu, Cy, 1,1,3,3-tetramethylbutyl
R_2 = Me, Et
R_3 = CO_2Et, OEt
X = N, CH
Y = N, CH

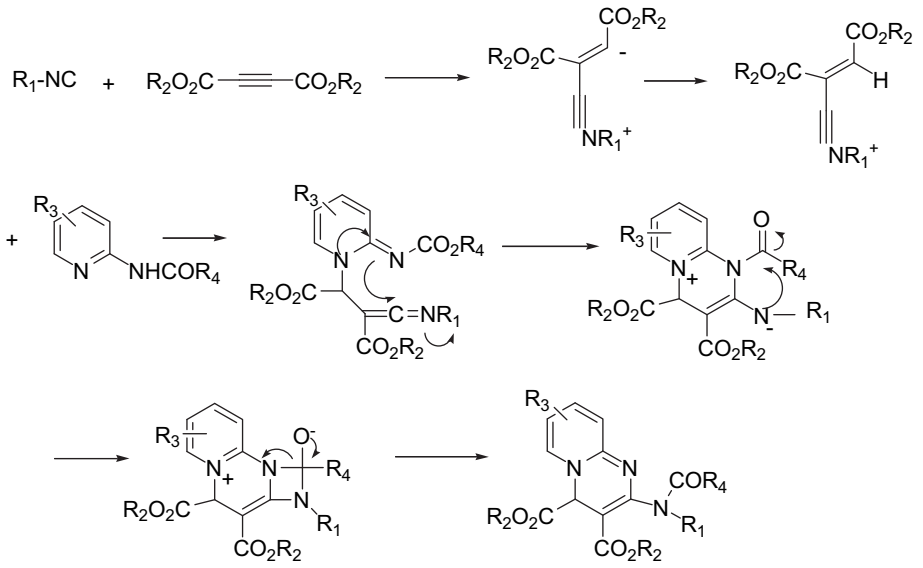
Scheme 101.



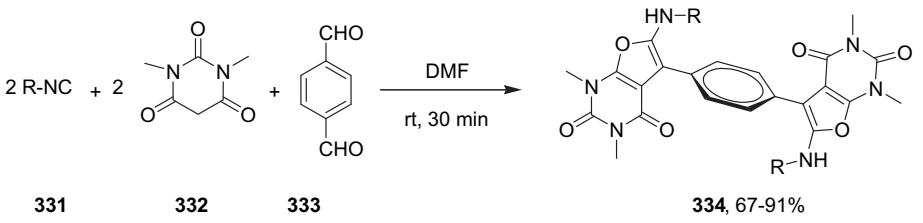
327 **328** **329** **330**, 82-92%

R_1 = *t*-Bu, Cy
R_2 = Me, Et
R_3 = H, 7-Me, 8-Me
R_4 = CO_2Et, OEt

Scheme 102.

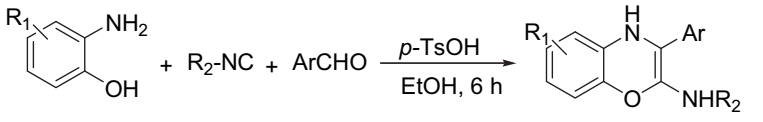


Scheme 103.



R = *t*-Bu, Benz, Cy, 2-ClPh, 1,1,3,3-tetramethylbutyl, tosylmethyl, 2,6-di-MeC_6H_3

Scheme 104.



p-TsOH = *p*-Toluenesulfonic acid
R_1 = H, Me, Cl
R_2 = Cy, *t*-Bu
Ar = Ph, 3-$NO_2C_6H_4$,4-$NO_2C_6H_4$, 4-$OMeC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 4-OHC_6H_4

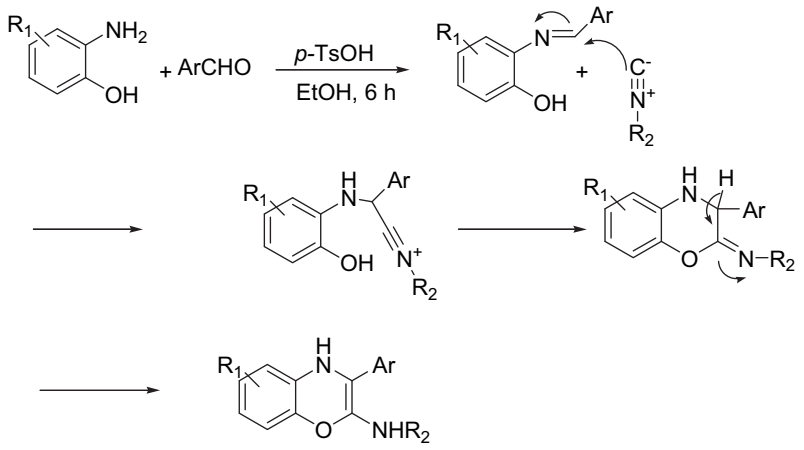
Scheme 105.

Reaction of benzo[1,4]oxazin-3-one **339**, aldehydes **340**, carboxylic acids **341** and isocyanides **342** led to the formation of oxazines **343** (Scheme 107).[81]

A two-step reaction of amines **345**, glycolaldehyde dimer **346**, isocyanides **347** and salicylic acids **344** afforded **348**, which can be transformed into 2*H*-benzo[*e*][1,3]oxazin-4(3*H*)-ones **349** via two routes (Scheme 108).[2]

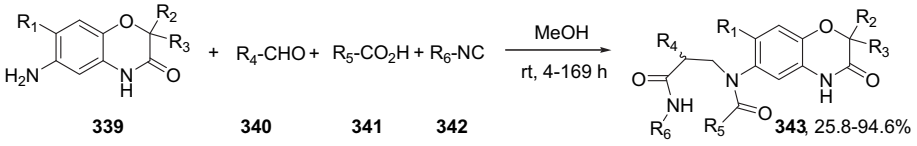
A series of 2-imino-1,4-benzoxazines **354** were prepared from two method. Firstly by a one-pot, three-component condensation of salicylaldehyde **350**, various *ortho*-aminophenols **351** and 2,6-dimethylphenyl isonitrile **352** and, secondly from the reaction of **352** and Schiff bases **353** (Scheme 109).[82]

α-Acyloxy-carboxamide azides **358**, obtained from a Passerini reaction of the easily accessible *o*-azidobenzaldehyde **356** with isocyanides **355** and carboxylic acids **357**, reacted with triphenylphosphine to give 4-aminocarbonyl-substituted 4*H*-1,3-benzoxazines **361** in moderate- to -high yields via sequential Staudinger and intramolecular aza-Wittig reactions α-hydroxy carboxamide azides **360** were, however, obtained in moderate yields when pyruvic acid **359** was used in the Passerini reaction. Further sequential reaction of α-hydroxy carboxamide azides **360** with triphenylphosphine and isocyanates produced 2-amino-4-aminocarbonyl-substituted 4*H*-1,3-benzoxazines **362** via tandem Staudinger/aza-Wittig/hetero-cumulene-mediated annulations (Scheme 110).[83]



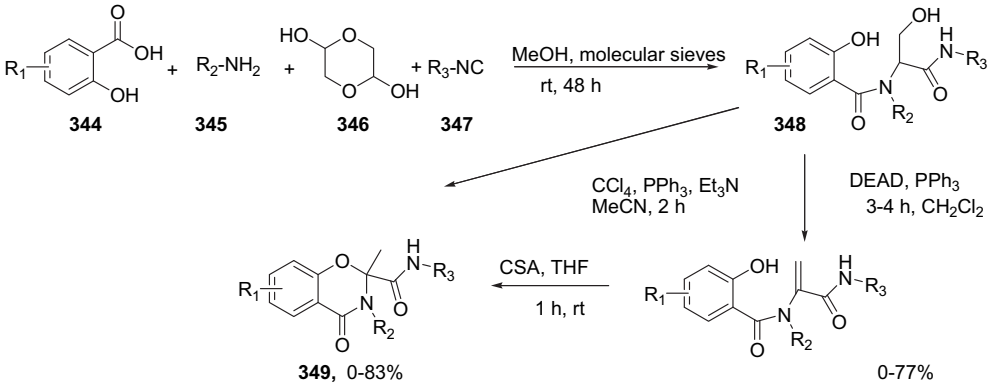
p-TsOH = *p*-Toluenesulfonic acid
R_1 = H, Me, Cl
R_2 = Cy, *t*-Bu
Ar = Ph, 3-$NO_2C_6H_4$,4-$NO_2C_6H_4$, 4-$OMeC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 4-OHC_6H_4

Scheme 106.



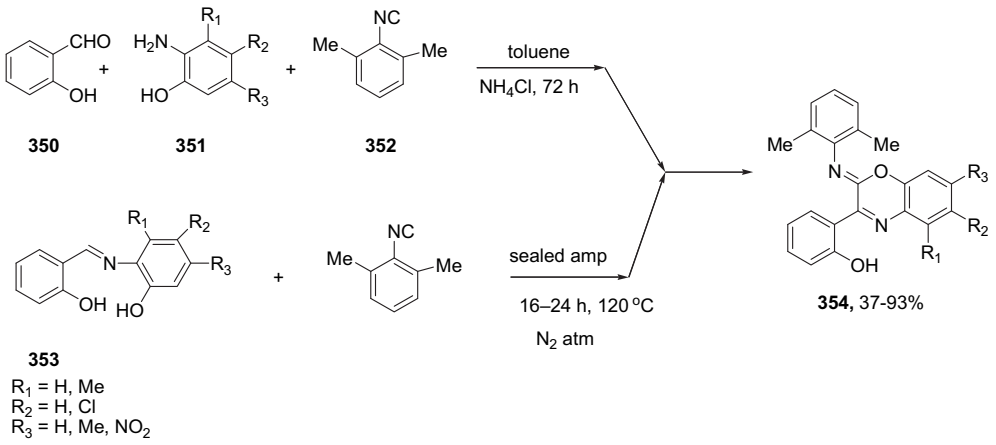
R_1 = F, Alk, Ar, Het
R_2 = Me, Ph, C_2H_4Ph
R_3 = H
R_4 = Alk, Ar, Het
R_5 = Alk, Ar, Het
R_6 = Alk, Ar

Scheme 107.



R_1 = H, 3-Cl, 3-MeO, 3-NO_2, 3-HO
R_2 = n-Bu, Bn, *p*-$MeOC_6H_4CH_2CH_2$, 2-Furyl-CH_2, 2-Thienyl-CH_2, $BnOCH_2CH_2$, *i*-Pr, *p*-ClC_6H_4
R_3 = *p*-$MeOC_6H_4$,t-Bu, t-BuO_2C-CH_2, Cy, EtO_2C-CH_2, nPent
CSA = Camphorsulfonic acid
DEAD = Diethyl azodicarboxylate

Scheme 108.

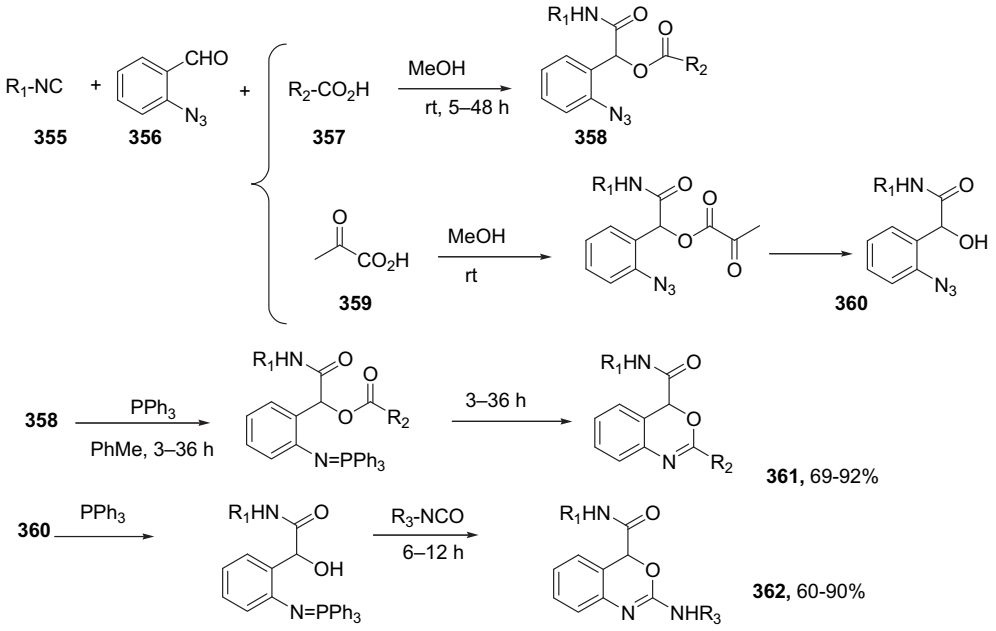


350 **351** **352**

353

R_1 = H, Me
R_2 = H, Cl
R_3 = H, Me, NO_2

Scheme 109.



355 **356** **357** **358** **359** **360**

R_1 = *t*-Bu, n-Bu
R_2 = Me, Et, Ph, 4-$CH_3OC_6H_4$, 3-$NO_2C_6H_4$, 4-ClC6H4, 2-ClC_6H_4, 3,5-di-MeC_6H_3
2,4-di-Cl-$C_6H_3OCH_2$, 4-$NO_2C_6H_4$, CH_2CH_2Ph, 2-HOC_6H_4, 2-MeC_6H_4
R_3 = *i*-Pr, 4-ClC_6H_4, 4-FC_6H_4, 3-MeC_6H_4, 4-ClC_6H_4

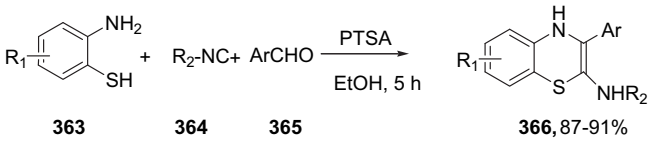
Scheme 110.

5.1.5. Thiazines. A high-yielding and rapid method for the synthesis of 3-aryl-4*H*-benzo[1,4]thiazin-2-ylamines **366** via a one-pot, three-component reaction of aromatic aldehydes **365**, isocyanide **364** and *o*-amino-thiophenols **363** using *p*-toluenesulfonic acid as a catalyst has been described (Scheme 111).[84]

The first step of the reaction, similar to a Ugi reaction, involves the reaction of the aromatic aldehyde with the *o*-amino-thiophenol followed by isocyanide attack on the resulting intermediate and then intramolecular trapping by the sulfur nucleophile to give the desired product (Scheme 112).

5.1.6. Pyrazines. By combining a three-component reaction of 2,3-diaminomaleonitrile **367**, ketones **368** and isocyanides **369** with a subsequent reaction of 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives **370** (obtained from isocyanide-based three-component reaction) with various alkyl and aryl isocyanates or isothiocyanates, a new class of highly substituted imidazo[1,5-*a*]pyrazine derivatives **371** can be assembled (Scheme 113).[85]

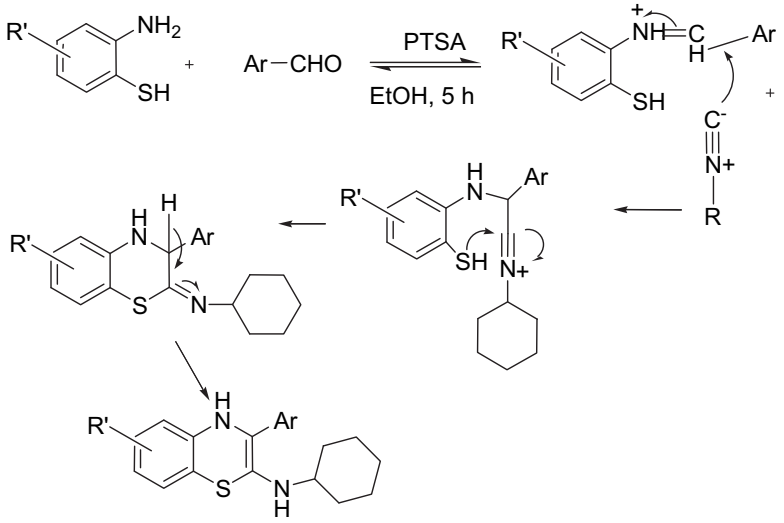
A new trimethylchlorosilane (TMSCl)-promoted multicomponent reaction (MCR) of ethylenediamine **374**, diverse carbonyl compounds **373** and isocyanides **372** has been proposed for the



363 **364** **365** **366,** 87-91%

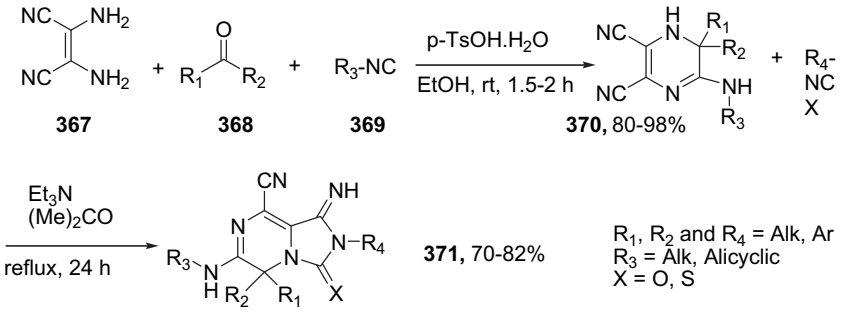
PTSA = p-Toluenesulfonic acid
Ar =Ph, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-OHC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$
R_1 = Cl, H,
R_2 = Cy, *t*-Bu

Scheme 111.



PTSA = p-Toluenesulfonic acid
Ar =Ph, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-OHC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$
R_1 = Cl, H,
R_2 = Cy, *t*-Bu

Scheme 112.



367 **368** **369** **370,** 80-98% **371,** 70-82%

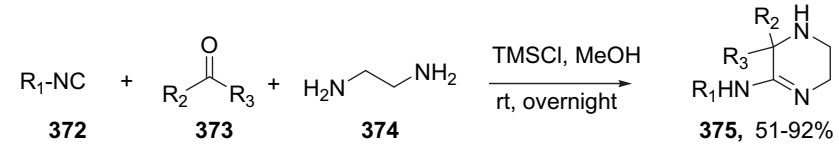
R_1, R_2 and R_4 = Alk, Ar
R_3 = Alk, Alicyclic
X = O, S

Scheme 113.

synthesis of a variety of highly substituted 3,4,5,6-tetrahydropyrazin-2-amines **375** including the corresponding spirocyclic compounds (Scheme 114).[86]

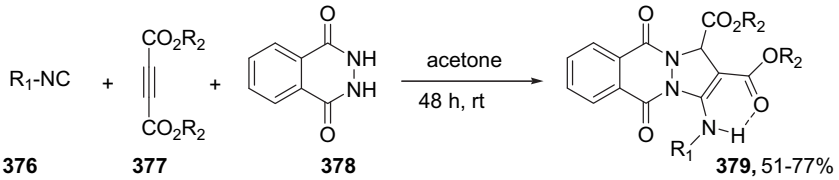
5.1.7. Phthalazines. The one-pot, three-component condensation reaction of alkyl isocyanides **376** with dialkyl acetylenedicarboxylates **377** in the presence of phthalhydrazide **378** was successfully applied to the synthesis of dialkyl 3-(alkylamino)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-1,2-dicarboxylate derivatives **379** (Scheme 115).[87]

In a first step of this reaction, nucleophilic attack of the isocyanide on the acetylenic ester and subsequent protonation of the



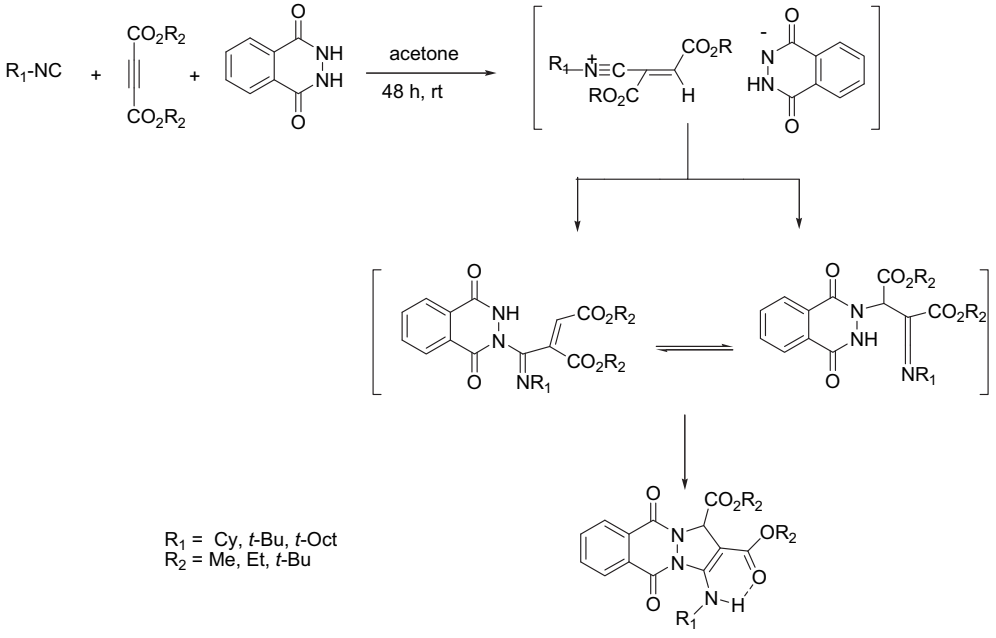
R_1 = Ar, Al
R_2, R_3 = Cyclic, Ar, Al, Het
TMSCl = trimethylchlorosilane

Scheme 114.



R_1 = Cy, *t*-Bu, *t*-Oct
R_2 = Me, Et, *t*-Bu

Scheme 115.



R_1 = Cy, *t*-Bu, *t*-Oct
R_2 = Me, Et, *t*-Bu

Scheme 116.

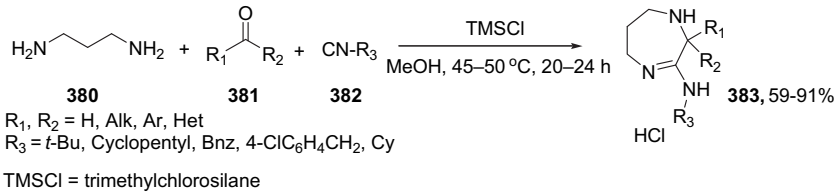
highly reactive 1:1 zwitterionic intermediate by NH-acid (phthalhydrazide) affords the vinylisonitrilium cation. The vinylisonitrilium cation could then undergo addition reactions with the nitrogen atom of the conjugate base of the NH-acid on the two possible electrophilic sites (1,2-addition and 1,4-conjugate addition) to produce two possible intermediates in equilibrium with each other. These intermediates can then cyclise under the reaction conditions employed to produce the dialkyl 3-(alkylamino)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-1,2-dicarboxylates **379** (Scheme 116).

6. Seven-membered ring heterocycles

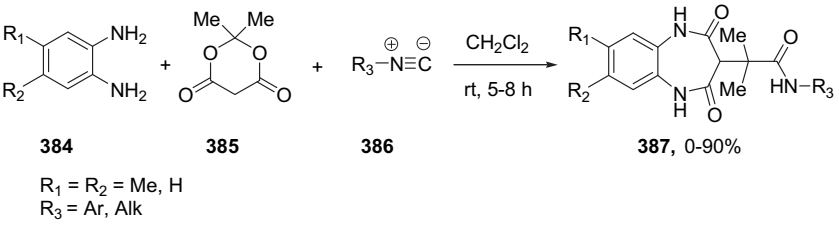
6.1. Diazepines

1,4-Diazepine-2-amines **383** were synthesised from a multicomponent reaction of 1,3-diaminopropane **380**, carbonyl compounds **381** and isocyanides **382**. It has been found that trimethylchlorosilane (TMSCl) can promote the reaction (Scheme 117).[88]

Tetrahydro-2,4-dioxo-1*H*-benzo[*b*][1,5]diazepin-3-yl-2-methylpropanamide derivatives **387** were synthesised using an aromatic



Scheme 117.

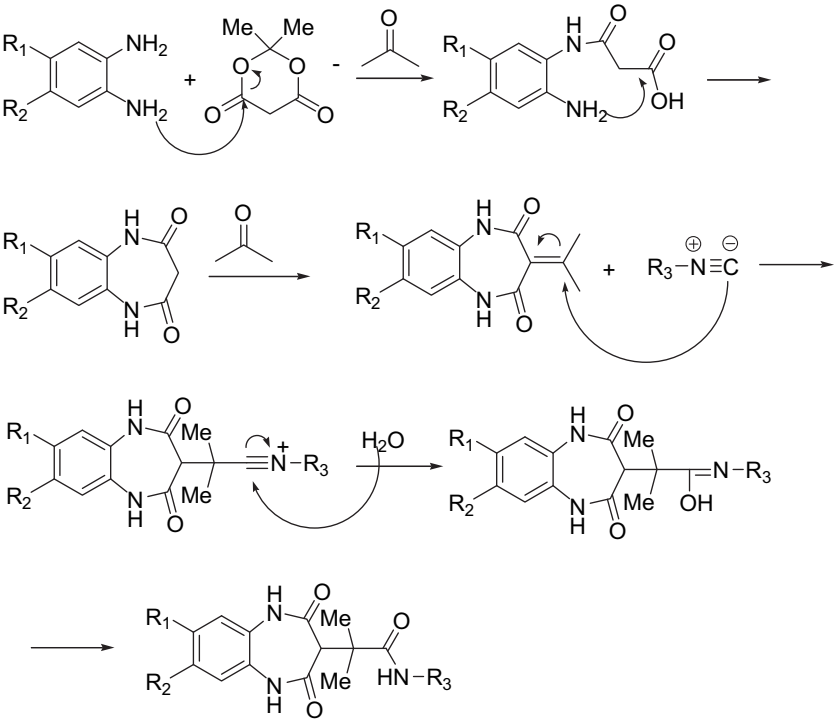


Scheme 118.

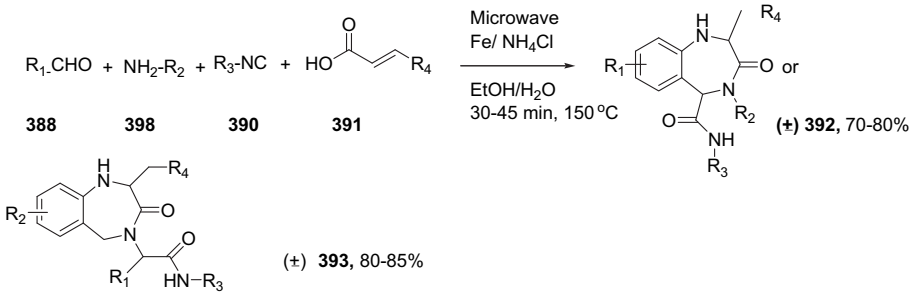
diamine **384**, Meldrum's acid **385** and an isocyanide **386** in CH_2Cl_2 at ambient temperature in high yields without using any catalyst or activation (Scheme 118).[89]

It is conceivable that the initial event is the formation of 1*H*-benzo[*b*][1,5]diazepine-2,4(3*H*,5*H*)-dione from a condensation reaction between **389** and **390**. The intermediate 1*H*-benzo[*b*][1,5]diazepine-2,4(3*H*,5*H*)-dione under a Knoevenagel condensation reaction with the in situ-liberated acetone then produces the 3-(propan-2-ylidene)-1*H*-benzo[*b*][1,5]diazepine-2,4(3*H*,5*H*)-dione intermediate. On the basis of the well-established chemistry of the reaction of isocyanides with electron-deficient α,β-unsaturated carbonyl compounds, the new intermediate was produced by nucleophilic attack of an isocyanide on 3-(propan-2-ylidene)-1*H*-benzo[*b*][1,5]diazepine-2,4(3*H*,5*H*)-dione via a Michael-type addition reaction, followed by nucleophilic attack of a H_2O molecule on the nitrilium moiety. Finally, tautomerisation produces **392** (Scheme 119).

A one-pot, two-step synthesis of regiochemically pure 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones **392** and **393** from a multicomponent Ugi condensation reaction of **388**, **389**, **390** and **391** using Fe(0) as a reductant under microwave irradiation has been reported (Scheme 120).[90]



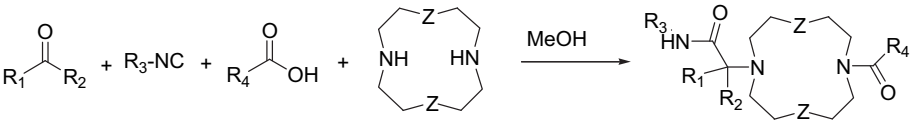
Scheme 119.



388 398 390 391

R_1 = i-Pr, 2-NO_2Ph, 4,5-DiOMe 2-NO_2Ph, 2-NO_2-4-(CF_3) Ph
R_2 = Benz, 4-BrBenz, Allyl, Piperonyl, 2-NO_2Benz, 4-aminoacetophenone
R_3 = t-Bu, Benz, Cyclopentyl, Cyclohexyl
R_4 = Ethoxycarbonyl, 4-Methylbenzoyl, Bz, H

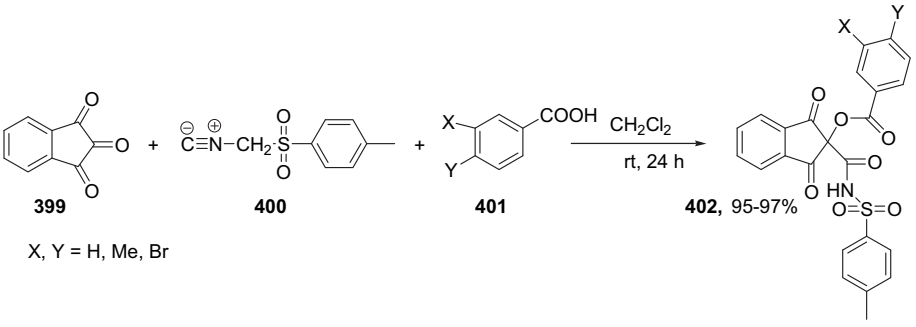
Scheme 120.



394 395 396 397 **398,** 34-64%

Z = NH, N-Me, n-Cbz, O
R_1 = H
R_2 = Pr, Ph, H
R_3 = Bn, *t*-Bu
R_4 = Me, Ph, Ph-CH=CH-, CbzNH-CH_2-

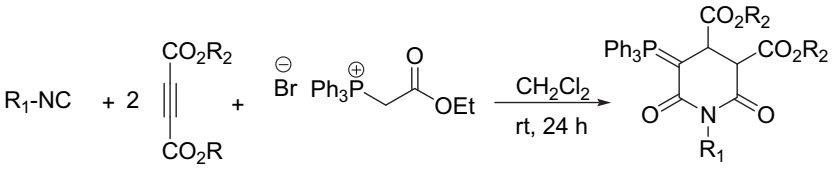
Scheme 121.



399 400 401

X, Y = H, Me, Br

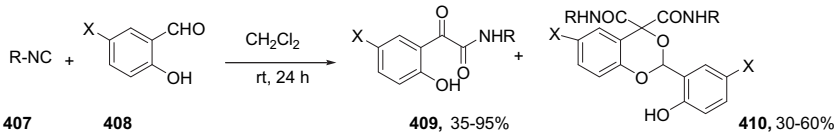
Scheme 122.



403 404 405 **406,** 51-63%

R_1 = Cy, *t*-Bu
R_2 = Me, Et, *t*-Bu

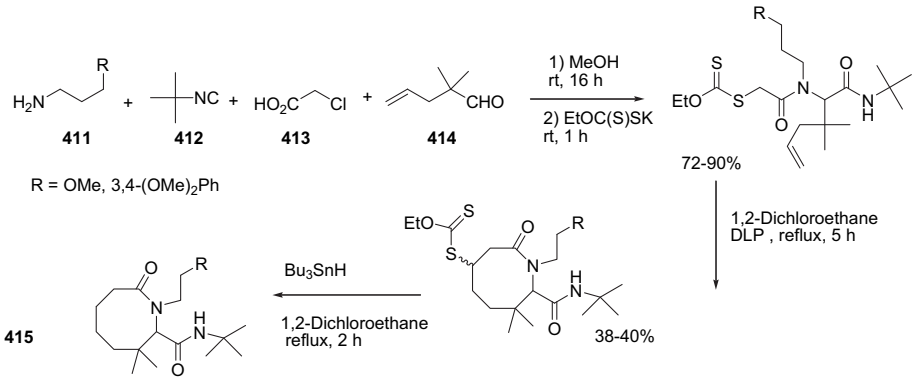
Scheme 123.



407 **408** **409,** 35-95% **410,** 30-60%

R = t-Bu, Bn, 2,6-di-MeC_6H_3, 1,1,3,3-tetramethylbutyl
X = H, NO_2

Scheme 124.

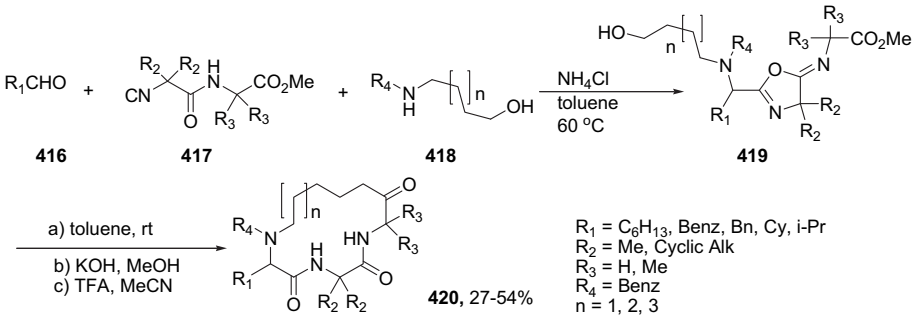


411 **412** **413** **414**

R = OMe, 3,4-$(OMe)_2$Ph

415

Scheme 125.

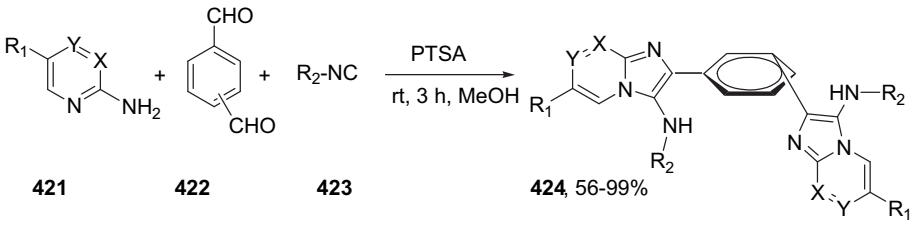


416 **417** **418** **419**

420, 27-54%

R_1 = C_6H_{13}, Benz, Bn, Cy, i-Pr
R_2 = Me, Cyclic Alk
R_3 = H, Me
R_4 = Benz
n = 1, 2, 3

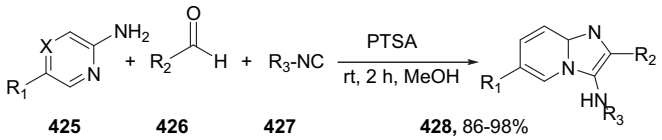
Scheme 126.



421 **422** **423** **424**, 56-99%

R_1 = H, Me, Br
R_2 = Cy, *t*-Bu
X =CH
Y = CH, N

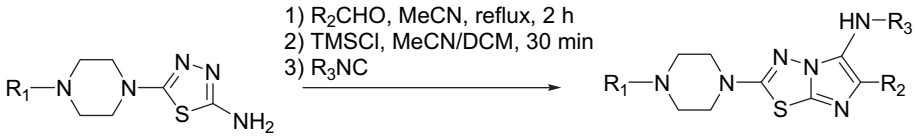
Scheme 127.



425 **426** **427** **428,** 86-98%

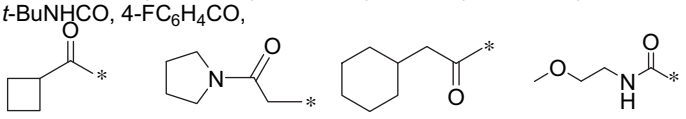
R_1 = Me, H, Br
R_2 = Ph, 4-$OMeC_6H_4$, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 4-MeC_6H_4, 4-pyr
R_3 = Cy, *t*-Bu, 2,6-di-MeC_6H_3
X = N, CH

Scheme 128.



429 **430,** 56-62%

R_1 = 3-$ClC_6H_4CH_2$, 4-$NCC_6H_4CH_2$, Bn, 2-$PyCH_2$, Allyl, 3-$MeOC_6H_4CH_2$,
R_2 = Ph, 4-FC_6H_4, 4-EtC_6H_4, 3-MeC_6H_4, 3-FC_6H_4, 4-MeC_6H_4
t-BuNHCO, 4-FC_6H_4CO,



R_3 = Cy, *t*-Bu

Scheme 129.

7. Miscellaneous

Unsymmetrical difunctionalised cyclin amines **398** and related derivatives using a modified Ugi reaction (*N*-split Ugi) have been developed. The scope of this methodology was further extended by the successful use of various isocyanides **395**, highly functionalised carboxylic acids **396**, cyclic amines **397** and aldehydes **394** (Scheme 121).[91]

The Passerini reactions of indane-1,2,3-trione **399**, tosylmethyl isocyanide **400** and benzoic acid derivatives **401** proceeded at room temperature to give sterically congested 2,2-disubstituted indane-1,3-dione derivatives **402** in quantitative yield (Scheme 122).[92]

A three-component condensation reaction between an isocyanide **403**, an electron-deficient acetylenic ester **404** and (ethoxycarbonylmethyl)triphenylphosphonium bromide **405** efficiently provided fully substituted *N*-alkyl-2-triphenylphosphoranylidene glutarimides **406** in a one-pot reaction without any activation or modification (Scheme 123).[93]

Alkyl isocyanides **407** reacted with 2-hydroxybenzaldehyde or 2-hydroxy-5-nitrobenzaldehyde **408** to afford *N*-alkyl-2-aryl-2-oxoacetamides **409** and N^2,N^4-dialkyl-2-aryl-4*H*-1,3-benzodioxine-2,4-dicarboxamides **410** in nearly 1:1 ratios. Treatment of 2,6-dimethylphenyl isocyanide with 2-hydroxy-5-nitrobenzaldehyde afforded only the 2-oxoacetamide derivative (Scheme 124).[94]

For the construction of eight-membered ring lactams **415**, commercial 2,2-dimethyl-4-pentenal **414** was coupled with chloroacetic acid **413**, *tert*-butyl isocyanide **412** and homoveratrylamines, **411** to form the products in high yield (Scheme 125).[21]

A three-component reaction of an α,α-disubstituted α-isocyanoacetamide **417**, an aldehyde **416** and an amino alcohol **418** afforded the 5-iminooxazoline **419**, which, upon saponification, cyclised under acidic conditions to provide the macrocyclodepsipeptide **420** in good overall yield (Scheme 126).[95]

Bis-3-aminoimidazo[1,2-*a*]-pyridines, -pyrimidines and -pyrazines **424** as extended π-conjugated systems were synthesised for the first time by a novel pseudo five-component condensation of 2-amino-pyridine, -pyrimidine and -pyrazins derivatives **421** with terephthalaldehyde or isophthalaldehyde **422** and isocyanides **423** in the presence of *p*-toluenesulfonic acid in methanol (Scheme 127).[96]

p-Toluenesulfonic acid catalysed the one-pot, three-component synthesis of 3-aminoimidazo[1,2-*a*]-pyridines **428** and -pyrazines through a condensation reaction of a 2-aminoazine **425**, an aldehyde **426** and an isocyanide **427** at room temperature to afford a number of 3-aminoimidazo[1,2-*a*]pyridines **428** in reasonable yield (Scheme 128).[97]

N-Substituted 5-piperazin-1-yl-1,3,4-thiadiazol-2-amines **429** that fail to undergo a Groebke–Blackburn type MCR with aldehydes and isocyanides provide fair- to -good yields of the respective 2-piperazin-1-ylimidazo[2,1-*b*][1,3,4]thiadiazoles **430** when the reaction is promoted by an equimolar quantity of trimethylsilyl chloride in an aprotic medium (Scheme 129).[98]

8. Conclusions

In this review, we have presented numerous isocyanide-based processes for the synthesis of heterocycles that have been reported in recent years. The most of the reactions proceed under

catalyst-free conditions and tolerate a wide variety of functional groups. We hope this review will generate strong interest among the general readership of this journal.

Acknowledgements

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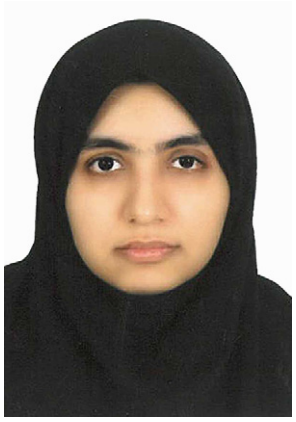

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