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MTBSTFA
TFAA
OH
Hal₂
R
BuCF
PFBBr

p.653

p.555

NH₂
R
EWG

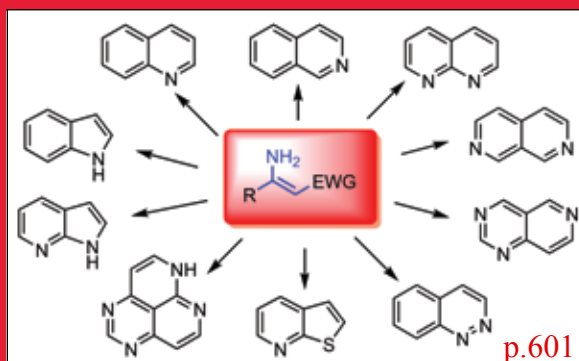p.601

gas
β-casein
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Surface tension
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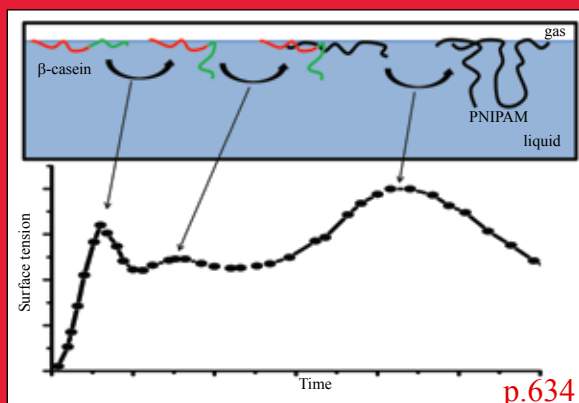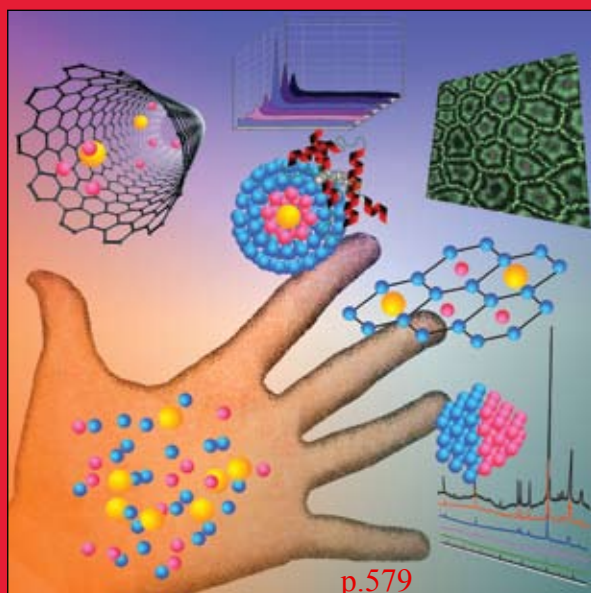
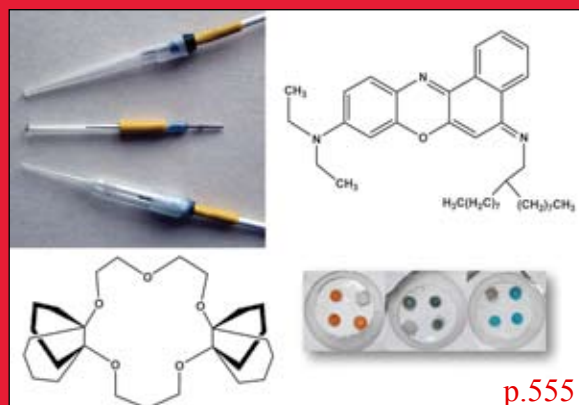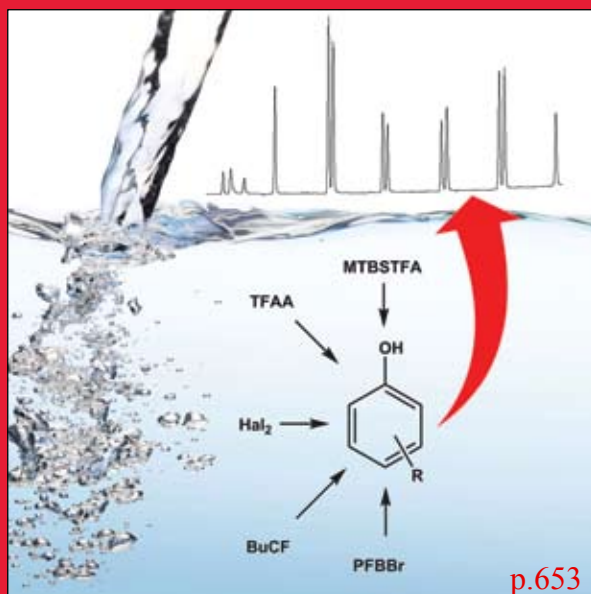**Reviews on current topics in chemistry**

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Push-pull enamines in the synthesis of fused azaheterocycles

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The review summarizes published data on the methods of the synthesis of fused nitrogen-containing heterocycles *via* push-pull enamines (mainly enaminones). Both intermolecular (cyclocondensations) and intramolecular (cyclizations) transformations of enamines, in which both nucleophilic centres of enamine (carbon and nitrogen) are incorporated into the resulting heterocycle, are considered. The data on the reactivity of enamines cover a broad range of facile methods for the preparation of diverse fused pyridines (quinolines, isoquinolines, pyridopyridines, *etc*.) and pyrroles (indoles, tetrahydro-carbazoles, pyrrolopyridines, *etc*.).
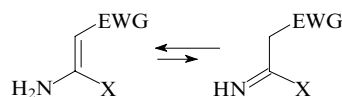The bibliography includes 191 references.

Contents

I. Introduction

Fused nitrogen-containing heterocycles have attracted great attention of researchers due to a complex of unique properties, primarily, a broad spectrum of biological activities. The synthesis of new heterocyclic systems, the development of facile procedures for the synthesis of these compounds and the improvement of available methods have been, and still remain, important areas of research in synthetic organic chemistry for many decades.

Enamines are convenient starting compounds in the synthesis of various N-heterocycles. Due to high reactivity and availability of most enamines, these compounds are highly useful in the synthesis of many types of compounds.[1−4] Enamines have diverse applications in the synthesis of heterocyclic systems. Therefore, in the present review, we have focused principally on certain, to some extent arbitrary issues, which was necessary to keep the review to a reasonable length.

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Current research interests of the authors: organic synthesis, synthesis of heterocyclic compounds, new approaches to the synthesis of fused nitrogen-containing heterocycles.

First, we confine ourselves to the consideration of so-called push-pull enamines, *i.e.*, enamines of the $N-C=C-EWG$ type, where EWG is the electron-withdrawing group. A carbonyl group (in ketone, ester or amide) generally serves as EWG, but nitrile, nitro and sulfonyl groups are also involved, though more rarely, in enamines. Under the common term 'enamines' the authors mean also tautomeric forms of amidines, imino esters and their sulfur-containing analogues. In the presence of an electron-withdrawing group in the α position, such amidines and imino esters as free bases exist predominantly or completely in the enamine tautomeric form and react exactly in this form,[5] although these compounds are, by tradition, often referred to as amidines or imino esters (Scheme 1).

Scheme 1

X = NH$_2$, OR, SR (R = Alk, Ar)

Second, the review deals with the synthesis only of fused N-heterocycles, mainly aromatic ones.

Third, only reactions, in which the enamine nitrogen atom is involved in the heterocycle that formed, are described. Therefore, we do not consider reactions, in which the enamine function acts in the masked form and serves as a synthetic equivalent of the carbonyl group (most often of aldehyde), and the nitrogen atom is a leaving group. There is a great number of such reactions and the latter are, in essence, analogues of the reactions of carbonyl compounds. Therefore, we excluded these reactions from the consideration.

Finally, the present review covers almost exclusively the results published in the last 15–20 years. Earlier publications are summarized in previous reviews.[6–9] For well-known reactions, we consider only the latest data published in the above-mentioned period of time.

II. Intermolecular transformations (cyclocondensations) of enamines

II.1. Formation of fused pyrroles
II.1.a. Reactions of enamines with ninhydrin

Usually, indane-1,2,3-trione monohydrate (ninhydrin, **1**) readily reacts under mild conditions with nucleophiles, including enamines of different structures. In 1995 it was shown that aminocrotonic ester **2** reacts with ninhydrin to form the corresponding indeno[1,2-*b*]pyrrole **3** in high yield (Scheme 2).[10] Later on, it was found that this reaction can be performed under solvent-free conditions to obtain the cyclocondensation product in quantitative yield.[11]
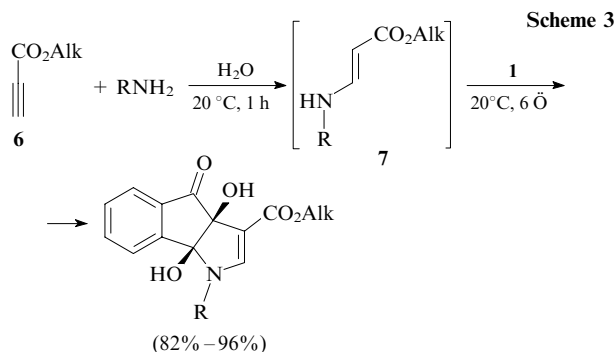
Scheme 2
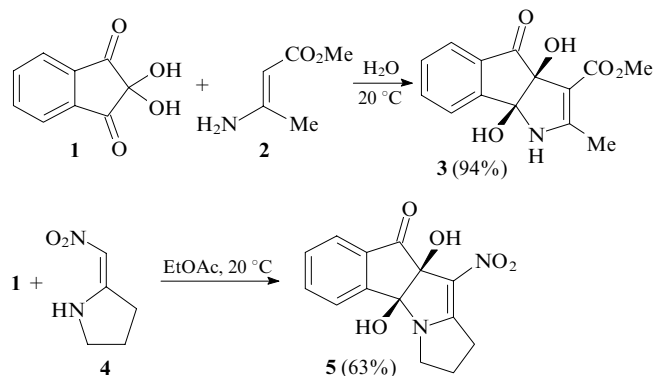
Ninhydrin reacts in a similar way with nitroenamine **4** and gives tetracyclic compound **5** in good yield (see Scheme 2).[12]

Many enaminones can be synthesized in quantitative yields from the corresponding precursors under mild conditions, due to which they can be introduced into further transformations without the isolation (*in situ*). This approach was successfully implemented using propiolic esters **6** as the starting compounds; primary amines add to the triple bond of these esters at room temperature to form N-substituted 3-aminoacrylic esters **7** (Scheme 3).[13]
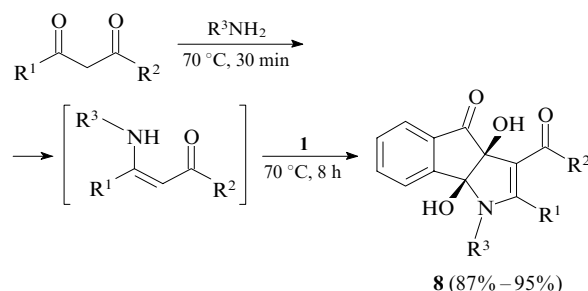
1,3-Dicarbonyl compounds are also convenient precursors for enaminones. This approach underlies a very facile

Scheme 3

Alk = Me, Et; R = Bu^n, Cy, Bn; Cy is cyclohexyl

procedure for the synthesis of N-alkylindenopyrroles **8**, which is characterized by the simplicity and does not require the use of a solvent (Scheme 4).[14]

Scheme 4

R^1 = R^2 = Me; R^1 = Ph, R^2 = Me; R^1 = Me, R^2 = OEt;
R^3 = Me, Pr^n, Bu^t

It was shown than not only N-alkyl but also N-aryl derivatives of indenopyrroles can be prepared.[15] This method is based on the use of easily available N,N-dimethyl enaminones **9** and consists in grinding of these compounds with ninhydrin and the corresponding amine in the presence of a small amount of acetic acid without a solvent (Scheme 5).
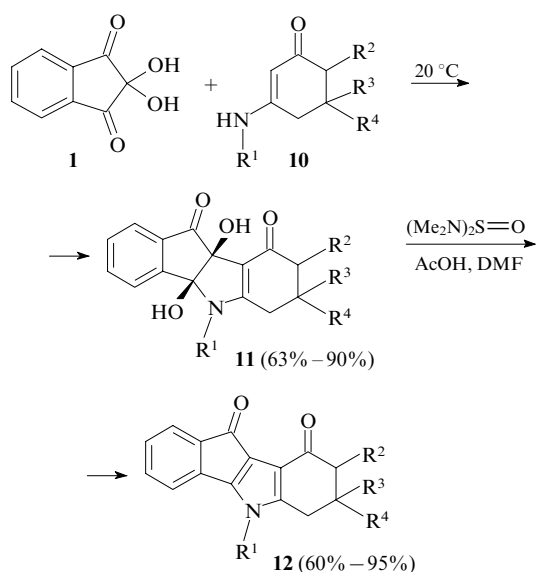
Scheme 5
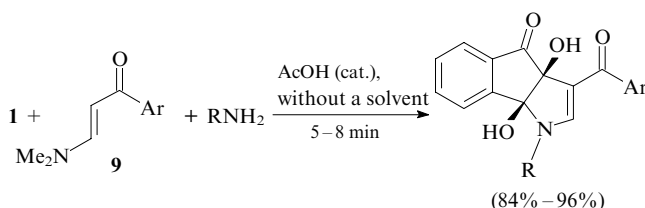
Ar = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 2-Th, 2-Fu;
R = Pr^n, cyclo-C$_3$H$_5$, Bu^n, Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$;
Th is thienyl, Fu is furyl

The above-considered reactions involve the double nucleophilic addition, in which enamine acts as a 1,3-C,N-dinucleophile and ninhydrin serves as a 1,2-dielectrophile. All reactions are characterized by high regioselectivity. Thus, the nucleophilic carbon centre of enamine is attached exactly to the C(2) atom of ninhydrin, whereas the nucleophilic nitrogen centre attacks one of the two adjacent carbonyl groups. Evidently, the C—C bond is formed in the initial step because the C(2) atom of ninhydrin is the most electrophilic, which is, in particular, confirmed by the results of the reactions of ninhydrin with various mono-C-nucleophiles.[16, 17] In the second step, the nucleophilic addition of the amino group takes place. Since the geometry of the intermediate is such that the attack on the carbonyl carbon atom can occur only from the side of the newly formed C—C bond, the reaction affords exclusively *cis* isomers of vicinal dihydroxy derivatives.

It was found that the reaction of ninhydrin with substituted cyclic enaminones **10** gives partially saturated dihydroxyindeno[1,2-*b*]indoles **11** (Scheme 6).[18, 19] Hemmerling and Reiss[18] demonstrated that the pyrrole ring can be aromatized *via* *vic*-dehydroxylation with N,N,N′,N′-tetramethylthionylamide (TMTA)[20] to obtain compounds **12**.

Scheme 6

R^1 = Alk, Ph; R^2 = H, CO$_2$Me; R^3 = R^4 = H, Me;
R^3 = H: R^4 = Me, Ph

This scheme was applied to synthesize a series of compounds **12**, the cyclohexanone moiety of which was subjected to oxidative aromatization using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to form the phenol group (for R^3 = H).[21, 22] In biological tests, these indoles exhibited high potential as a new class of CK2 protein kinase inhibitors.

Recently, a new modification of the synthesis of indenoindoles was proposed based on the reaction of cyclic enaminones **10** with ninhydrin.[23] The microwave (MW) heating of the starting compounds in the presence of anilines in acetic acid afforded compounds **13**, in which the hydroxy group of the hemiaminal moiety was replaced by the arylamino group (Scheme 7). Meanwhile, the heating of the starting compounds in acetic anhydride gave fused indoles **14**.

It is interesting that the cyclohexene moiety of enamine is transformed into the aromatic moiety even in the presence of two geminal methyl groups (R^2 = Me). This reaction is accompanied by the migration of the methyl group. Jiang et al.[23] suggested the mechanism for this unusual double dehydration of the intermediate dihydroxy derivative that takes place under the action of acetic anhydride (Scheme 8).
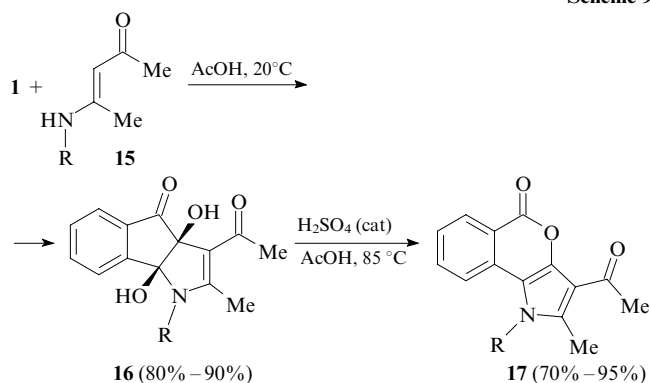
Scheme 7
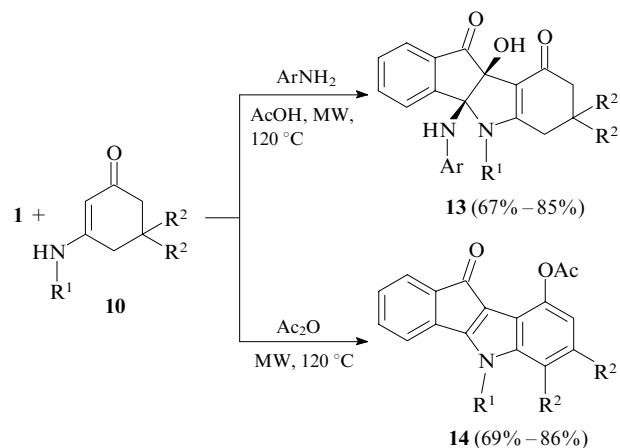
R^1 = Me, cyclo-C$_3$H$_5$, Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-MeOC$_6$H$_4$,
4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$; R^2 = H, Me;
Ar = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$

Pathak et al.[24] described, in addition to the reaction of ninhydrin with enaminones **15** (generated from acetylacetone) to give adducts **16**, their further transformation into isocoumarin derivatives **17** (Scheme 9). The rearrangement of dihydroxy derivatives **16** takes place under heating in acetic acid in the presence of sulfuric acid.

Scheme 9

R = Pr^n, Bn, Ph, 2-MeOC$_6$H$_4$, 4-MeOC$_6$H$_4$, 3-HOC$_6$H$_4$, 2-ClC$_6$H$_4$,
3-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 3-O$_2$NC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$

The proposed mechanism of the formation of compounds **17** involves the cleavage of the bond between carbon

Scheme 8

Scheme 10

$RNH_2 + AlkO_2C-\equiv-CO_2Alk \xrightarrow[Ac_2O, MW, 100\,^{\circ}C]{(1)}$ **18** (60% – 86%)

A $\xrightarrow{1}$ **B** $\xrightarrow{H^+}$ $\xrightarrow{-H^+}$ $\xrightarrow[-H_2O]{H^+}$

$\longrightarrow$ $\longrightarrow$ $\xrightarrow{-H^+}$ **18**
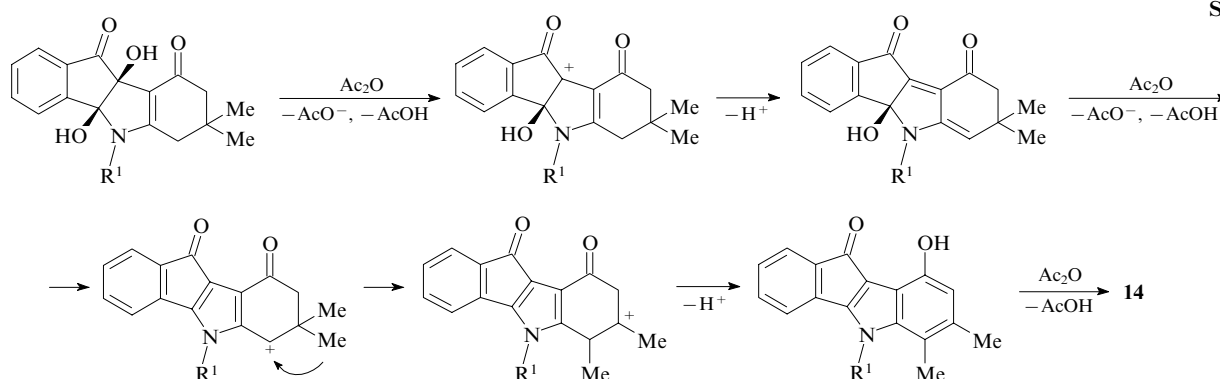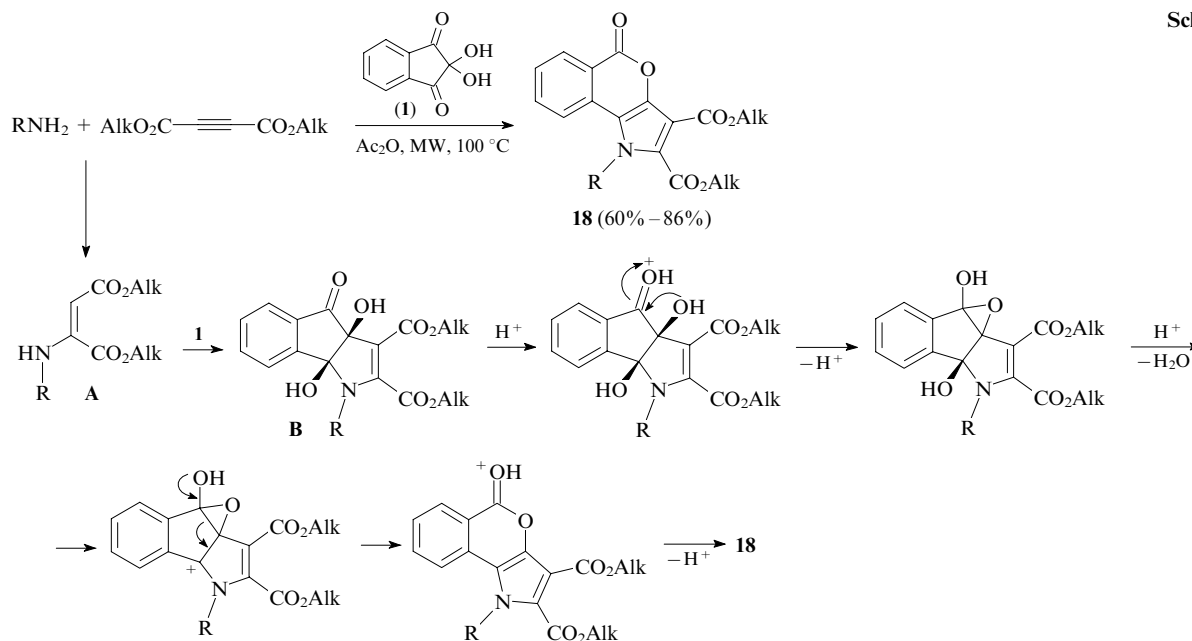
R = Me, cyclo-C_3H_5, Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 3-FC_6H_4, 3,4-$Cl_2C_6H_3$, 3,5-$Cl_2C_6H_3$, 3,5-$F_2C_6H_3$; Alk = Me, Et

atoms bearing hydroxy groups to form an eight-membered ring. In our opinion, a more probable scheme of this rearrangement was suggested by Sun *et al.*,[25] who described similar transformations resulting in the formation of pyrroloisocoumarins **18** (Scheme 10). In this case, acetylenedicarboxylates are precursors for enamines. The three-component reaction is conducted as a one-pot procedure without the isolation of intermediate aminomaleates **A** and their adducts with ninhydrin — dihydroxyindenopyrroles **B** (see Scheme 10).

An unusual result was obtained by Yan *et al.*,[26] who studied the reaction of ninhydrin with cyclic enediaminones **19**. They showed that this reaction performed under reflux in dioxane in the presence of acetic acid also gave pyrroloisocoumarins **20** in high yields (Scheme 11).

Scheme 11

1 + **19** $\xrightarrow[\Delta, 6\,h]{AcOH-1,4-dioxane}$ **20** (73% – 88%)

$\longrightarrow$ [**21**] $\xrightarrow{H^+}$
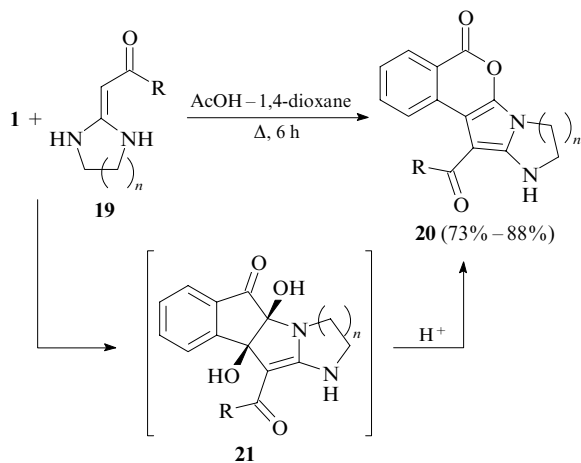
R = EtO, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4; n = 1 – 3

The proposed mechanism of this rearrangement is similar to that described above. This scheme involves the initial

formation of dihydroxyindenopyrroles **21** *via* the binding of the nucleophilic carbon centre of enamine to the C(1) atom of ninhydrin and the attachment of the nitrogen atom to the C(2) atom. This result of the reaction is unusual, because the reaction of enediamines **19** with ninhydrin proceeds with high regioselectivity inverse to that observed for all the above-considered enamines.

Another rearrangement of adducts of ninhydrin with enaminones has been described.[27] The reaction proceeds under mild conditions in the presence of an oxidizing agent (orthoperiodic acid) to form spiro compounds **22** in high yields (Scheme 12).

Scheme 12

1 + $\xrightarrow[20\,^{\circ}C, 3\,h]{EtOH-H_2O}$ $\longrightarrow$ $\xrightarrow[20\,^{\circ}C, 1\,h]{H_5IO_6}$ **22** (80% – 90%)
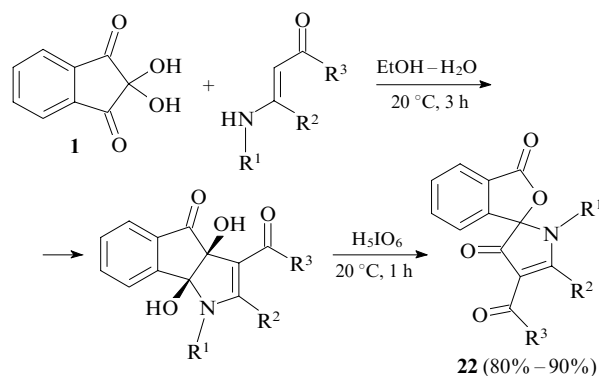
R^1 = Bn, $(CH_2)_2Ph$, Ar; $R^2 = R^3$ = Me, Ph; R^2 = H, R^3 = OEt; R^2 = CO_2Me, R^3 = OMe

Yet another example of the application of the reaction of enamines with ninhydrin in the synthesis of polycyclic compounds has been reported.[28] The first step affords the condensation product of ninhydrin with malononitrile (compound **23**), which is then introduced into the reaction with cyclic enaminones without the isolation (Scheme 13). The result of the reaction depends on the ring size of the

substrate. Thus, five-membered enaminones selectively form spiro compounds **24**, whereas their six-membered analogues give heterocyclic [3.3.3]propellanes **25**.

Scheme 13

24 (63% – 75%)

(10) (R = H, Me)

25 (70% – 80%)

Ar = Ph, 2-MeOC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$
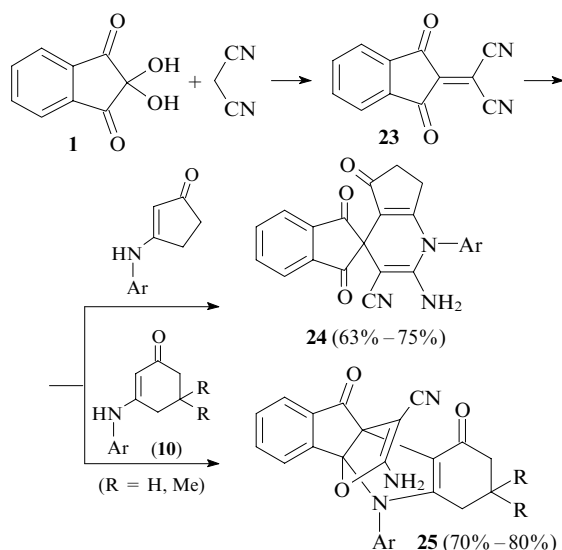
This difference in the reactivity is determined by the geometry of the intermediate that is formed after the addition of enamine *via* the nucleophilic carbon centre to the activated double bond of compound **23**. In the case of aminocyclopentenones, the subsequent cyclization occurs at the nitrile group to form the spiro-fused six-membered ring. The whole chain of transformations resulting in the formation of dihydropyridines **24** is analogous to the Hantzsch reaction. Enamines with a six-membered ring tend to undergo the ring closure to form the dihydropyrrole ring followed by the formation of an additional ring *via* the addition of the hydroxy group to the C≡N triple bond.

II.1.b. Reactions of enamines with quinones
In the reaction with enamines, quinones containing no additional reactive substituents give 5-hydroxyindoles.[29] This reaction has been known for 85 years as the Nenicesku reaction; it is well-studied and is widely used as a convenient method for the synthesis of indoles. 1,4-Benzoquinone, its
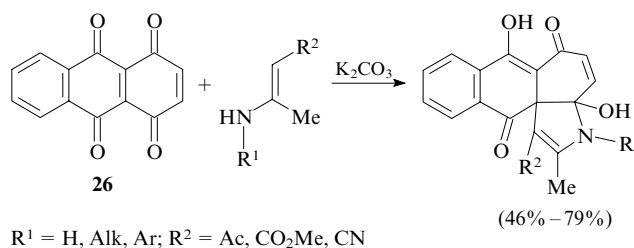
Scheme 14

19

R^1, R^2, R^3 = H, Me, OMe; R^4 = OEt, Ar
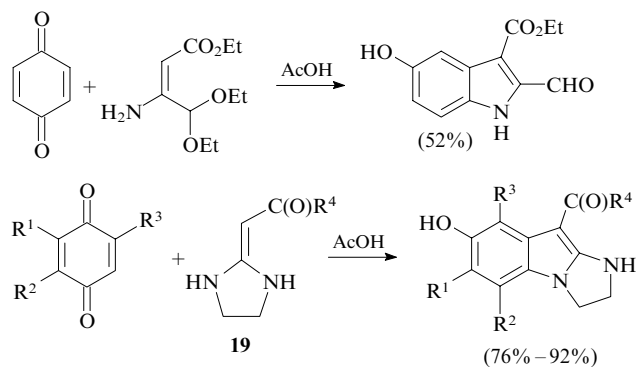
methyl and methoxy derivatives and 1,4-naphthoquinones easily enter into this reaction. A very broad range of enamines can be introduced into the Nenicesku reaction. These are primarily aminocrotonic ester and its analogues, various aminovinyl ketones and enediamines, both acyclic and cyclic.[30–38] Some most interesting, in our opinion, examples are given in Scheme 14.[39, 40]

Anthradiquinone **26** reacts in a similar way but with the involvement of two quinone rings (Scheme 15).[41]

Scheme 15

R^1 = H, Alk, Ar; R^2 = Ac, CO$_2$Me, CN

(46% – 79%)

The reactions of dicarboxylate **27** with aminocrotonic esters proceed in a similar manner (Scheme 16).[42] The structure of the final product depends on the degree of substitution of the nitrogen atom in enamine. The reaction of N-substituted aminocrotonic esters is accompanied by the migration of the ethoxycarbonyl group followed by decarboxylation.

Scheme 16

27

(R = H) (42%)

(R = Me, Ar)

(70% – 80%)
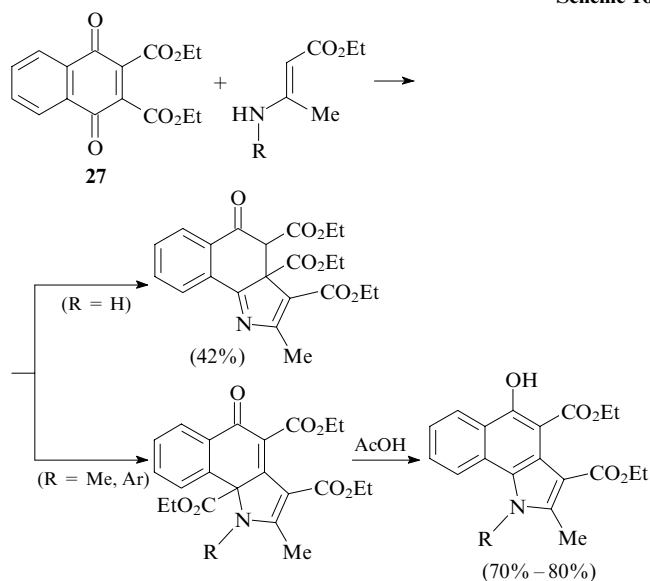
The study of the effect of Lewis acids on the Nenicesku reaction showed that the yields of indoles are substantially higher in the reactions catalyzed by weak Lewis acids, for example, by zinc chloride.[43, 44]

The reaction of naphthoquinone with enamines in the presence of oxygen and catalytic amounts of divalent copper salts proceeds in a different way.[45] Under these conditions, the reaction produces indolediones **28** in high yields (Scheme 17). Sun *et al.*[45] suggested the following sequence of steps: the Michael addition of enamine to naphthoquinone, isomerization of adduct **29** to hydroquinone **30**, oxidation of hydroquinone to quinone **31**, cyclization *via* the addition of a nitrogen atom to the activated double bond, isomerization of intermediate **32** to hydro-

quinone **33** and oxidation of the latter to the reaction product.

Scheme 17

R = Alk, Ar
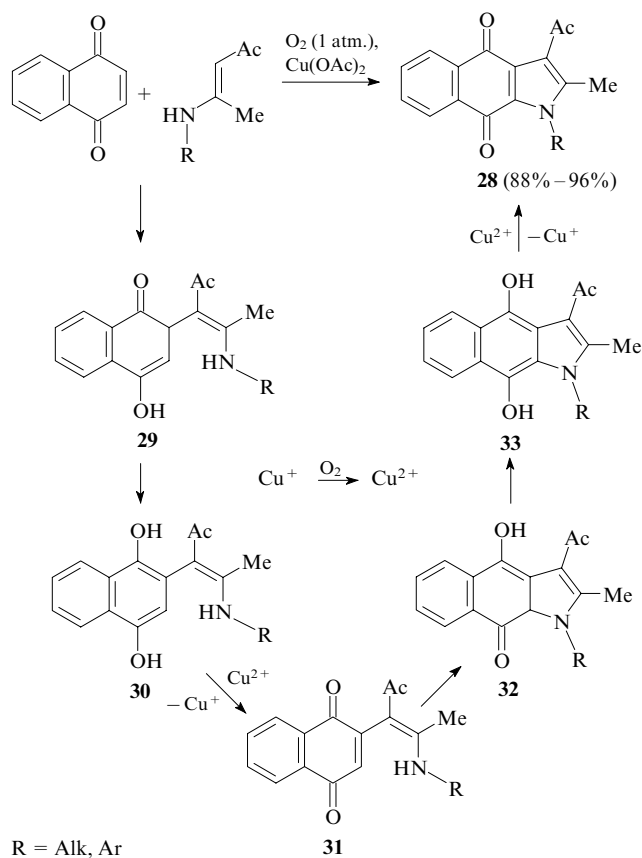
Indolediones can also be synthesized by the reaction of halogenated quinones with enamines. Monobromoquinones **34** react with enamines and, in the presence of an oxidizing agent, form indolediones **35** (Scheme 18). Atmospheric oxygen in the presence of divalent copper salts can serve as an oxidizing agent.[46, 47]
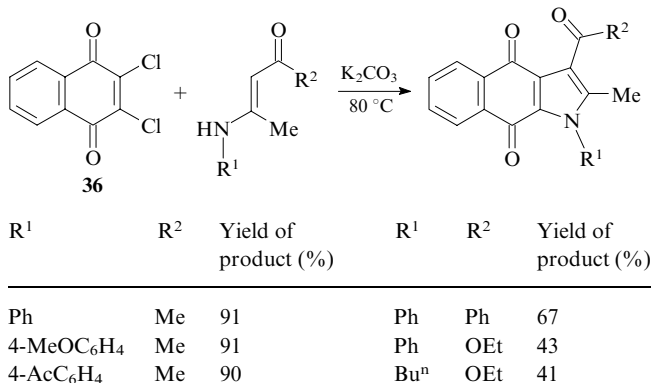
Scheme 18
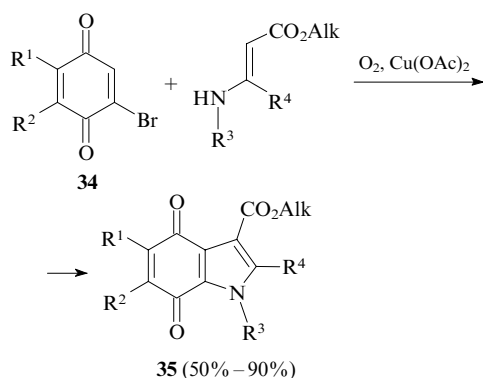
R^1, R^2 = H, OMe, Br, Et; R^3 = Alk, Ar; R^4 = H, Me, CO_2Me

The reaction proceeds with 100% chemoselectivity. Thus, the nitrogen atom of enamine replaces the bromine atom in bromoquinone. Cerium ammonium nitrate (CAN) was proposed as the oxidizing agent.[48] The similar transformation that occurs in the presence of the complex Ph_3PAuCl and silver triflate was described by Abdukader

et al.[49] However, in this case the nature of the oxidizing agent remains unclear.

The reaction with the use of dichloroquinone **36** as the starting compound does not require an oxidizing agent and proceeds in the presence of a base (Scheme 19).[50, 51]

Scheme 19

R^1	R^2	Yield of product (%)	R^1	R^2	Yield of product (%)
Ph	Me	91	Ph	Ph	67
4-MeOC$_6$H$_4$	Me	91	Ph	OEt	43
4-AcC$_6$H$_4$	Me	90	Bu^n	OEt	41

II.1.c. Other reactions producing fused pyrroles

Enamines add to the highly electrophilic ring of 1,2,4-triazines **37** to form fused pyrrolines **38** (Scheme 20).[52] This reaction formally involves the addition of both nucleophilic centres of enamine to two C=N bonds of triazine.
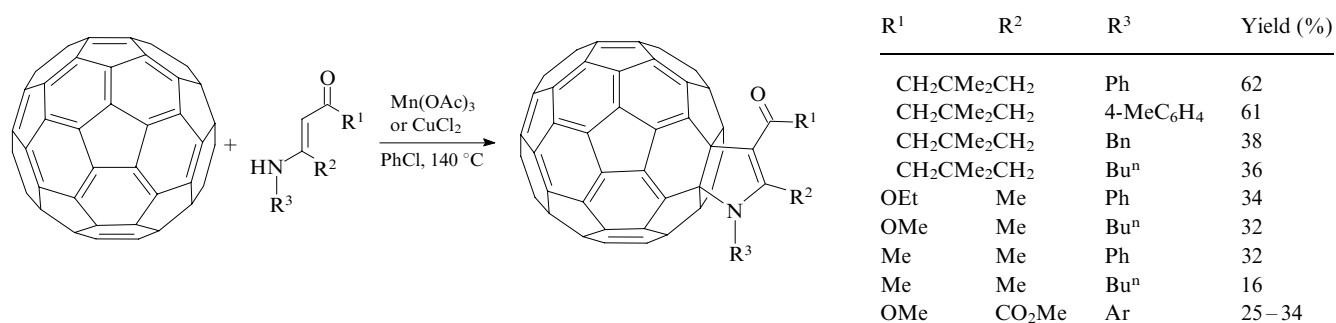
Scheme 20
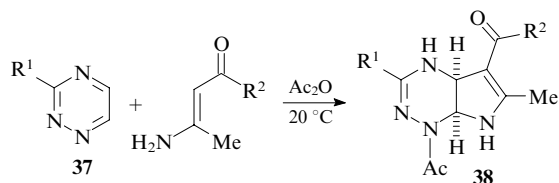
R^1	R^2	Yield of **38** (%)	R^1	R^2	Yield of **38** (%)
Ph	OEt	59	SEt	OEt	13
4-MeOC$_6$H$_4$	OEt	58	Ph	Me	49
4-O$_2$NC$_6$H$_4$	OEt	18	Ph	Ph	50
SBn	OEt	54			

The annulation with fullerene C_{60} was performed for a broad range of substituted enamines (Scheme 21). The reaction occurs in the presence of $Mn(OAc)_3$ (Ref. 53) or $CuCl_2$ (Ref. 54) and, apparently, follows a radical mechanism.
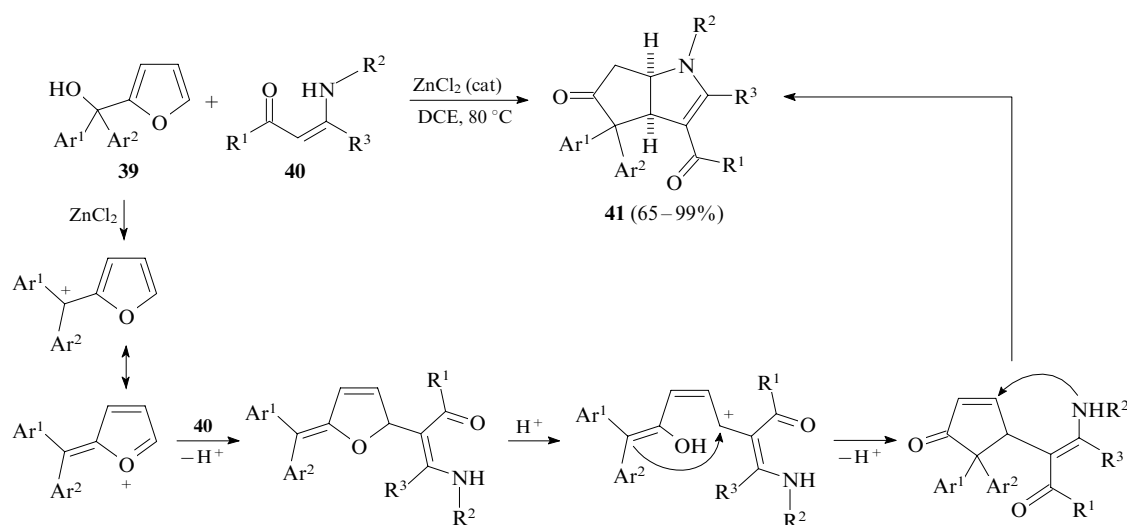
The zinc chloride-catalyzed reactions of α-substituted furfuryl alcohols **39** with substituted enaminones **40** in 1,2-dichloroethane (DCE) afford cyclopenta[*b*]pyrroles **41** (Scheme 22).[55] The reaction involves the dehydration of the alcohol in the presence of Lewis acid as the first step. The resulting carbocation binds an enamine molecule, the furan ring is opened under the action of Lewis acid, and the ring transformation gives cyclopentenone, in which the intramolecular nucleophilic addition to the activated double bond takes place.

Electrochemical reactions of pyrocatechols with enaminones **42** were shown to form indole derivatives **43** and **44** (Scheme 23).[56, 57] The synthesis is conducted under mild conditions and gives products in good yields.
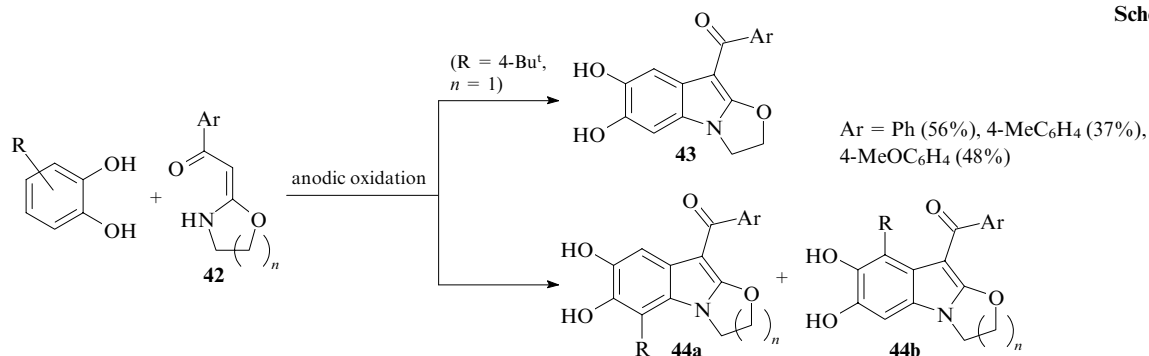
R^1	R^2	R^3	Yield (%)
$CH_2CMe_2CH_2$		Ph	62
$CH_2CMe_2CH_2$		4-MeC_6H_4	61
$CH_2CMe_2CH_2$		Bn	38
$CH_2CMe_2CH_2$		Bu^n	36
OEt	Me	Ph	34
OMe	Me	Bu^n	32
Me	Me	Ph	32
Me	Me	Bu^n	16
OMe	CO_2Me	Ar	25 – 34

$Ar^1 = Ar^2 = Ph$, 4-ClC_6H_4; $Ar^1 = Ph$, $Ar^2 = 4\text{-ClC}_6H_4$; $R^1 = Bu^n$, Cy, Ph, 4-ClC_6H_4; $R^2 = Bn$, $n\text{-}C_6H_{13}$, Bu^t, Ph, 4-ClC_6H_4, $2,6\text{-Me}_2C_6H_3$, $3,4,5\text{-(MeO)}_3C_6H_2$; $R^3 = H$, Ph

Ar = Ph (56%), 4-MeC_6H_4 (37%), 4-MeOC_6H_4 (48%)

| R	Ar	n	Yield of **44a** + **44b** (%)	**44a** : **44b**	R	Ar	n	Yield of **44a** + **44b** (%)	**44a** : **44b**
3-MeO	Ph	1	51	2 : 1	3-MeO	Ph	2	25	2 : 1
3-MeO	4-MeC_6H_4	1	71	2 : 1	3-MeO	4-MeC_6H_4	2	45	2 : 1
3-MeO	4-MeOC_6H_4	1	40	2 : 1	3-Me	4-MeC_6H_4	1	62	1 : 1

The reaction proceeds apparently *via* the formation of *o*-benzoquinone. The indole ring is closed with the involvement of the C(4) and C(5) atoms of pyrocatechols. It should be noted that in the case of 3-substituted substrates, the

reaction produces a mixture of regioisomers **44a** and **44b**, whereas the reaction of 4-*tert*-butylpyrocatechol leads to the replacement of the *tert*-butyl group.

II.2. Formation of fused pyridines

II.2.a. Reactions of enamines with acylquinones

The reaction of 2-acetyl-1,4-benzoquinone with aminocrotonic ester **2** in dichloromethane (DCM) at room temperature affords isoquinoline **45** in high yield (Scheme 24).[58] This transformation is similar to the reaction of enamines with α,β-unsaturated carbonyl compounds, which proceeds *via* the addition of the nucleophilic carbon centre of enamine to the activated double bond followed by the cyclization of the amino group at the carbonyl carbon atom and elimination of a water molecule. In the presence of an appropriate oxidizing agent, the dihydroxybenzene ring of compound **45** can be oxidized to the quinone one to form isoquinolinequinone **46**.

Scheme 24
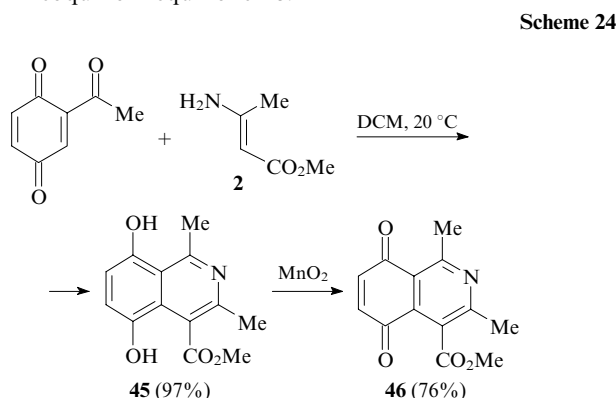
In a series of studies,[59–64] isoquinolinequinones were synthesized from both aminocrotonic ester (**46**)[59–62] and cyclic enaminones (**47**)[63–65] employing an approach, in which acylquinones were prepared *in situ* from the corresponding 2-acylhydroquinones (Scheme 25). In this case, silver oxide proved to be a convenient oxidizing agent. In the presence of the latter, the hydroquinone ring underwent successive oxidation before and after the cyclocondensation with enamine.

Scheme 25
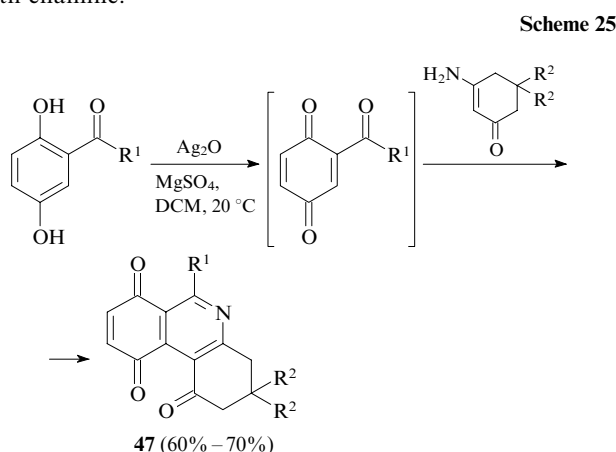
$R^1, R^2 = H, Me$

Due to the presence of the quinone ring in fused heterocycles **46** and **47**, the latter compounds can be further modified. This was employed to prepare benzannulated and heteroannulated derivatives by the cycloaddition reaction (Scheme 26).[58, 63, 64] Halogen, arylamino and arylthio derivatives can also be synthesized.[59–62, 65, 66] It was shown

that many of the synthesized isoquinolinequinone derivatives exhibit high antitumour activity.

Scheme 26
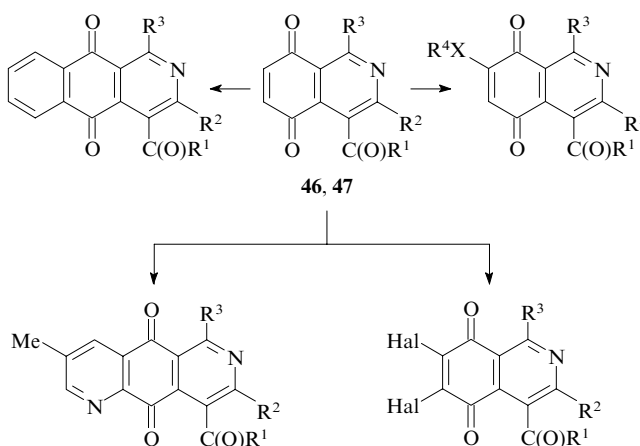
46, 47: $R^1 = OMe$, $R^2 = Me$: $R^1 - R^2 = (CH_2)_3$; $R^3 = H, Me, Ph$; $X = S, NH$; $R^4 = Me, Ar$; $Hal = Cl, Br$

The reaction of 1,4-dihydroxynaphthalene-2-carboxylate with substituted β-aminoacrylic acid esters in the presence of manganese(IV) oxide followed by heating in toluene with acetic acid gives benzo[*g*]isoquinoline-1,5,10(2*H*)-triones **48** (Scheme 27).[67]

Scheme 27
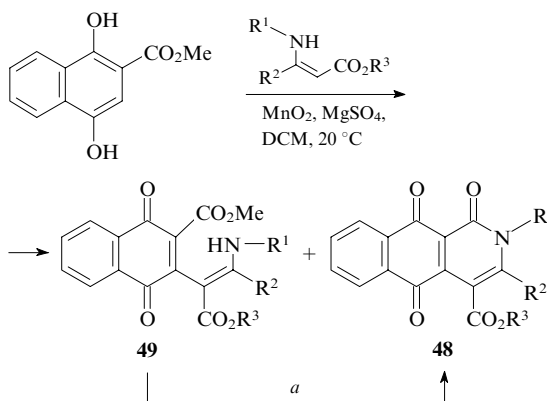
(*a*) AcOH, PhMe, Δ

R^1	R^2	R^3	Yield of **48** (%)	R^1	R^2	R^3	Yield of **48** (%)
Et	Et	Me	69	Pr^n	Me	Et	29
Pr^n	Me	Me	46	Pr^n	Ph	Et	56
Pr^n	Et	Me	71	Et	Ph	Et	32

The reaction is similar to the above-considered transformations of acylbenzoquinones, but it radically differs from that shown in Scheme 16. It was found that the reaction in the presence of an oxidizing agent at room temperature initially affords a mixture containing, apart from the final product, compound **49**. Therefore, the addition of enamine to the activated double bond of naphthoquinone, that is produced *in situ* from the starting ester, gives an adduct, in which two competitive processes,

viz., the cyclization *via* the attachment of the nitrogen atom to the ester group and the oxidation to napthoquinone **49**, take place. Compound **49** is subjected to cyclization under more severe condition.

It should be noted that compounds **50** containing the additional lactone ring are produced if the reaction is initially performed with naphthoquinone in the absence of an oxidizing agent (Scheme 28). It was hypothesized that this is due to the fact that intermediate **51** undergoes cyclization *via* the hydroxy group of the hydroquinone ring. This approach made it possible to prepare compounds **50** in moderate yields only in the case of three enamines.
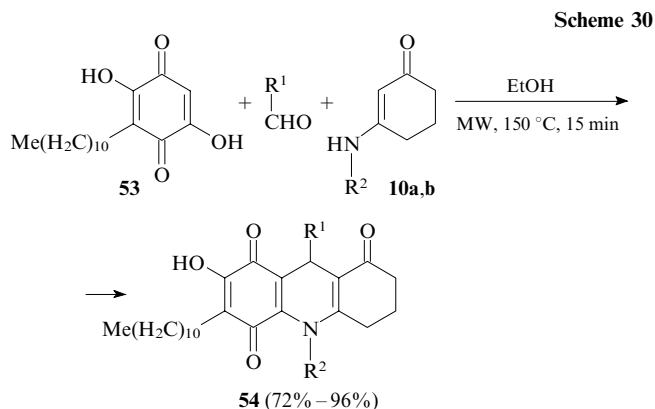
Scheme 28
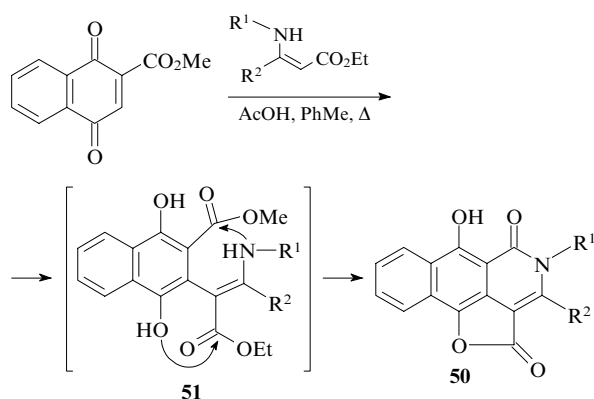
50: R^1 = Et: R^2 = Me (33%), Et (46%); R^1 = Pr^n, R^2 = Me (19%)

Wen *et al.*[68] developed an efficient procedure for the synthesis of benz[*g*]imidazo[1,2-*a*]quinolinediones **52** based on the three-component reaction involving 2-hydroxynaphthoquinone, aldehydes and cyclic enediamines **19** (Scheme 29). The reaction performed under solvent-free conditions in the presence of triethyl amine as the catalyst proceeds with high chemoselectivity. Presumably, the reaction involves the condensation of quinone with aldehyde to form the trioxo derivative followed by the addition of enediamine to the activated double bond.

A similar synthesis was described by Peña *et al.*[69] starting from the natural 2,5-dihydroxybenzoquinone embeline (**53**) and cyclic enaminones **10a,b** (Scheme 30). Due to microwave irradiation, this reaction was brought to completion in a very short period of time. The synthesis is very simple and produces compounds **54** in high yields.

Scheme 30

54 (72% – 96%)
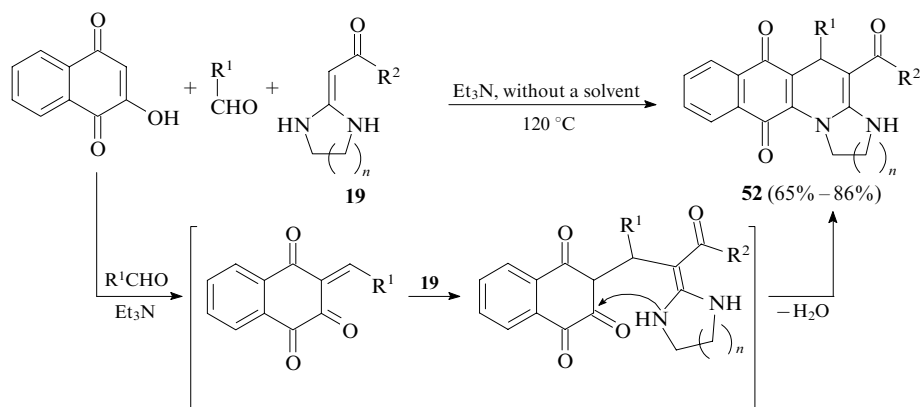
R^1 = Alk, Ar; **10**: R^2 = H (**a**), Bn (**b**)

II.2.b. Reactions of enamines with 3-acylcoumarins and 3-acylchromones
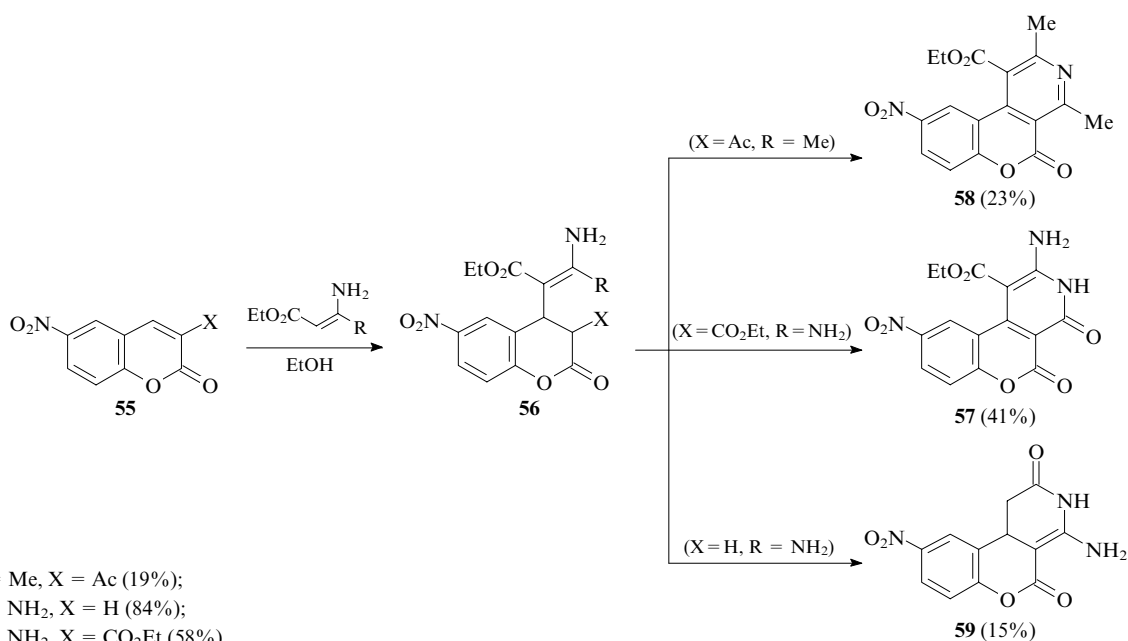
Adducts **56** were produced in a study[70] concerned with reactions of 6-nitrocoumarins **55** with aminocrotonic (R = Me) and diaminoacrylic (R = NH$_2$) esters (Scheme 31). The yields of the products varied in a broad range depending on the reactivity of both the double bond of coumarin (which is determined by the nature of the substituent X) and enamine. The cyclization of adducts **56** gave benzopyrano[4,3-*c*]pyridines in low yields. Compound **57** was synthesized by refluxing the corresponding adduct in xylene. Compounds **58** and **59** were prepared by refluxing in glacial acetic acid. In the reactions producing compounds **57** and **58**, the ring closure was accompanied by its oxidative aromatization. Compound **59** was synthesized *via* the rearrangement involving the pyran ring opening in the corresponding adduct.

In the presence of a leaving group (chlorine atom) in position 4, related fused heterocycles can be synthesized under milder conditions in substantially higher yields. Thus, the reaction of 4-chloro-3-formylcoumarins **60** with cyclic enediamines **19** in the presence of triethylamine proceeds at room temperature in a short period of time to form polyheterocyclic structures **61** in yields up to 96% (Scheme 32).[71]
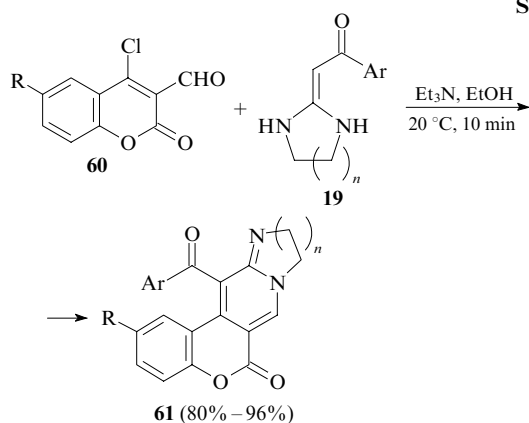
The reaction of 4-chloro-2*H*-chromene-3-carbaldehydes **62** with β-aminocrotonic ester (Scheme 33, hereinafter, the positions of substituents in the starting compound are given) was documented.[72, 73] This cyclocondensation reac-

Scheme 29

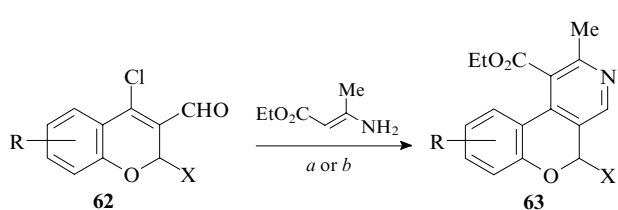**52** (65% – 86%)

R^1 = Et, Pr^n, Ar; R^2 = Me, Ar; *n* = 1, 2

Scheme 31

56: R = Me, X = Ac (19%);
  R = NH$_2$, X = H (84%);
  R = NH$_2$, X = CO$_2$Et (58%)

Scheme 32

R = H, Br; Ar = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-ClC$_6$H$_4$,
4-ClC$_6$H$_4$, 4-FC$_6$H$_4$; n = 1, 2

tion is also chemoselective and gives fused pyridines **63** in high yields.

Scheme 33

R = H, 6-Cl, 6-Br, 6-Me, 6-OH, 7-OMe, 8-Me, 8-Cl; X = H, Ar;
(*a*) (for X = H) MeOH, Δ, 6 h (85%); (*b*) (for X = Ar) AcOH, 20 °C,
48 h (70%)

Unlike the reactions of coumarin and 2*H*-chromene derivatives, the reactions of chromone derivatives with mono- and dinucleophiles (including enamines) often involve the rearrangement accompanied by the pyran ring opening. This is due to the fact that, after the addition of a nucleophile to the double bond *via* the attack on position 2 of chromone, the C(2)—O bond can easily be cleaved.

It was found [74] that the reactions of benzo[*h*]- and benzo[*f*]chromonecarbonitriles **64** with β-aminocrotonic ester and 4-aminopent-3-en-2-one afford compounds **65** (Scheme 34). The structures of the resulting esters (**65**, X = OEt) were confirmed by the independent synthesis starting from aldehyde **66** by the reaction of the latter with acetoacetic ester.
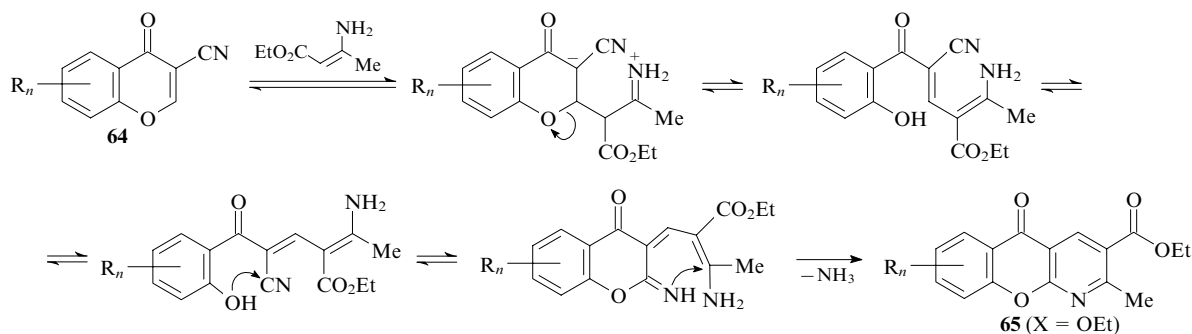
Scheme 34
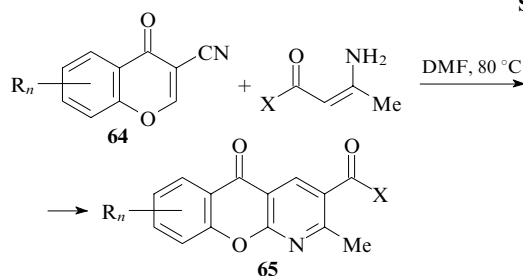
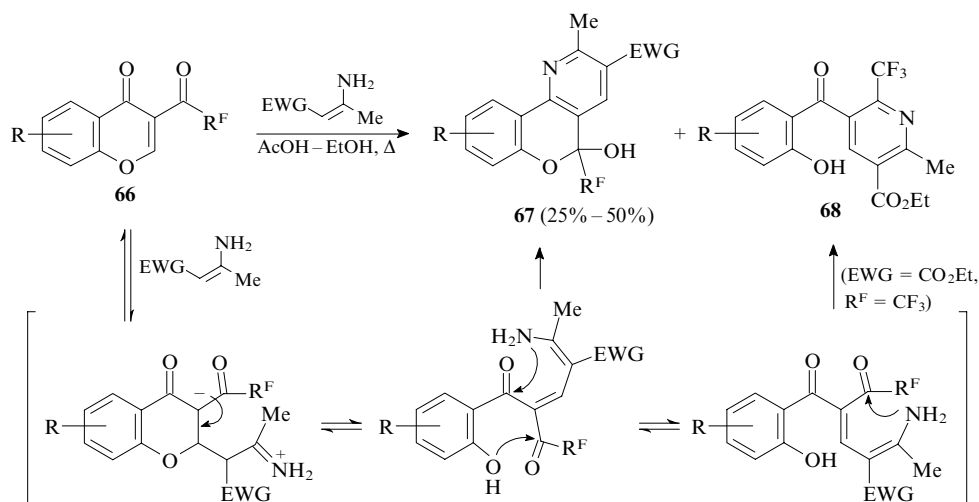X = OEt, Me: R$_n$ is benzo[*h*] (60%), benzo[*f*] (70%)
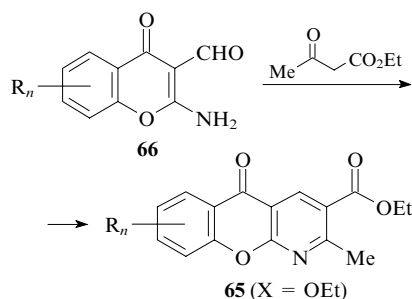
R$_n$ is benzo[*h*], benzo[*f*]

The proposed mechanism of the transformation involves the chemoselective addition of enamine to the activated double bond of chromone followed by the ring opening *via* the elimination of the phenol moiety (accompanied by the restoration of the conjugation). Then the ring transforma-

Scheme 35

Scheme 36

$R^F = CF_3, CF_2H$; $R = H$, 6-Me, 6-Cl, 7-MeO; EWG = CO_2Et, CN

tion at the nitrile group occurs followed by the pyridine ring closure (Scheme 35). It is quite probable that all steps of the reaction, except the last one, are reversible.

The reaction of 3-(polyfluoroacyl)chromones **66** with aminocrotonic ester and nitrile also proceeds through the pyran ring opening (Scheme 36).[75] In most cases, chromenopyridines **67** were isolated as the major reaction products. Aminocrotonic ester was also used as such or it was generated *in situ* from acetoacetic ester in the presence of ammonium acetate. In some cases, the reaction of this ester with trifluoroacetyl derivatives **66** gave mixtures of isomeric products — fused pyridines **67** and pyridines **68**.

Scheme 37

$R = H$, Me, Cl; **70**: X = OEt or OMe (46% – 57%); Me (18% – 25%)

By contrast, the reactions of aldehyde **69** with enamines, which are generated *in situ* from acetoacetic ester or acetylacetone, afford exclusively chromenopyridines **70** (Scheme 37).[76] The oxidation of the latter by chromium(VI) oxide produces carbonyl derivatives **71**.

II.2.c. Reactions with aromatic 1,3-dielectrophiles

Aromatic aldehydes, ketones, nitriles, esters and aromatic carboxylic acid chlorides, as well as nitro compounds containing the labile halogen atom in the *ortho* position with respect to an electrophilic group, readily react with various push-pull enamines. The reaction can follow two pathways to form either quinoline derivatives **72** or isoquinoline derivatives **73** (Scheme 38).[77] In most cases, only isoquinolines **73** were isolated. However, in some cases reactions afforded a mixture of two isomers, which were separated by chromatography.
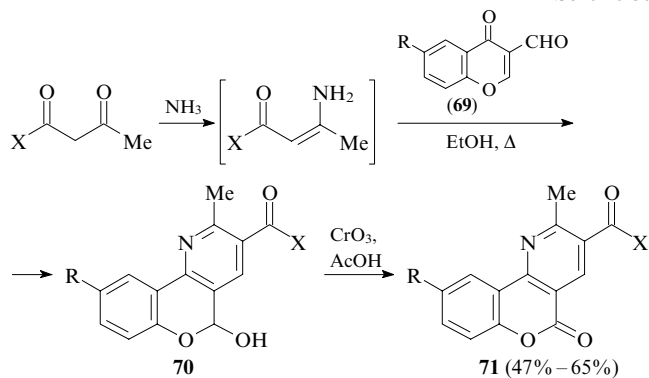
In some cases, the second step of the reaction (cyclization) is slow or requires more severe conditions. In these cases, cyclocondensation products **74** and **75** are isolated along with noncyclized intermediate **76** (Scheme 39).[78]

The similar cyclocondensations giving exclusively quinoline[79] or only isoquinoline[80] (Scheme 40) are also known.
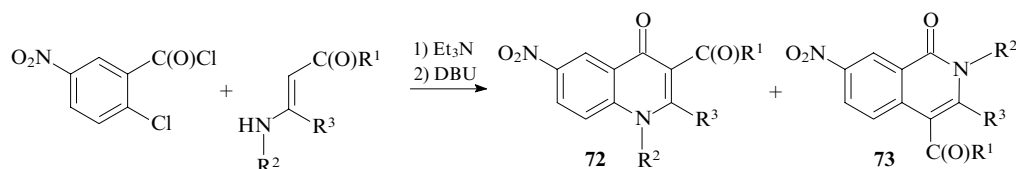
The reactions of enamines with some π-deficient aromatic aldehydes proceed in a similar way (Scheme 41).[81]

The electrophilic atom of the aromatic ring not necessarily should bear a halogen atom. The oxidative replacement of the hydrogen atom was described (Scheme 42).[82]
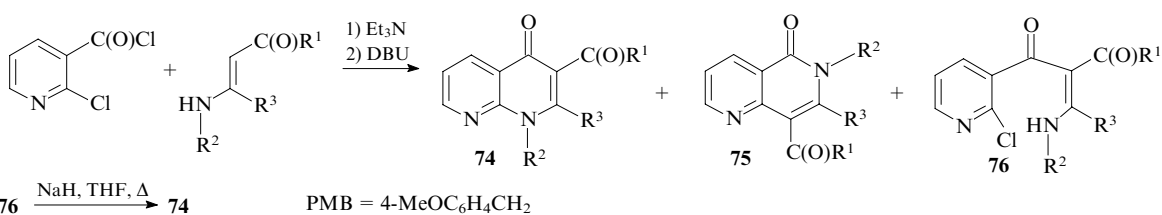
Scheme 38

DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene

R^1	R^2	R^3	Yield of **72** (%)	Yield of **73** (%)	R^1	R^2	R^3	Yield of **72** (%)	Yield of **73** (%)
Me	Pr^n	Me	–	71	Ph	Pr^n	Bn	23	54
Me	Ph	Me	–	68	Ph	Ph	Bn	40	14
Ph	Pr^n	Me	–	70	Ph	NMe$_2$	Me	–	51
Ph	Ph	Me	26	52	Ph	NMe$_2$	Ph	–	32

Scheme 39

$$76 \xrightarrow{\text{NaH, THF, }\Delta} 74 \qquad \text{PMB} = 4\text{-MeOC}_6\text{H}_4\text{CH}_2$$

R^1	R^2	R^3	Yield of **74** (%)	Yield of **75** (%)	Yield of **76** (%)	R^1	R^2	R^3	Yield of **74** (%)	Yield of **75** (%)	Yield of **76** (%)
Me	H	Me	–	–	48	Ph	Pr^n	Me	26	–	71
Ph	H	Me	–	–	59	Ph	Pr^n	Bn	–	52	–
Me	Pr^n	Me	–	–	84	Ph	Ph	Bn	10	39	–
Me	Ph	Me	7	–	78	Ph	PMB	Bn	13	47	–
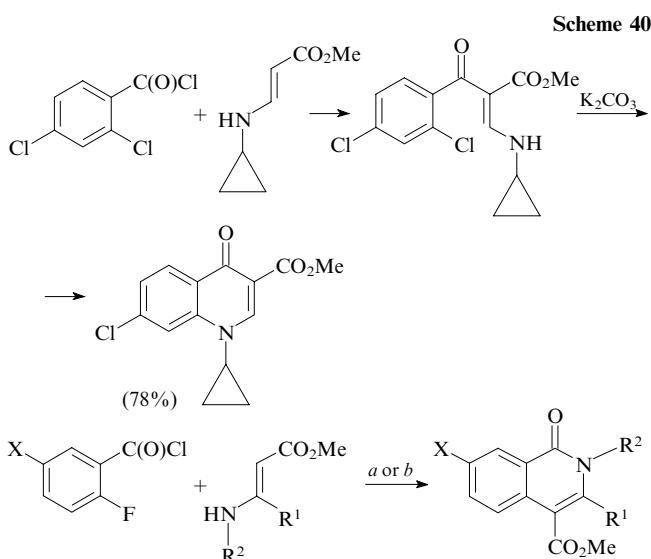
Scheme 40

R^1 = Me, Bn; R^2 = Me, Et, Pr^n, Bu^n, (CH$_2$)$_2$Ph;
(*a*) (for X = NO$_2$) Et$_3$N, 80 °C (68% – 85%);
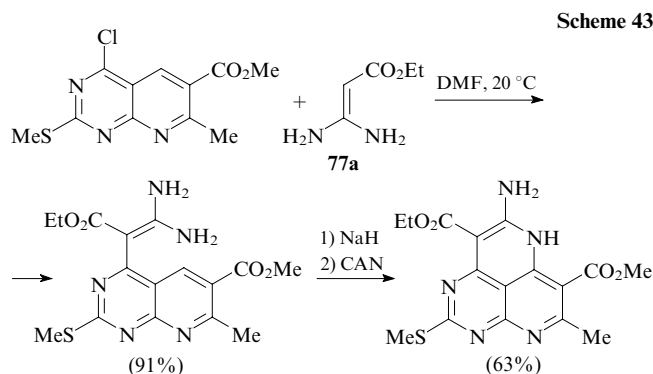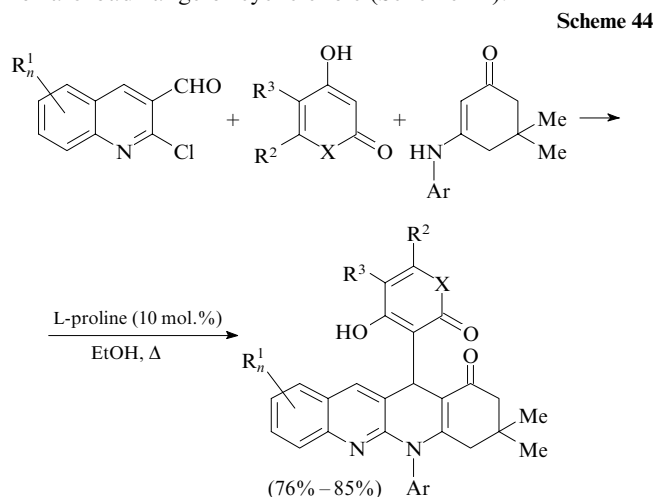(*b*) (for X = H) DBU, 130 °C (50% – 60%)
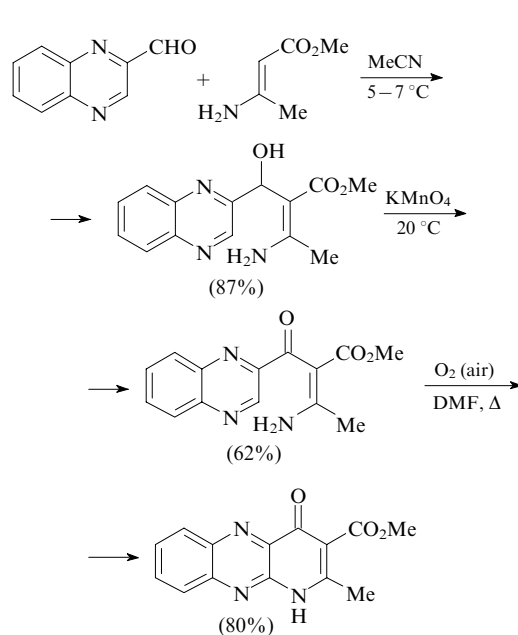
Scheme 42
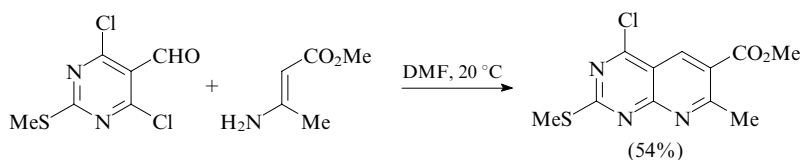
Scheme 41

Another example of the oxidative replacement of the hydrogen atom involves the addition of both nucleophilic centres of enamine to two aromatic rings (Scheme 43).[81]

Scheme 43

(91%)   (63%)

The three-component cyclocondensation was described for a broad range of cyclic enols (Scheme 44).[83]

Scheme 44

$R_n^1 = $ 6-Me, 6-Bu^t, 5,7-Me$_2$, 7,8-Me$_2$, 6-MeO, 6-EtO;
$R^2 = $ Me, $R^3 = $ H, X = O; $R^2 - R^3$ is benzo: X = O, NH

The reactions of enediamines with aromatic dielectrophiles were studied in sufficient detail. In contrast to enamines, almost all reactions of enediamines (with rare exceptions) follow one main pathway. Thus, the halogen atoms in the aromatic ring is replaced by the carbon atom of enediamine, and the nitrogen atom binds to the exocyclic electrophilic group. Alternative products are formed, if at all, as minor components. 2-Fluoro-5-nitrobenzaldehyde reacts with enediamines **77** to give predominantly or exclusively isoquinolines **78**. In some cases, quinolines **79** were found in trace amounts. Only the reaction of ethyl 3,3-diaminoacrylate (**77**, R = OEt) affords comparative amounts of isoquinoline **78** and dihydropyridine **80**, which is produced by the Hantzsch reaction (Scheme 45).[84, 85]

The reaction of pyrimidine-5-carbaldehyde **81** proceeds in a similar way and gives pyridopyrimidines **82** as the major or only products (Scheme 46).[86, 87] Only in one case, compound **83** was found in trace amounts. Hantzsch dihydropyridine is not produced at all.

2,4-Dichloroquinoline-3-carbaldehyde (**84a**) reacts with ethyl 3,3-diaminoacrylate (**77a**) to form benzonaphthyridine **85** in high yield (Scheme 47). This compound is analogous to product **82** produced from dichloropyrimidinecarbaldehyde **81**.
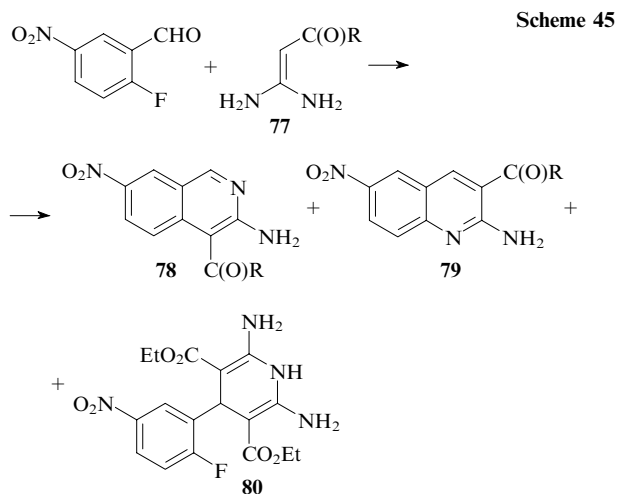
Scheme 45

R	Yield (%)			R	Yield (%)		
	78	**79**	**80**		**78**	**79**	**80**
NH$_2$	63	1	—	OEt	37	2	33
cyclo-N(CH$_2$)$_4$	77	—	—	Ph	48	—	—

Scheme 46
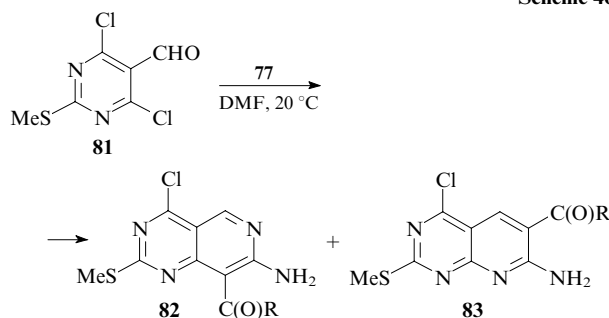
R	Yield of **82** (%)	Yield of **83** (%)
OEt	86	—
Ph	57	6
cyclo-N(CH$_2$)$_4$	51	—

Monochloro derivatives **84b,c** form Hantzsch dihydropyridines **86** as the major products, the reaction with 2-chloroquinoline-3-carbaldehyde giving also the unexpected product — benzonaphthyridine **87**.[88] The latter is produced *via* the oxidative replacement of the hydrogen atom.
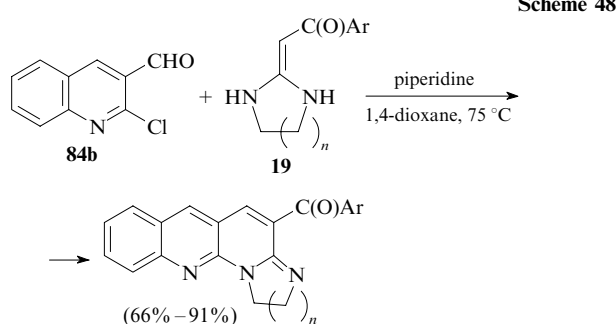
In the reaction of aldehyde **84b** with cyclic enediamines **19**, the nucleophilic carbon centre of enediamine binds to the formyl carbon atom of aldehyde, and the nitrogen atom replaces the halogen atom (Scheme 48).[89] This is apparently due to the low lability of the chlorine atom in aldehyde **84b**.

Ketones react with compounds **77** like most aldehydes (Scheme 49).[90, 91] The only difference is that ketones, quite expectedly, do not form dihydropyridines **80** due to substantially lower reactivity of the acetyl group compared to the formyl one.
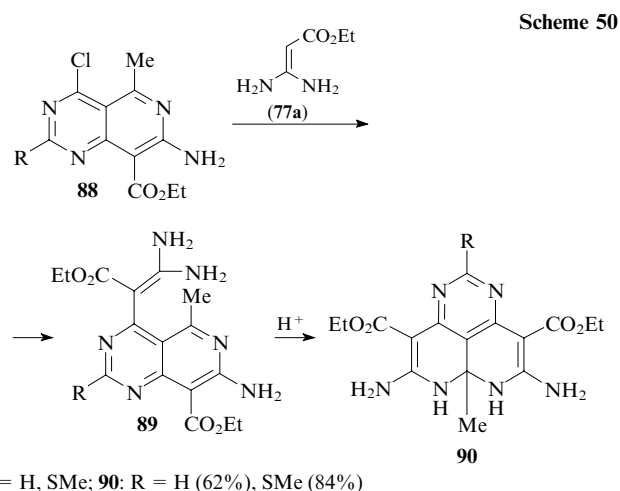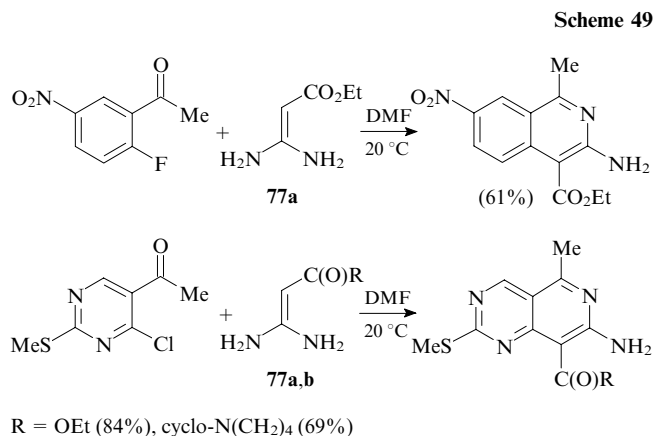
Pyridopyrimidines **88** bearing a rather labile chlorine atom react with ethyl 3,3-diaminoacrylate to form products **89** *via* the replacement of the halogen atom. In an acidic medium, these products unexpectedly cyclized to *peri*-fused compounds **90** *via* the nucleophilic addition of the amino
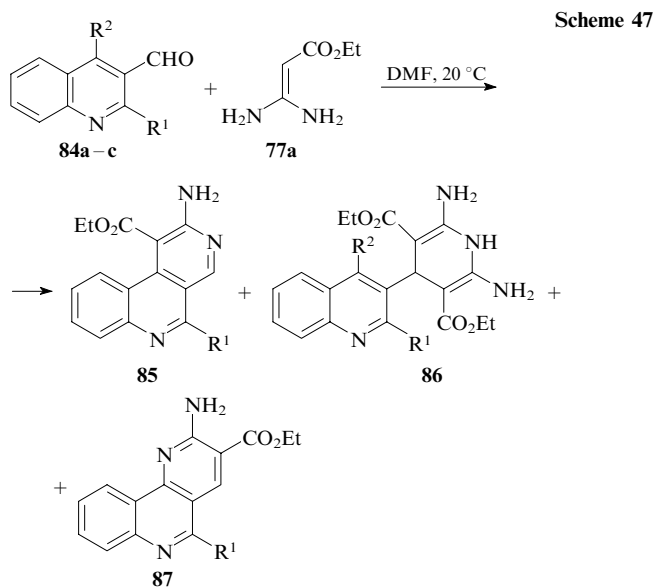
Scheme 47

R^1	R^2	Yield (%)		
		85	**86**	**87**
Cl	Cl	77	—	—
Cl	H	—	42	25
H	Cl	—	72	—

Scheme 48

Ar = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$; n = 1–3

Scheme 49

R = OEt (84%), cyclo-N(CH$_2$)$_4$ (69%)

Scheme 50

R = H, SMe; **90**: R = H (62%), SMe (84%)

group of the enediamine moiety to the formally double C=N bond of the pyridine ring (Scheme 50).[90, 91]

This approach underlies the method for the synthesis of pyrimidonaphthyridines **91**, which involves the successive reactions of aldehyde **81** with two equivalents of enediamine (one or two different enediamines) (Scheme 51).[92] In the last step, the pyridine ring of the *peri*-fused heterocycle undergoes spontaneous aromatization through the oxidation with atmospheric oxygen.

Scheme 51

R^1, R^2 = OEt, Ph, NHPh;
R^3 = R^4 = H; R^3 = H,
R^4 = *p*-Tol; R^3–R^4 = (CH$_2$)$_2$;
Tol is tolyl, TNP = 2,4,6-(O$_2$N)$_3$C$_6$H$_2$OH

91 (52%–90%)

(80%–95%)

(80%–90%)
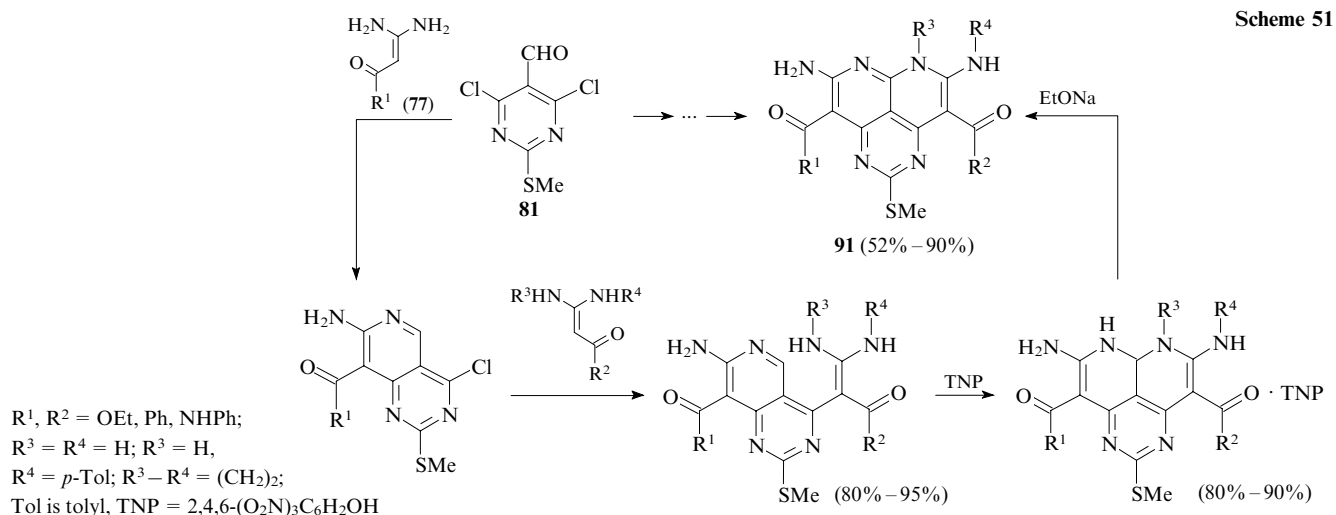
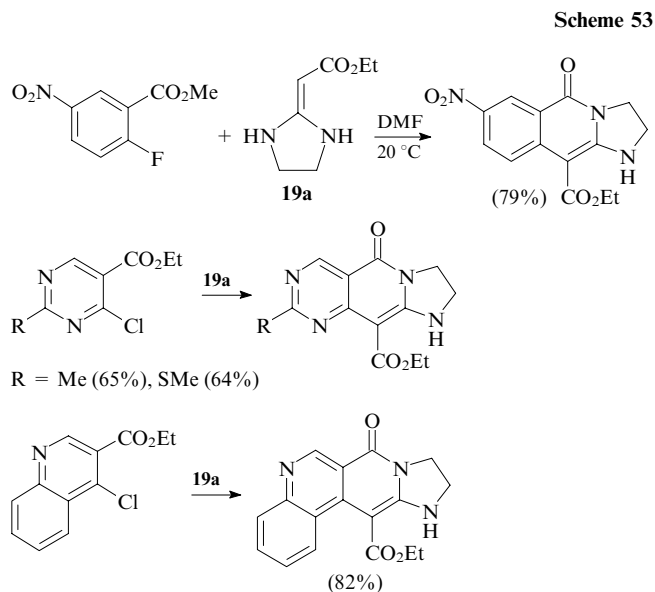The chemoselectivity of the reactions of *o*-halocarboxylates with enediamines **77** is the same as that observed in the reactions with aldehydes and ketones (Scheme 52).[93]

Scheme 52

R = OEt (**a**), cyclo-N(CH₂)₄ (**b**), Ph (**c**)

Scheme 53

R = Me (65%), SMe (64%)
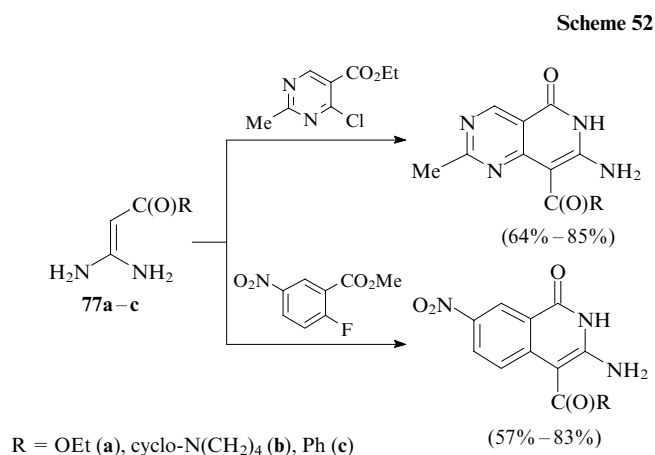
These cyclocondensation reactions with cyclic enediamine **19a** allow for the preparation of polyfused heterocycles with an additional saturated ring (Scheme 53).[94] It should be noted that cyclic enediamine **19a** exhibits higher reactivity than its acyclic analogue **77a**.
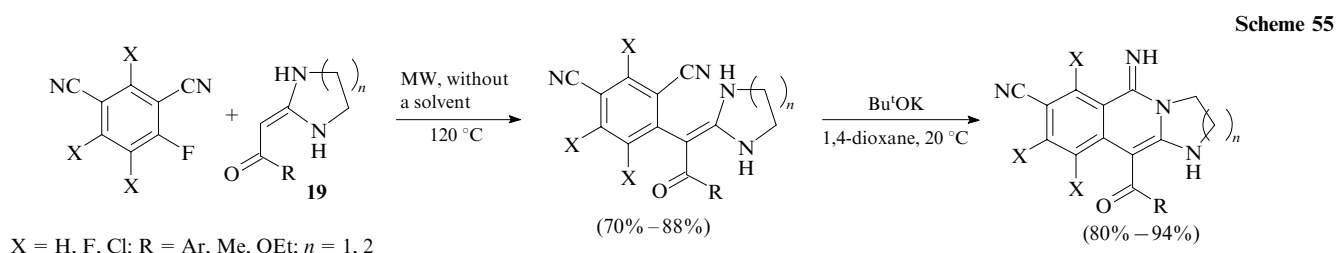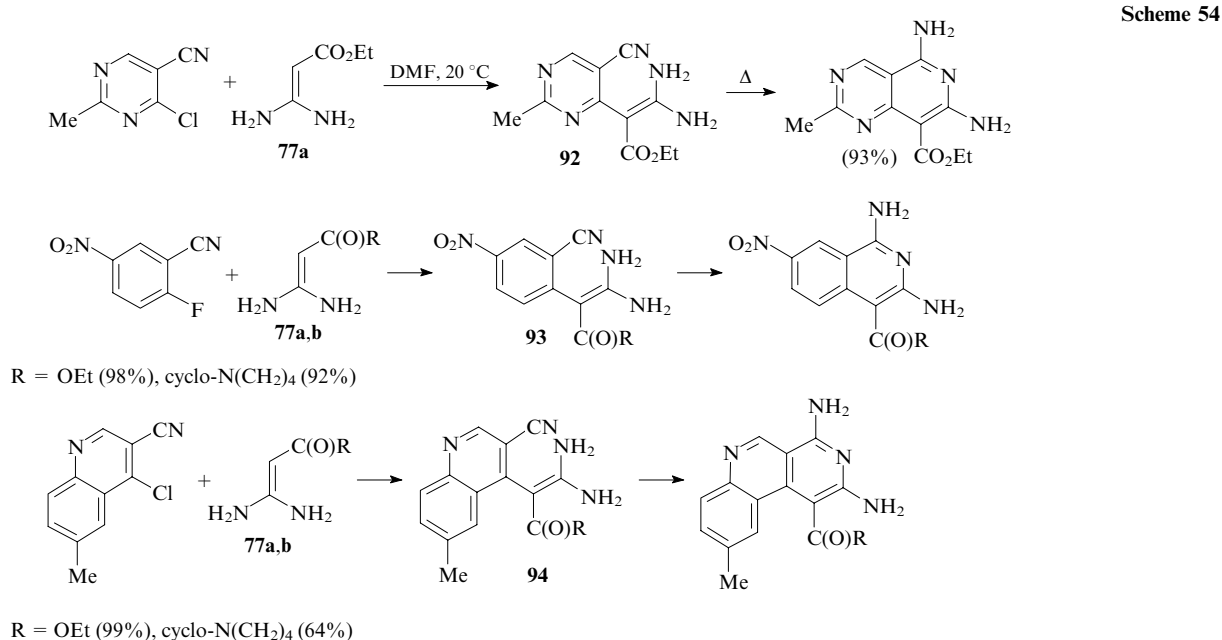
o-Halocarboxylic acid nitriles react with enediamines under mild conditions and, in the first step, they often give stable compounds **92–94**, which are products of the replacement of a halogen atom in the aromatic ring by the α-carbon atom of enediamine. Under certain heating, these products cyclize to form the pyridine ring (Scheme 54).[90, 95]

Cyclic enediamines **19** react with polyhalogenated isophthalonitriles exactly in the same way (Scheme 55).[96–98]

The reactions of enediamines **77** with *o*-fluoronitrobenzenes involve the replacement of the fluorine atom by the α-carbon atom to form stable products **95**. The latter undergo cyclization to cinnoline 1-oxides **96** upon the treatment with sodium hydride (Scheme 56).[99, 100]

Scheme 54

R = OEt (98%), cyclo-N(CH₂)₄ (92%)

R = OEt (99%), cyclo-N(CH₂)₄ (64%)

Scheme 55

X = H, F, Cl; R = Ar, Me, OEt; *n* = 1, 2

Scheme 56
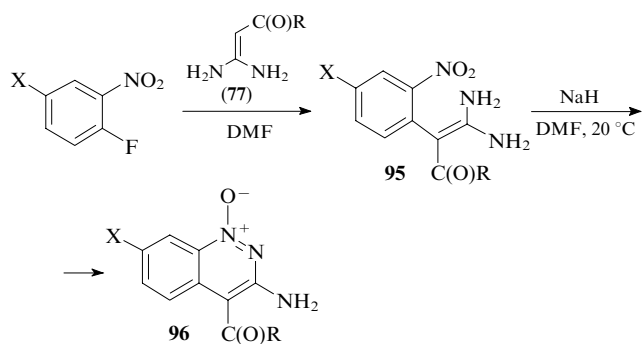
| X	R	Temperature of the first step /°C	Yield (%)	
			95	**96**
NO₂	cyclo-N(CH₂)₄	20	85	31
NO₂	OEt	20	91	68
NO₂	Ph	20	90	56
CN	OEt	20	92	90
H	OEt (**95**), OH (**96**)	130	53	52

Azinecarboxylate and azinecarbaldehyde N-oxides belong to a radically different type of aromatic dielectrophiles. These N-oxides enter into the cyclocondensation with enediamines **77** promoted by benzene sulfochloride, the nucleophilic carbon centre of enediamine replacing the hydrogen atom in the 'activated' position of azine (Scheme 57).[101, 102] In the case of methyl nicotinate N-oxide (**97**), the nucleophilic attack of enediamine occurs somewhat unexpectedly at position 4 of the pyridine ring to form naphthyridinone **98** in moderate yield. The product of nucleophilic attack at position 2, naphthyridinone **99**, is formed in trace amounts.
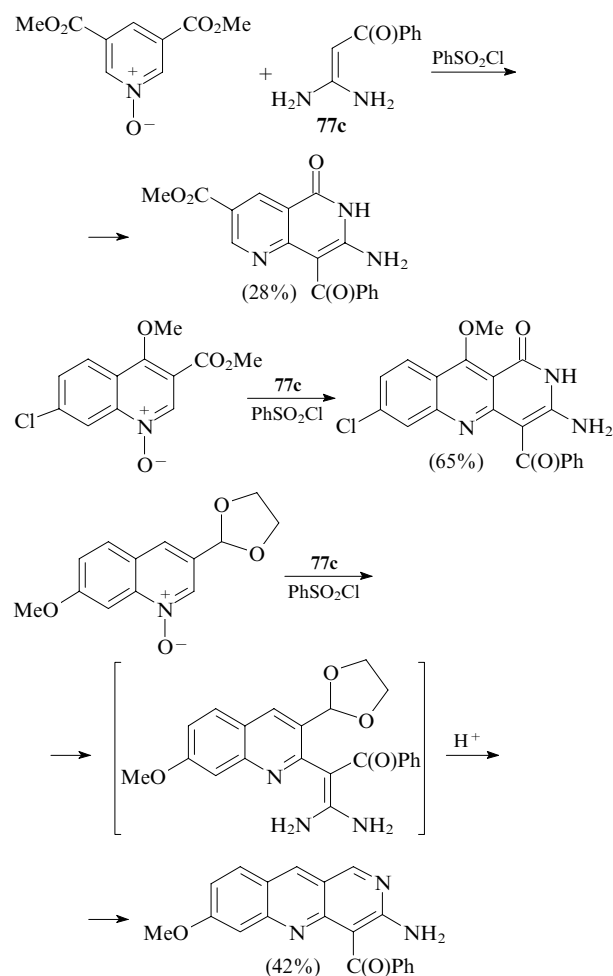
Scheme 57
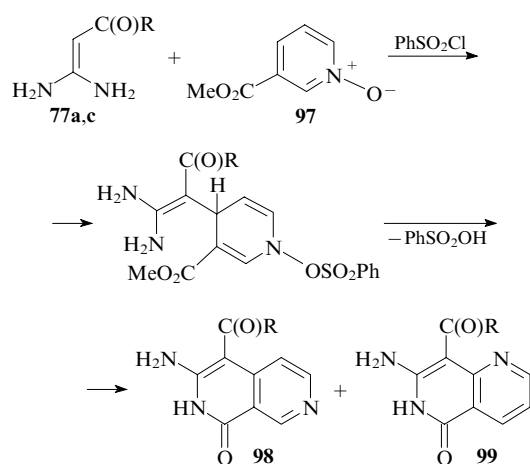
R	Yield of **98** (%)	Yield of **99** (%)
OEt	41	4
Ph	49	—

Other examples of the use of this approach to the synthesis of fused azines starting from enediamine **77c** are given in Scheme 58.[101, 102]

Scheme 58

II.2.d. Other reactions producing fused pyridines

3-Aroylmethylidene-2-oxoindolines **100** react with cyclic enaminones **10** to give indolo[2,3-*b*]quinolines **101** (Scheme 59).[103] The reaction occurs in the presence of a base under microwave heating within a few minutes and gives final products in high yields.

Scheme 59
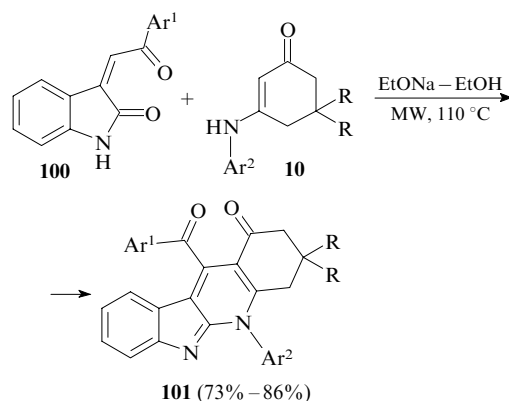
Ar¹ = 4-XC₆H₄ (X = Me, MeO, F, Cl);
Ar² = Ph, YₙC₆H₅₋ₙ [Yₙ = 4-F, 4-Cl, 4-Br, 2-Br, 4-I, 2-I, 3,4-(MeO)₂];
R = H, Me

Benzhydrol **102** reacts with cyclic enamines **103** in a similar way as aromatic carbonyl compounds to form, as a result of the two-step reaction, compounds **104**. The latter are aza analogues of podophyllotoxin (Scheme 60),[104] which

is a natural compound exhibiting antitumour activity. Both steps — the acid-catalyzed C-alkylation of enamine and the copper(I) iodide-catalyzed cyclization — occur in high yields.
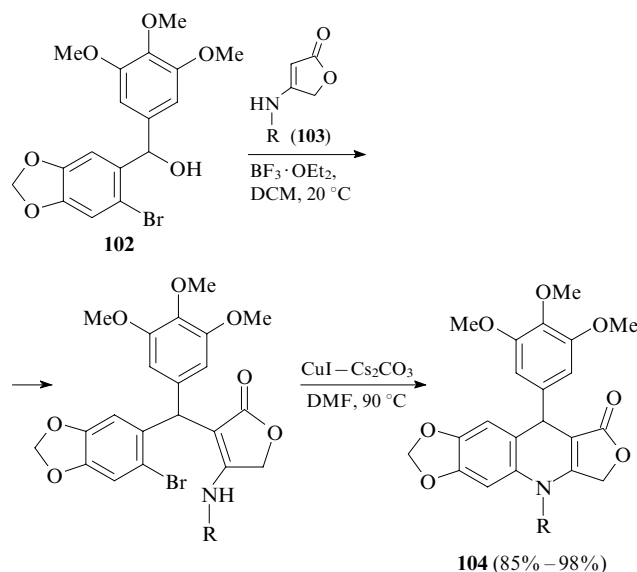
Scheme 60

R = Bn, Ph, 4-MeOC$_6$H$_4$CH$_2$

The reactions of *o*-halobenzaldehydes with enamines **10** (2 equiv.) produce hexahydroacridine derivatives **105** (Scheme 61). In these reactions, cyclic enamines behave differently to acyclic analogues (for example, aminocrotonic ester, *etc.*), which react with aldehydes, also involving two molecules, to form usually Hantzsch dihydropyridines. In the case of cyclic enaminones, the formation of dihydropyridine derivatives from intermediate **106** is hindered, due to which the cyclization can be performed by replacing a halogen atom under the action of palladium acetate [105] or nanoparticles of mixed oxide Fe$_3$O$_4$.[106]

Scheme 61

Hal	Yield of **105** (%)
I	70–98
Br	60–88
Cl	60–81
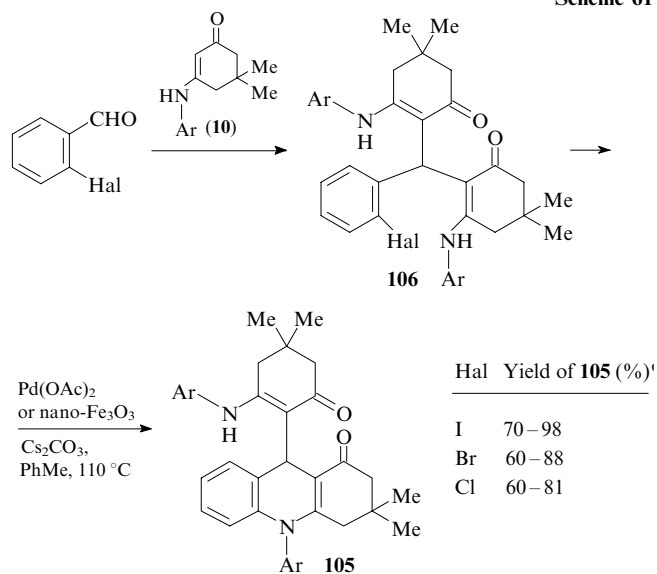
Hal = I, Br, Cl; Ar = XC$_6$H$_4$ (X = H, 2-Me, 3-Me, 4-Me, 4-MeO, 2-Cl, 3-Cl, 4-Cl, 4-Br, 4-I)

III. Intramolecular transformations (cyclizations) of enamines

### III.1. Formation of fused pyrroles

III.1.a. Cyclization of N-aryl enamines with the C$_{arom}$−C bond formation

N-Aryl enaminones are available substrates because they can be quite easily prepared from the corresponding aryl-amines. Therefore, these compounds hold great promise in the synthesis of fused azaheterocycles. New methods for the synthesis based on these compounds have been actively developed since the past decades of the 20th century.

The reactions accompanied by the C$_{arom}$−C bond formation provide one of key approaches to the construction of organic molecules. The intramolecular cross-coupling underlies numerous new facile methods for the synthesis of various fused heterocycles. The fact that push-pull *N*-aryl enamines can undergo such transformations is well-known for a rather long time. This opened up broad avenues for synthetic chemists and provided a new powerful tool for solving problems of the synthesis of diverse derivatives of the indole system.

One of the first publications on the use of the cross-coupling for the cyclization of push-pull enamines (intramolecular Heck reaction) to form 3-acylindoles (Scheme 62) dates back to 1990.[107] α,β-Unsaturated β-(2-haloarylamino) ketones and esters **15** were synthesized using one of the three approaches. The cyclization *via* the replacement of a halogen atom by the α-carbon atom is conducted in the presence of Pd^{II} as the catalyst. The use of palladium acetate is sufficient to perform the reaction with iodo-substituted compounds **15**, whereas the cyclization of bromo derivatives requires the presence of a phosphine ligand. In both cases, the yields of indoles **107** vary from moderate to high.

Scheme 62
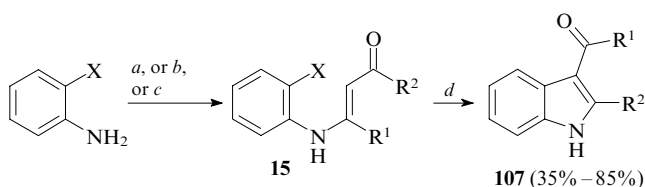
X = I, Br; R^1 = H, Me, Ph, CO$_2$Et; R^2 = Me, Ph, OEt; R^1−R^2 = (CH$_2$)$_3$;

(*a*) R^1—C(O)—C(O)—R^2, TsOH, PhH; (*b*) R^1≡C(O)R^2, MeOH−DMSO; (*c*) R^1—C(O)R^2, Pd-cat, 1,4-benzoquinone;

(*d*) Pd(OAc)$_2$, P(*o*-Tol)$_3$ (for X = Br), Et$_3$N, DMF, 120 °C, 6 h

Later on, this approach and the conditions of cyclization were used for the synthesis of biologically active tetrahydrocarbazole derivatives **108** (Scheme 63).[108] A method for the synthesis of annulated indoles from *o*-iodoaniline and cyclic ketones without the isolation of intermediate enamines **109** was developed based on the catalysis by Pd(OAc)$_2$ (see Scheme 63).[109]

Enaminones **110**, which were synthesized from *o*-bromoanilines and N-substituted piperidine-3,5-diones, are cyclized to aza analogues of tetrahydrocarbazoles **111** (Scheme 64).

Scheme 63

some important indole-containing biologically active compounds, in good yields (Scheme 66).[113]

Scheme 65

X = Br, I; R = H, Me

112 (85% – 95%)

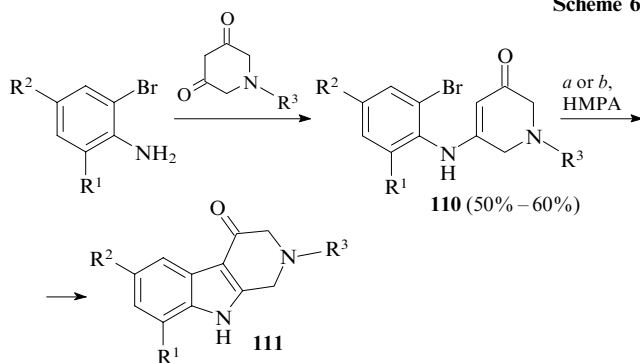**Scheme 66**

X = H, 4-Me, 4-Cl, 5-MeO; EWG = NO₂, CO₂Et, CN;

R = Me, Ph, thiazol-4-yl
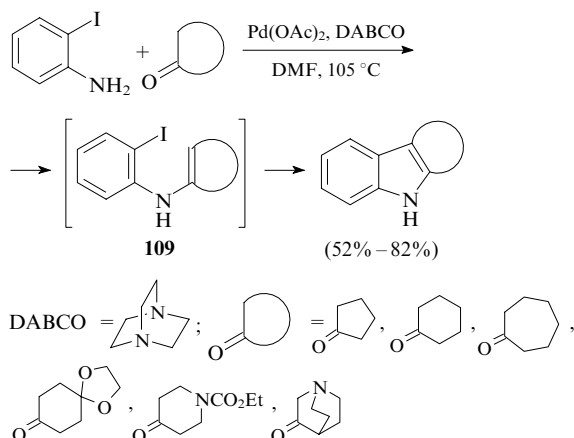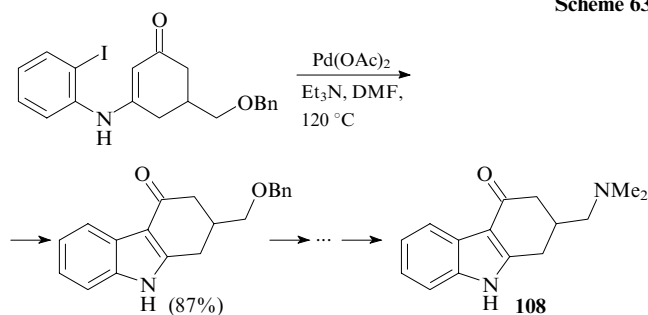
Yang et al.[110] used copper(I) iodide (2 equiv.) as the catalyst and sodium hydride in hexamethylphosphoramide (HMPA) as the base. In the further study,[111] these authors showed that the yields of the products in the cyclization can be increased by performing the reaction in the presence of Pd(PPh₃)₄ (2 mol.%) as the catalyst without using a strong base.

Scheme 64

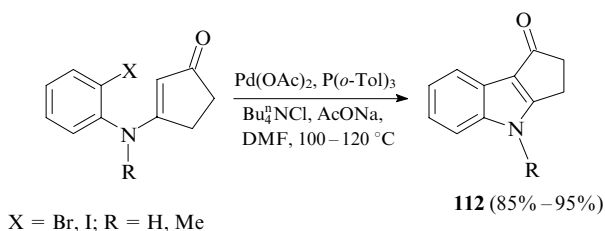R¹ = R² = H, Me; R¹ = Me, R² = H; R³ = CO₂Et, Bn;
(*a*) NaH (2 equiv.), CuI (2 equiv.), 120 °C (60% – 67% yield of **111**);
(*b*) Pd(PPh₃)₄, NaHCO₃, 140 °C (70% – 76%)

A similar method was developed for the synthesis of cyclopenta[*b*]indoles **112** (Scheme 65).[112] Under moderately severe conditions, cyclization products were obtained in high yields both from iodo- and bromo-substituted substrates.
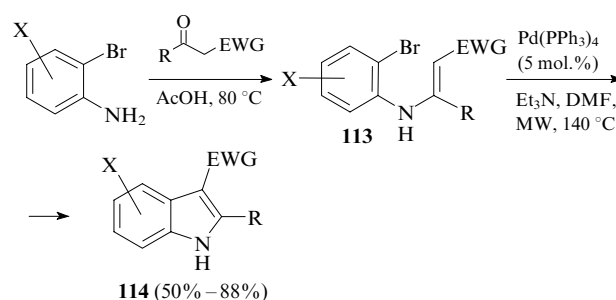
The Pd-catalyzed cyclization of push-pull N-(*o*-bromoaryl)enamines **113** activated by microwave irradiation affords substituted indole-3-carboxylic acid esters and nitriles and can be employed to synthesize 3-nitroindole derivatives (**114**, EWG = NO₂), which are precursors for
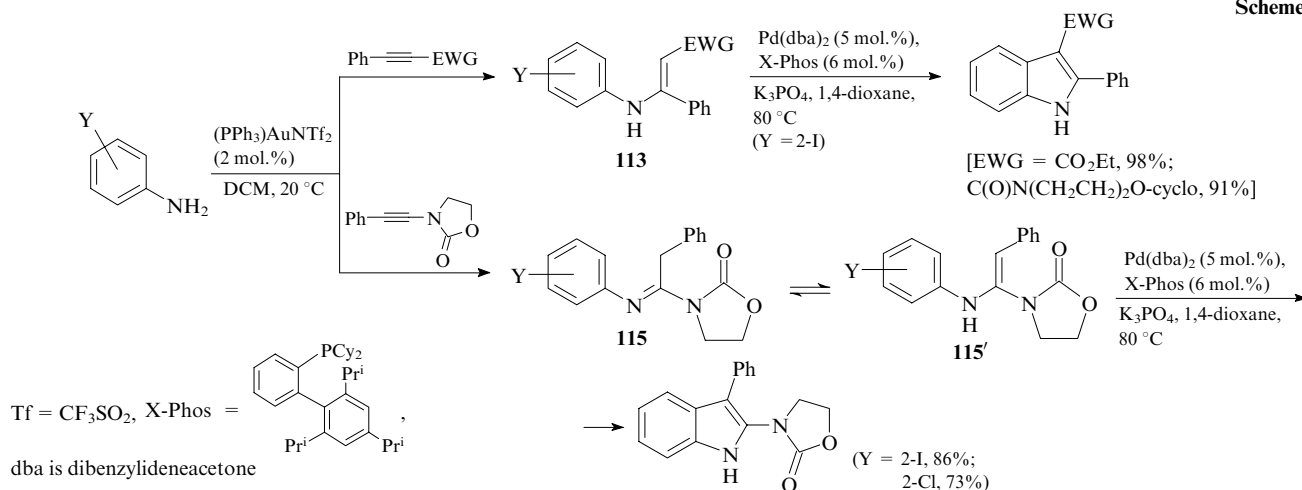
Kramer et al.[114] suggested a method for the synthesis of enamines **113** and amidines **115** by the Auᴵ-catalyzed hydroamination of electron-deficient and electron-excessive alkynes performed under mild conditions. It was shown that N-(*o*-haloaryl)-substituted enamines and amidines undergo cyclization to the corresponding indoles. Amidines apparently enter into the intramolecular Heck reaction in the enediamine tautomeric form (**115′**) (Scheme 67).

A facile method for the synthesis of cyclic N-aryl enaminones by the Pdᴵᴵ-catalyzed N-arylation with bromides and even chlorides has been described[115] (Scheme 68). Conditions were found which made it possible to perform this reaction with a wide range of haloarenes and prepare target compounds in high yields. A key issue is the use of the special ligand — 2-(dimethylamino)-2′-(dicyclohexylphosphino)biphenyl (L). It is interesting that in the reaction with *o*-dibromobenzene, N-arylation is accompanied by the intramolecular Heck reaction to form indoles.

Azatetrahydrocarbazolones, which are promising substrates for the synthesis of aza analogues of natural alkaloids and other biologically active compounds based on tetrahydrocarbazolone, can also be synthesized by the intramolecular Heck reaction of N-pyridyl enaminones **116** and **117** (Scheme 69). Tetrakis(triphenylphosphine)palladium is an efficient catalyst for this reaction. In the HMPA – NaHCO₃ system with the convection heating, cyclization products are produced in moderate yields,[116] whereas the reactions with the use of pyridine and di(cyclohexyl)methylamine under microwave irradiation afford these products in high yields.[117]

Another example of the successful application of the Cuᴵ-catalyzed cyclization of N-(*o*-haloaryl)enaminones in the synthesis of substituted 3-acylindoles has been described.[118] Enaminones **118** can be easily prepared by

Scheme 67

Tf = CF$_3$SO$_2$, X-Phos =

dba is dibenzylideneacetone

[EWG = CO$_2$Et, 98%;
C(O)N(CH$_2$CH$_2$)$_2$O-cyclo, 91%]

(Y = 2-I, 86%;
2-Cl, 73%)

Scheme 68

X = 4-NO$_2$, 4-CN, 4-Me, 4-MeO, 3-CF$_3$, 3-MeO, 2-Me; Hal = Br, Cl

Scheme 69

(R = Me, 89%; Br, 57%)

(*a*) (for X = N, Y = CH) Cy$_2$NMe, Py, MW, 160 °C (95%);
(*b*) (for X = CH, Y = N) NaHCO$_3$, HMPA, 140 °C (39%)

Scheme 70

X = H, Me, F, Cl;
R = n-C$_5$H$_{11}$, Ph, 3-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-NCC$_6$H$_4$
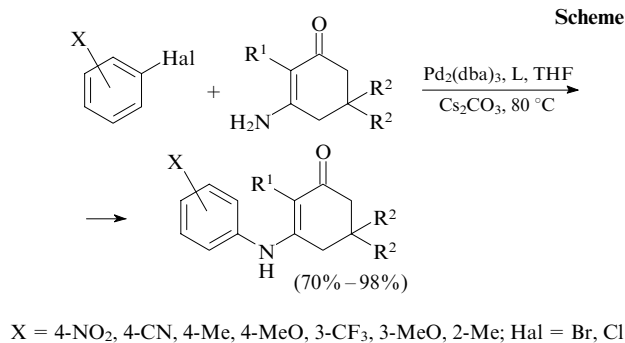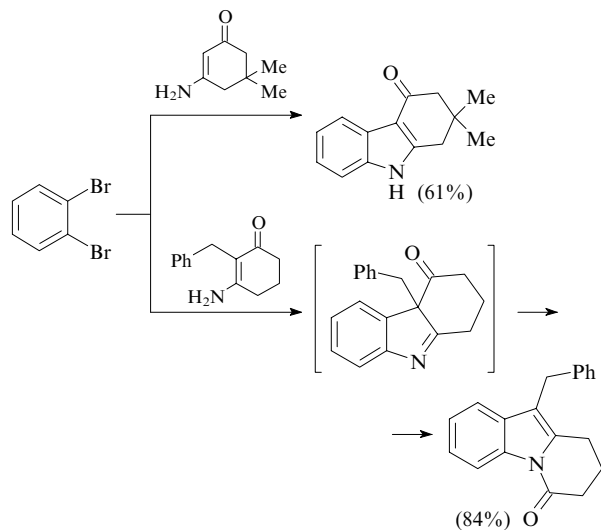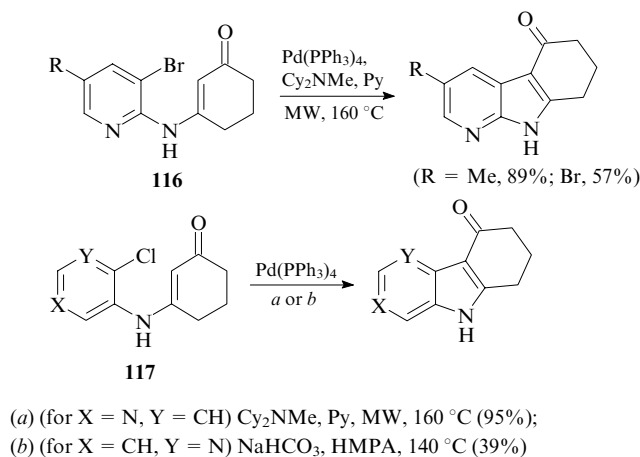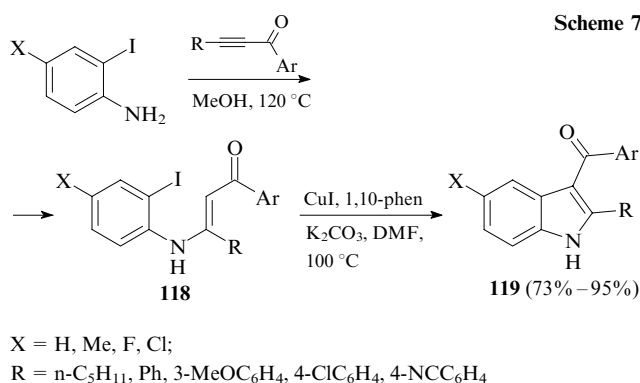
the reaction of *o*-iodoanilines with benzoylalkynes (Scheme 70). The best yields of cyclization products were observed in the reactions with the use of 1,10-phenanthroline (1,10-phen) as the ligand. It was also shown that 3-aroylindoles **119** can be synthesized by a one-pot method from *o*-iodoanilines and benzoylalkynes without the isolation of enaminones **118**.

It should be noted that the reaction of *N*-(*o*-bromophenyl)enaminone **118a** performed under analogous conditions affords, apart from the expected indole **119a**, benzoxazepine **120** (Scheme 71). In the case of iodo-substituted derivatives, the competition between the C–C and C–O bond formation was not observed.

Scheme 71

119a (30%)   **120** (36%)

Scheme 72

123 (60%–90%)
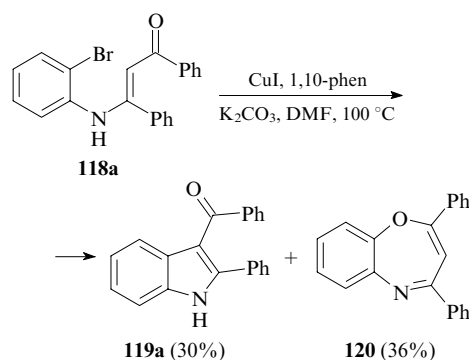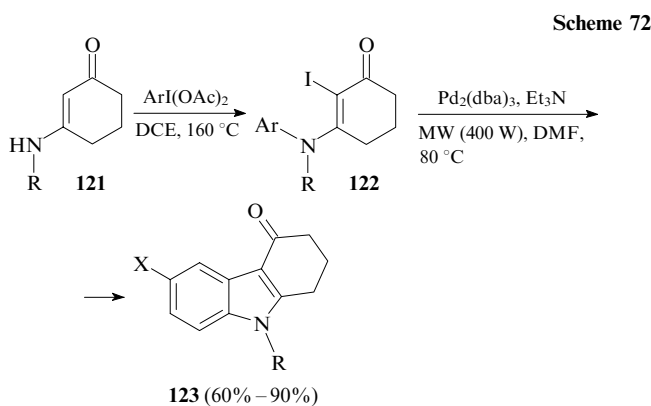
X = H, R = Ph; X = NO$_2$, R = 4-O$_2$NC$_6$H$_4$; X = Cl, R = 4-ClC$_6$H$_4$;
X = Br, R = 4-BrC$_6$H$_4$; X = 4-MeO$_2$CC$_6$H$_4$: R = Me, Bn

An alternative approach to the synthesis of N-substituted tetrahydrocarbazolones was developed based on the Pd-catalyzed intramolecular coupling reaction of cyclic *N*-aryl enaminones.[119, 120] This synthesis involves the initial reaction of enaminones **121** with substituted (diacetoxy)iodobenzenes giving compounds **122** as a result of the simultaneous α-iodination and N-arylation (Scheme 72).[119] Conditions were found for the cyclization of iodo-substituted enaminones **122** to target c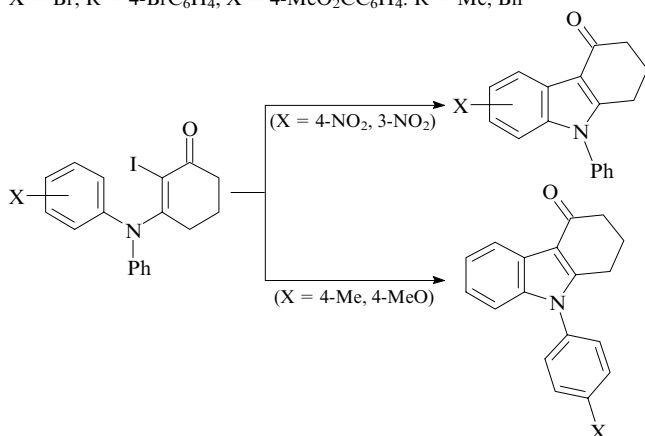ompounds **123** in high yields. It was also noted that the reaction of unsymmetrically substituted *N,N*-diaryl enamines proceeds with selectivity involving the ring having a lower π-electron density.[120]

In the past years, a new promising approach to the synthesis of indoles was developed based on the oxidative cyclization of *N*-aryl enamines. The evident advantage of this procedure is that a hydrogen (rather than a halogen) atom can be replaced, which substantially extends the range of substrates accessible for the reaction. Meanwhile, for compounds with both free *ortho* positions in the *meta*-substituted N-phenyl moiety, the selectivity of the cyclization presents a problem, and mixtures of regioisomeric indoles were isolated in many cases.

The research group headed by Glorius [121, 122] conducted the direct Pd-catalyzed oxidative coupling of *N*-aryl enamines **124** and obtained substituted indoles **125** (Scheme 73). After the thorough examination, the optimal conditions of the reaction were found. The best results were obtained in the presence of Pd(OAc)$_2$ as the catalyst, Cu(OAc)$_2$ as the oxidizing agent and K$_2$CO$_3$ in dimethylformamide. The reaction was studied for a very wide range of compounds, which differ both in the substitution in the phenyl moiety and the nature of the electron-withdrawing group (EWG)

and the substituent in the β position of enaminone (X). The variation of substituents in the enamine moiety has only a slight effect on the course of the cyclization. The reaction was performed with esters, nitriles and cyclic ketones. It should be noted that more severe conditions are required for the reactions of β-aryl-substituted enaminones (X = Ar) compared to other compounds (X = CF$_3$, Me, Pr^i, OEt).

Scheme 73

125 (60%–80%)
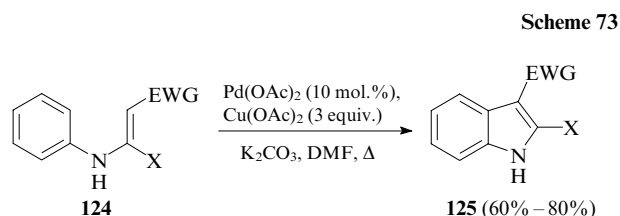
EWG = CO$_2$Et: X = Me, CF$_3$;
EWG = CO$_2$Me: X = Pr^i, OEt, Ph, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-Th;
EWG–X = C(O)(CH$_2$)$_3$

The effect of substituents in the aniline moiety was studied in detail. The reactions of all *N*-arylaminocrotonic esters **124** gave the corresponding indoles in good yields (Scheme 74). In the reactions of bromo-substituted substrates, a by-product was obtained *via* debromination. In the reactions with *meta*-substituted compounds, the selective formation of one regioisomer (6-R) was unexpectedly observed for substrates containing electron-withdrawing groups (R = Ac and CF$_3$) and for the methoxy derivative. By contrast, the reactions of *meta*-halogen- and *meta*-methyl-substituted enamines gave mixtures of both isomers (with 6-R-indole prevailing).

Scheme 74

124   (50%–80%)
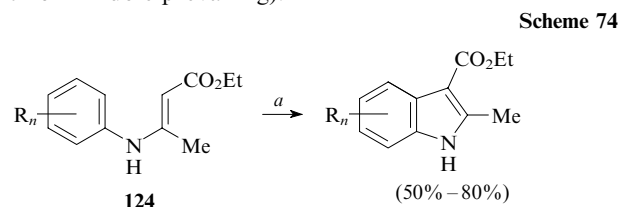
R$_n$ = H, 4-NO$_2$, 4-CN, 4-Ac, 4-CO$_2$Et, 4-CF$_3$, 4-F, 4-Cl, 4-Br, 4-Me,
4-NHPiv, 4-OAc, 4-OMe, 4-NMe$_2$, 2,4-Me$_2$, 2-CF$_3$, 2-F, 2-Cl,
2-Ph, 2-Me, 2-Et, 2-Pr^i, 2-Bu^t, 2-OMe; Piv is pivaloyl;
(*a*) Pd(OAc)$_2$ (10 mol.%), Cu(OAc)$_2$ (3 equiv.), K$_2$CO$_3$, DMF, Δ
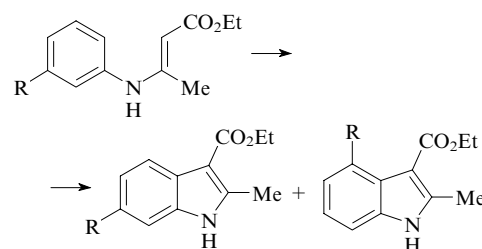
R = Ac (54%, 6-Ac), CF$_3$ (54%, 6-CF$_3$), F (74%, 6-F:4-F = 53:47),
Cl (75%, 6-Cl:4-Cl = 88:12), Me (68%, 6-Me:4-Me = 92:8),
OMe (64%, 6-OMe)

It was also shown [122] that the synthesis can be performed starting from anilines and acetoacetic ester in a one-pot fashion. Besides, it was found that the reaction with *N*-methyl-*N*-phenyl-β-aminocrotonic ester does not give a cyclization product.

Based on the observed characteristic features (electron-donating substituents in the ring reduce the rate of cycliza-

tion, *etc.*), it was concluded that this cyclization reaction is not electrophilic.

A method for the synthesis of substituted indoles by the Pd(OAc)$_2$-catalyzed oxidative cyclization was documented.[123] The reaction was performed in an oxygen atmosphere, in which oxygen acts as the oxidizing agent. Anilines and acetylenecarboxylates were used as the starting compounds, from which enamines required for the cyclization were generated *in situ* (Scheme 75). It should be emphasized that, unlike the above-considered examples, the cyclization products were isolated also in the case of N-monosubstituted anilines (indoline and tetrahydroquinoline).
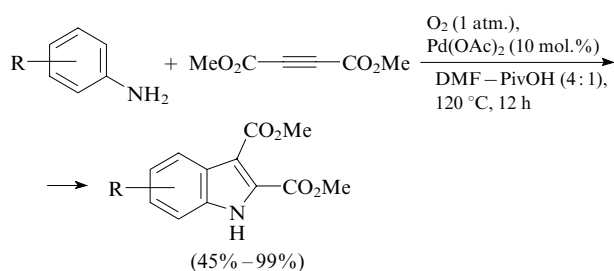
R = 2-Me, 3-Me, 4-Me, 3-Pr^i, 4-Cy, 2-MeO, 4-MeO, 2,4-(MeO)$_2$, 2,5-(MeO)$_2$, 3,4-(MeO)$_2$, 4-CF$_3$O, 4-EtO$_2$C, 4-F, 4-Cl, 4-OH; PivOH is pivalic acid

n = 1 (46%), 2 (83%)
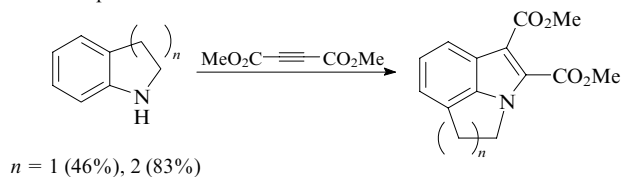
The Pd(OAc)$_2$-catalyzed oxidative cyclization in the presence of oxygen is also well-applicable for the synthesis of tetrahydrocarbazoles from cyclic enaminones.[124, 125] A procedure with the use of 40 mol.% of Cu(OAc)$_2$ was proposed[124] (Scheme 76). The cyclization was performed in boiling ethanol in an oxygen atmosphere. The target compounds can be synthesized from anilines and cyclohexane-1,3-diones without the isolation of enaminones.
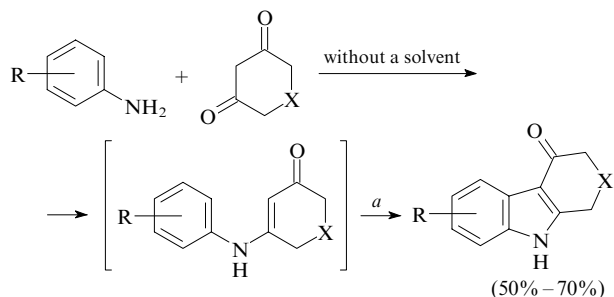
X = CH$_2$, CMe$_2$; R = H, 2-Me, 4-Me, 4-MeO, 2-Cl, 4-Cl, 4-Br;
(*a*) O$_2$, Pd(OAc)$_2$ (15 mol.%), Cu(OAc)$_2$ (40 mol.%), EtOH, 80 °C

Bi *et al.*[125] showed that N-substituted carbazoles can be synthesized by the intramolecular oxidative coupling of N-alkylated enaminones (Scheme 77). In this case, acetic acid proved to be the solvent of choice for the cyclization, and the reaction performed in an oxygen atmosphere did not require the presence of Cu(OAc)$_2$.
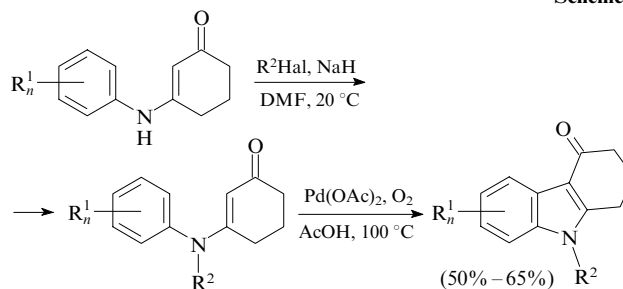
R$_n^1$ = H, 4-Me, 2-Me, 4-OMe, 2-Cl, 4-Cl, 4-Br, 2,4-F$_2$, 4-NO$_2$, 3-NO$_2$, 3-CF$_3$; R^{2}Hal = MeI, BnCl

The mechanism of the above-considered Pd(OAc)$_2$-catalyzed oxidative cyclizations of *N*-aryl enamines apparently involves the initial electrophilic palladation of enamine at the nucleophilic carbon centre followed by the cyclization *via* electrophilic attack on the ring or *via* CH-activation through σ-bond metathesis (Scheme 78). The final step involves the reductive elimination of Pd^0 and the formation of the indole ring. The role of the oxidizing agent is to transform Pd^0 into the active form Pd^{II}, which re-enters into the catalytic cycle.
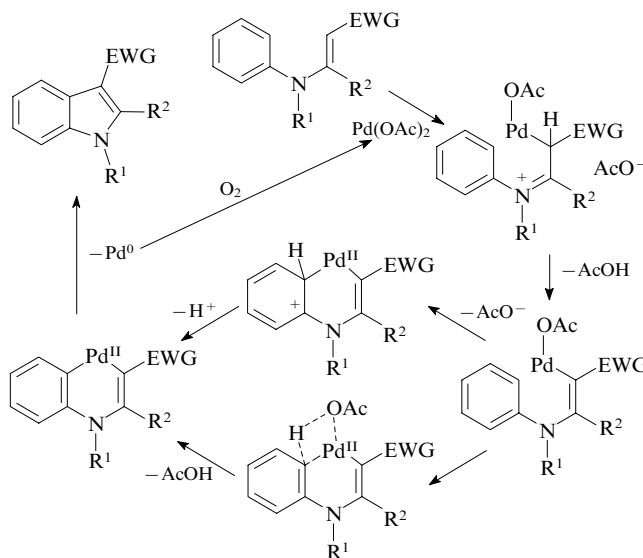
Bernini *et al.* proposed[126] an efficient procedure for the synthesis of substituted indoles based on the Cu^I-catalyzed oxidative cyclization of *N*-aryl enaminones **118**
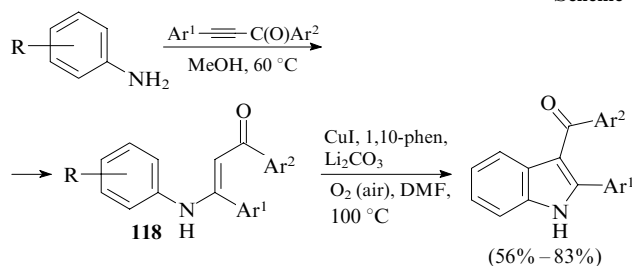
R = H, 4-Me, 2-Ph, 2-MeO, 4-MeO, 4-F, 4-Cl, 2-Br, 4-Br, 4-I, 4-Ac; Ar^1 = Ph, 3-MeC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-NCC$_6$H$_4$, 4-EtO$_2$CC$_6$H$_4$; Ar^2 = Ph, 3-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-FC$_6$H$_4$, 4-NCC$_6$H$_4$

(Scheme 79). It is evident that the catalysis by copper salts is attractive from both economic and environmental points of view, particularly in the case of large-scale synthesis. The proposed method was applied to a large number of compounds with varying substituents primarily in the aniline moiety of the substrate.

Indoles were isolated in good and even high yields. In the case of *meta*-substituted substrates, mixtures of regioisomers were obtained regardless of the nature of the *meta*-substituent. It was noted (see also Ref. 122) that in the presence of an additional methyl group at the nitrogen atom of enaminone, the reaction does not occur. The zero conversion was observed also in the reaction with the *para*-acetyl derivative (compound **118**, R = 4-Ac); however, the ketal protection allowed the authors to obtain the cyclization product in high yield.

The work of the cited authors describing the transformation of *N*-(*o*-haloaryl)enaminones into indoles (see Scheme 70) [118] was considered above. It is interesting that the conditions of both reactions are similar and differ, in essence, only by the nature of the base used (Li_2CO_3 or K_2CO_3). The study of the behaviour of enaminones **118a,b** under alternative conditions showed that the replacement of the metal cation plays a key role in this reaction (Scheme 80). For both substrates (Hal = Br, I), the results of reactions with different carbonates are substantially different. Thus, if M = Li, the reaction affords halogen-substituted indoles **126**.

Scheme 80
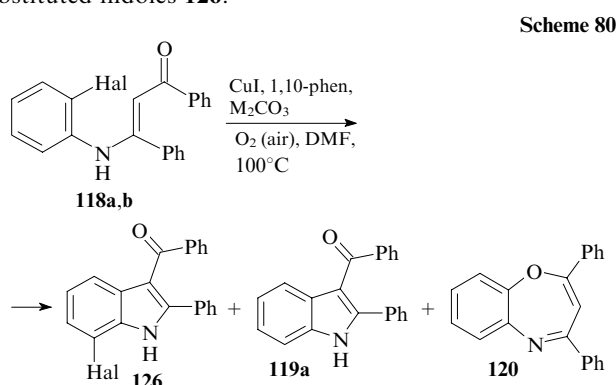
| Hal	M	Yield (%)		
		126	**119a**	**120**
Br	Li	51	–	–
Br	K	–	30	36
I	Li	27	51	–
I	K	–	92	–

It was reported [127] that the intramolecular oxidative coupling can be performed in the presence of iron salts as the catalyst. This method can be applied to transformations of β-(arylamino)crotonic esters **124** into substituted indoles **127** in yields from moderate to high (Scheme 81). In these reactions, copper(II) salts served as the oxidizing agents and the co-catalyst. Substrates containing *meta*-substituents form mixtures of regioisomeric indoles in comparable amounts. Guan *et al.*[127] hypothesized that the reaction produces a bimetallic chelate complex, in which the Fe atom is coordinated to the double bond and the carbonyl oxygen atom, and the Cu atom is coordinated to the enamine nitrogen atom.

An important advantage of this procedure over palladium-catalyzed cyclizations is that bromo- and even iodo-substituted substrates almost do not undergo the dehalogenation side reaction. Due to this fact, this procedure allows for the preparation of bromo- and iodo-substituted indoles. The latter are valuable building blocks, which can be further modified by cross-coupling reactions.

Scheme 81
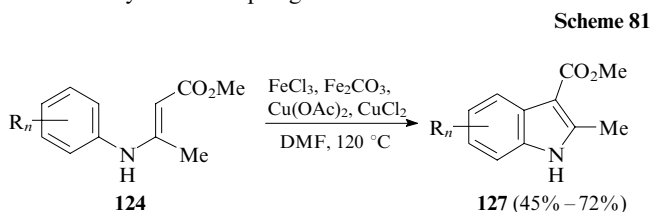
R_n = H, 2-Me, 3-Me, 4-Me, 2-MeO, 4-MeO, 2-Cl, 3-Cl, 4-Cl, 4-Ac, 2,3-benzo

A new convenient method for the cyclization of push-pull *N*-aryl enamines without using transition metals has been described.[128] The oxidative cyclization accompanied by the formation of a new C–C bond takes place in the presence of (diacetoxy)iodobenzene (Scheme 82). This method is suitable for the synthesis of various substituted indoles under mild conditions in yields from moderate to high.

Scheme 82
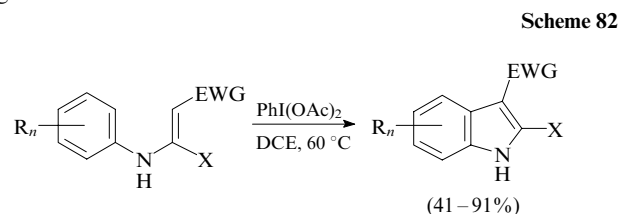
EWG = CN, NO_2, CO_2Me, C(O)Ph; X = Ar, Alk, CO_2Et;
R_n = H, 4-Me, 2-Me, 4-MeO, 4-Br, 3-F, 3,4-$(MeO)_2$

However, it should be noted that no examples of reactions with substrates bearing strong electron-withdrawing substituents in the aniline moiety were reported. Based on the proposed mechanism (Scheme 83), it can be concluded that both the first step of nucleophilic substitution of the iodine atom and the electrophilic cyclization are substantially hindered for such substrates.

Scheme 83
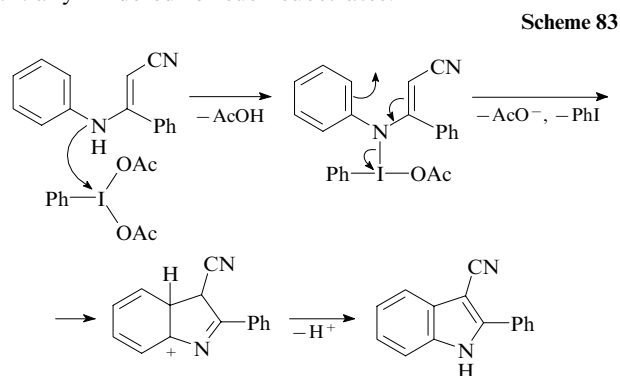
Alternative conditions for the oxidative cyclization of *N*-aryl enaminones to indoles were proposed by He *et al.*[129, 130] Cyclization of enaminones **118** in the presence of catalytic amounts of iodine and *N*-bromosuccinimide (NBS) as the oxidizing agent (Scheme 84) was reported.[129] In most cases, products were obtained in high yields. Substrates

containing a *meta*-substituent in the aniline moiety form mixtures of isomeric 4- and 6-substituted indoles.

Scheme 84
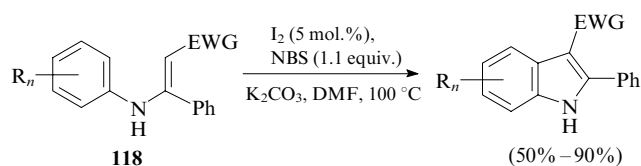
EWG = CO$_2$Et, C(O)Ph, C(O)NHPh; R$_n$ = H, 4-Me, 2-Me, 3-Me, 4-MeO, 3-MeO, 4-Br, 4-I, 4-CF$_3$, 2,3-benzo

It should be noted that in this case N-methyl derivative **128** also does not form the cyclization product, and the reaction affords only bromination products (Scheme 85). The authors concluded that the presence of a free NH group plays a key role in the formation of the indole ring.

The same research team reported[130] the method for the synthesis of 3*H*-indoles **129** starting from α,β-disubstituted β-(arylamino)acrylic esters (Scheme 86). The cyclization of enamines occurs under the action of iodine in the presence of a base and gives reaction products in high yields. Based on own experimental results and the analysis of the published data, the authors suggested the possible mechanism of transformations, which involves the iodination of enam-

Scheme 86

X = Me, Et, Bn, CH$_2$CH$_2$CN, CO$_2$Et, C$_6$H$_4$NO$_2$-4; R$_n$ = H, 4-Me, 2-Me, 4-MeO, 4-Cl, 4-I, 4-F$_3$C, 2,3-benzo

ine to form intermediate **130** followed by the intramolecular aromatic Friedel – Crafts alkylation.

In a recent study,[131] the Bu$_4^n$NI (30 mol.%) – Bu^{t}O$_2$H system was employed to conduct this intramolecular oxidative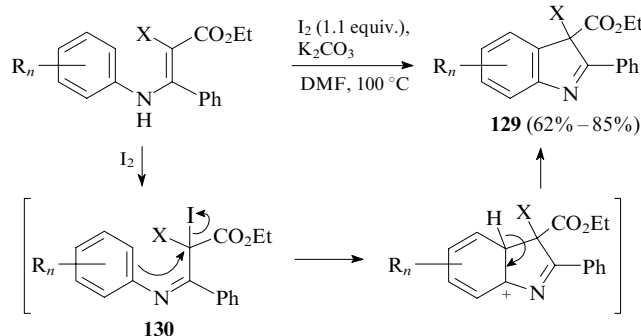 coupling in similar substrates. In most cases, products were obtained in very high yields in the reactions with substrates containing either electron-donating or -withdrawing substituents in the aniline moiety. Unfortunately, the regioselectivity of the cyclization of enamines with *meta*-substituents is low.

Cyclic *N*-aryl enaminones are also subjected to photo-induced cyclization. The photocyclization of enaminones **131** resulting in the formation of tetrahydrocarbazoles **112** and **123** (Scheme 87) was described.[132] The photochemical reaction directly produces dihydro derivative **132** (usually the *trans* isomer). This compound can be isolated in good yield, provided that the solvents were degassed beforehand. However, the cited authors focused on the development of the method for the synthesis of keto-indoles **112** and **123**. The latter were prepared by the treatment of the reaction mixture with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone or Mn(OAc)$_3$.

Scheme 87

R$_n$ = H, 4-Me, 2,4-Me$_2$, 3-MeO; n = 1, 2
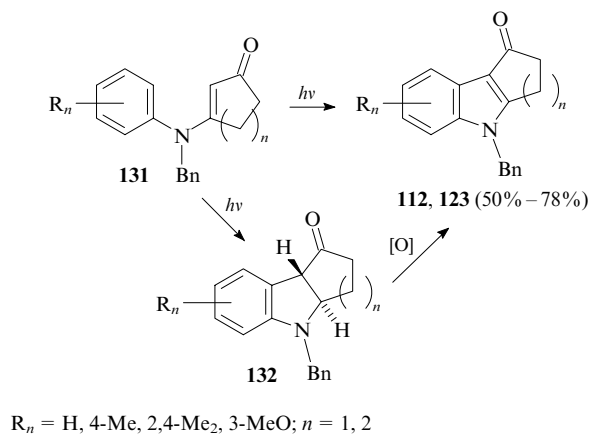
Aza analogues of tetrahydrocarbazoles can also be synthesized by oxidative photocyclization of the corresponding *N*-(pyridyl)- or *N*-(quinolinyl)enaminones.[133–135]

Scheme 85
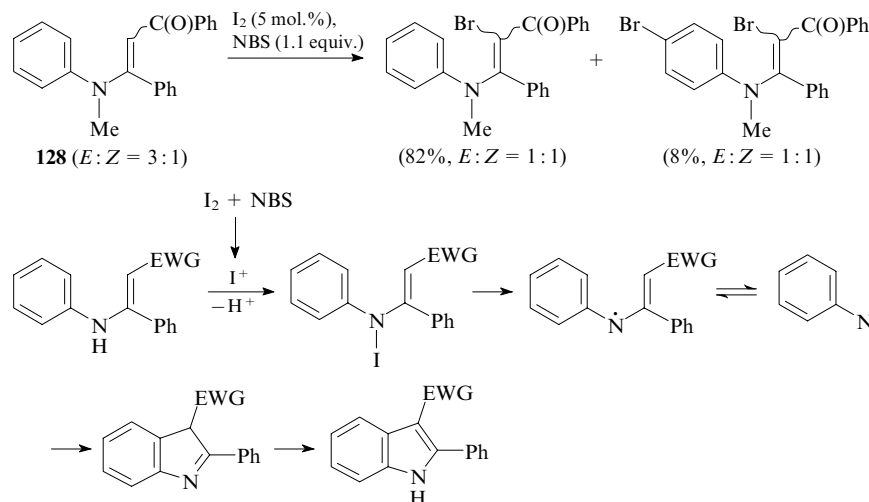
III.1.b. Cyclization of β-aryl enamines with the $C_{arom} - N$ bond formation

N-Arylation reactions have been actively used by synthetic chemists for many years. Numerous catalytic systems were developed for these reactions, due to which the latter can be performed with a very wide range of substrates, in particular, for the synthesis of various fused azaheterocycles. The intramolecular N-arylation of β-aryl enamines affords indoles. This approach to the synthesis of indoles from push-pull enamines is less commonly used because the latter compounds are less available compared to N-aryl enamines.

In a cycle of studies carried out by the research group headed by Yurovskaya,[136–138] a procedure was developed for the synthesis of N-substituted indole-3-carboxylates **133** based on the cyclization of α-(o-bromophenyl)-β-amino-acrylic esters **134** *via* intramolecular N-arylation (Scheme 88). The starting enamines were prepared by the formylation of o-bromophenylacetic ester followed by the treatment with amines. The $CuI - K_3PO_4$ system in DMF was shown to be an efficient catalyst for the $C - N$ bond formation.[136] The yields of reaction products vary from medium to high.

Scheme 88
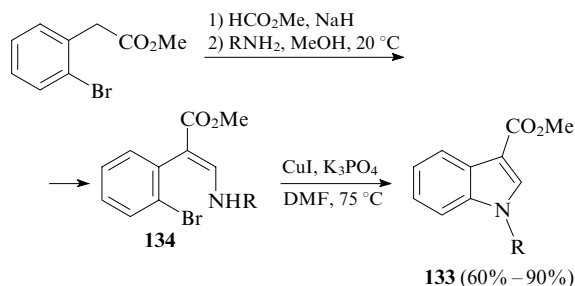
R = Bn, $(CH_2)_2Ph$, Bu^t, cyclo-C_3H_5, Cy, 2-MeC_6H_4, 3-$F_3CC_6H_4$, 2,4,6-$Me_3C_6H_2$, 4-$MeOC_6H_4$

It was found that the reaction is sensitive to steric hindrance. Heating over a much longer period of time is required for the reactions of derivatives of α-branched aliphatic amines and *ortho*-substituted anilines to occur. Unfortunately, attempts to synthesize enamines from low-reactive anilines (4-NO_2 and 2-CF_3) failed, thus limiting the potential of this approach to the synthesis of N-arylindoles **133** containing strong electron-withdrawing substituents in the phenyl moiety.

Melkonyan *et al.*[137] extended the scope of this procedure and applied it to synthesize N-aminoindole derivatives. In the step of the generation of enamines **134**, substituted hydrazines were used instead of amines. It was shown[138] that the cyclization of enamines **134** in the presence of iron(III) chloride as the catalyst ensures good yields of reaction products. Since catalysts based on iron salts are inexpensive and environmentally friendly, this modification of the method holds considerable promise.

A procedure was developed[139] for the Pd-catalyzed cyclization of zinc derivatives of enamines **135** (Blaise reaction intermediates). The latter are produced by the reaction of nitriles with the Reformatsky reagent generated *in situ* from dibromide **136** (Scheme 89). This tandem one-pot synthesis is suitable for the preparation of α-substituted indoles **125** in good yields both from aromatic and aliphatic nitriles. The reactions with γ-, δ- and ε-chloro-substituted aliphatic nitriles gave indoles **137** containing an annulated saturated ring. The treatment of the intermediate of this

Scheme 89
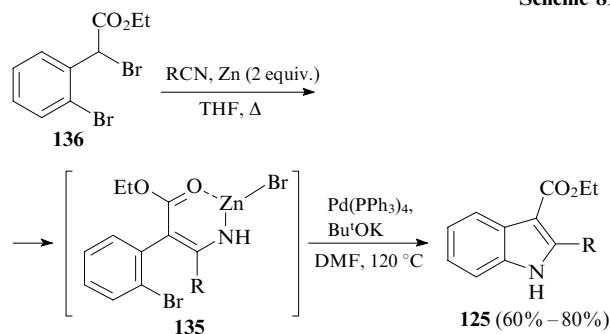
R = Bn, Et, 3-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 3-$F_3CC_6H_4$, 4-$EtO_2CC_6H_4$, 4-NCC_6H_4, 2-Fu, 3-Py; Py is pyridyl
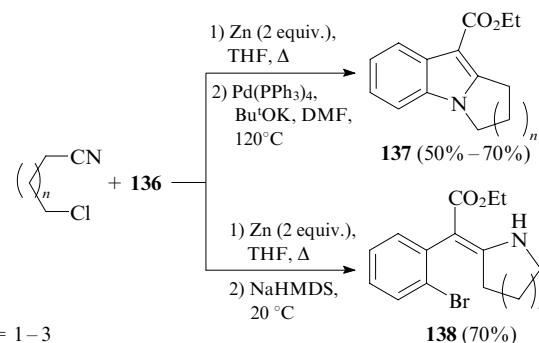
n = 1–3

reaction with a strong base — sodium bis(trimethylsilyl)-amide (NaHMDS) — produced cyclic enamines **138**.

Besides, it was demonstrated that indoles **125** can be synthesized from o-dibromo- or o-diiodobenzene by the reaction of the latter with intermediates **139**, which are formed from nitriles and bromoacetate (Scheme 90). In this case, both steps (intermolecular and intramolecular coupling) are catalyzed by the $CuI - 1,10$-phenanthroline system. Apparently, the reaction involves the N-arylation as the first step followed by the $C - C$ bond formation. The authors came to this conclusion based on the results of the reaction performed with bromobenzene, which selectively affords the N-arylation product of enamine.

Scheme 90
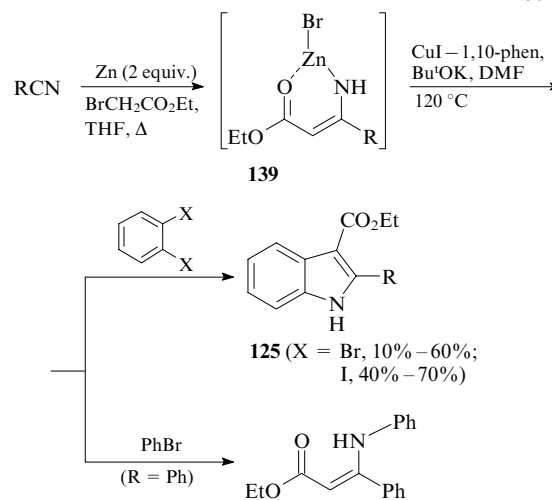
R = Et, Ph, 4-$MeOC_6H_4$, 4-FC_6H_4, 3-Py

Recently, a method was developed for the synthesis of α-aminoindole and pyrrolo[3,2-*d*]pyrimidine derivatives

based on the reaction of *o*-dihaloarenes with ethyl 2-(imidazolin-2-ylidene)acetate (**19a**) (Scheme 91).[140] The key step in the synthesis is the Cu[I]-catalyzed cyclization of β-(*o*-haloaryl)enediamines **140** and **141**. The latter are generated by the replacement of the active halogen atom in arene by the nucleophilic carbon centre of enediamine **19a**. In this case, the intramolecular arylation occurs under very mild conditions (at room temperature), which is not typical of such reactions.

Scheme 91

The cyclization of enamines **142** giving pyrrolopyridines **143** (Scheme 92) was reported.[141] The reaction is regioselective, requires moderate heating and proceeds in the absence of a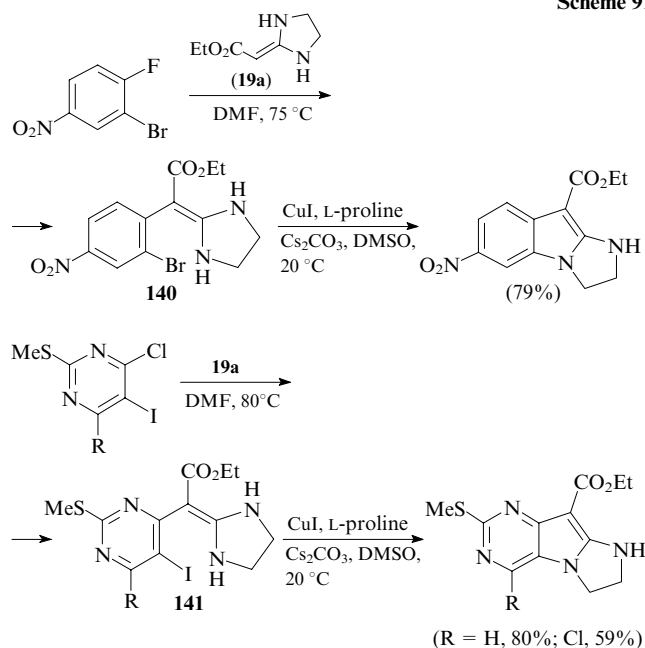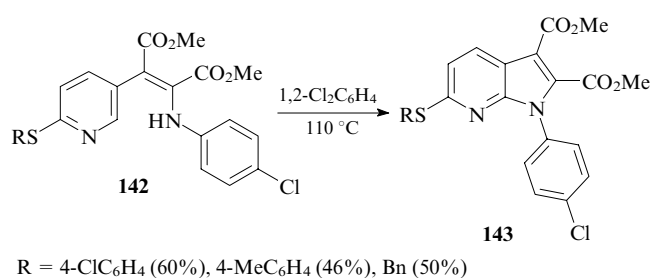 base as the catalyst. The electrophilicity of the α-position of the pyridine ring is apparently sufficient for the intramolecular nucleophilic attack followed by the oxidative aromatization with atmospheric oxygen.

Scheme 92

R = 4-ClC₆H₄ (60%), 4-MeC₆H₄ (46%), Bn (50%)

Zhao and co-workers[142] developed a procedure for the synthesis of N-substituted indoles **144** based on the cyclization of enamines **145** under the action of bis(trifluoroacetoxy)iodobenzene (PIFA) (Scheme 93). Enamines **145** are easily generated from the corresponding keto derivatives. This approach can be used to prepare both *N*-aryl- and *N*-alkylindole-3-carbonitriles **144** (EWG = CN) in high yields. Besides, it was shown for some examples that the cyclization can be conducted with substrates containing an ester group (**145**, EWG = CO₂Et).

Scheme 93
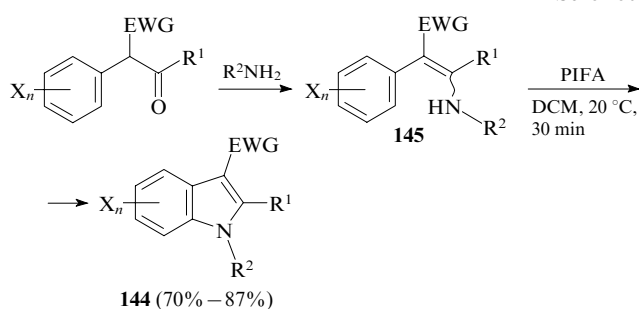
Xₙ = H, 4-F, 3-Cl, 4-Cl, 4-Br, 4-MeO, 3,4-(MeO)₂, 3-F₃C;
EWG = CN, CO₂Et; R¹ = Me, Prⁿ, Bn; R² = Ph, 4-MeC₆H₄,
2-MeOC₆H₄, 2-ClC₆H₄, 2,6-Cl₂C₆H₃, Prⁿ, Prⁱ, Buⁿ, Bn

The reactions of enamines containing a *meta*-substituents in the phenyl moiety that is involved in the cyclization afford regioisomers in equal amounts. It was noted that the presence of an electron-withdrawing substituent (X = 3-CF₃) does not reduce the reaction rate and has no effect on the yield of the product. Taking into account this fact, Zhao and co-workers revised the mechanism of electrophilic cyclization through the formation of the nitrenium ion that has been proposed earlier in favour of the scheme involving radical intermediates and the single-electron transfer (SET) step (Scheme 94). This scheme is additionally confirmed by the fact that N-alkyl-substituted enamines, which are less susceptible to the formation of an nitrenium intermediate compared with N-aryl derivatives, give cyclization products in good yields in a short period of time.

In subsequent studies, Zhao and co-workers have further elaborated this procedure and extended it to a wider range of substrates using alternative oxidizing agents for the cyclization. In particular, they demonstrated that substituted enamines **145** containing the nitrile group (EWG = CN) can be transformed into the corresponding indole-3-carbonitriles **144** by the reaction with *N*-bromosuccinimide in dichloroethane followed by the treatment with Zn(OAc)₂ (Scheme 95).[143]

Scheme 94

Scheme 95
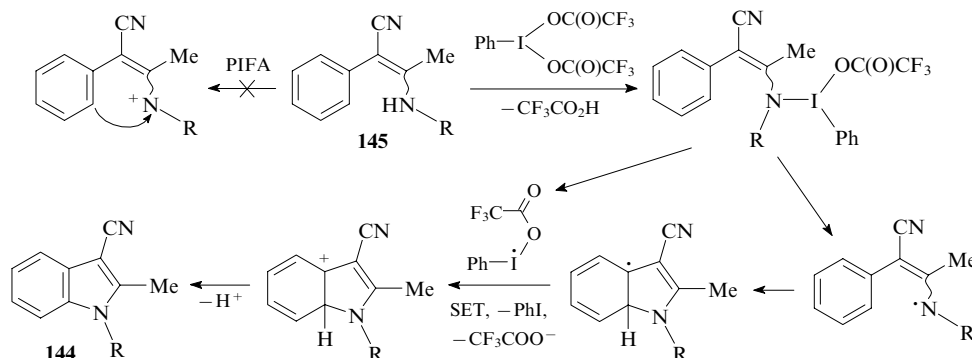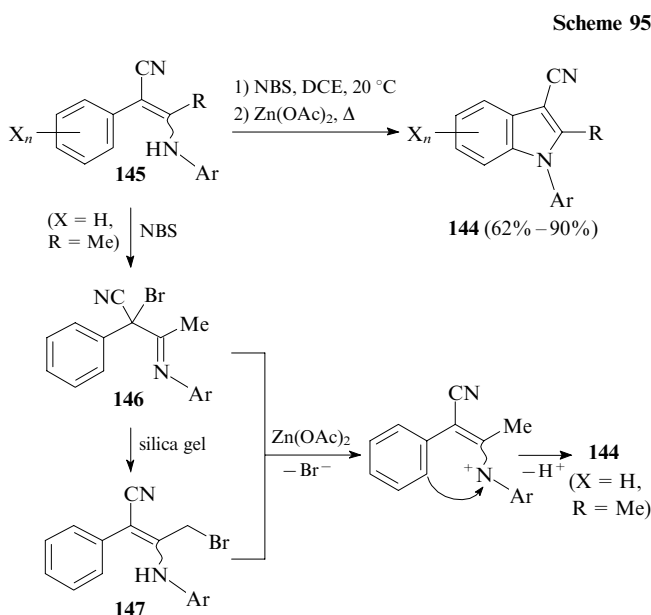
X_n = H, 4-MeO, 3,4-(BnO)$_2$, 2-Me, 4-Me, 4-F, 4-Cl, 3-Cl, 4-Br;
R = Me, Pr^n, Bn; Ar = Ph, 4-MeOC$_6$H$_4$, 2-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$,
3-FC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$

This process involves the bromination of enamine to form intermediate **146**, which was shown to be able to undergo either partial or complete isomerization into thermodynamically more stable structure **147**. This is not an obstacle because both intermediate bromides are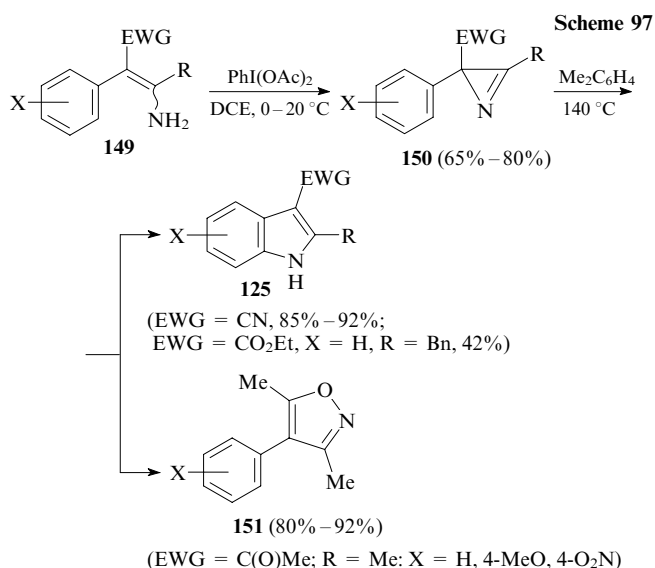 cyclized under the action of Lewis acid. The electrophilic character of cyclization is indirectly confirmed, first, by the fact that N-alkyl-substituted enamines do not form desired products due apparently to the insufficient (compared with aryl groups) stabilization of the nitrenium cation and, second, by the absence of examples of cyclization for substrates containing electron-withdrawing substituents in the benzene ring, which became a part of the indole system.

This research team showed that cyclic enaminones **148** are also subjected to oxidative cyclization using PIFA in dichloromethane to form tetrahydrocarbazoles **123** (Scheme 96) in high yields.[144]
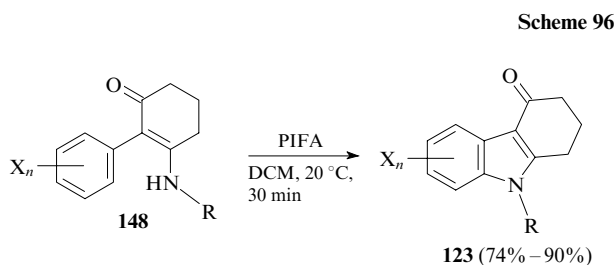
Scheme 96

X_n = H, 4-Me, 3,4-(MeO)$_2$, 3-F, 3-F$_3$C, 4-O$_2$N;
R = Me, Pr^n, Ph, 4-MeOC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$

In reactions with di(acetoxy)iodobenzene, N-unsubstituted enamines **149**, which form complex mixtures in reactions with PIFA, are transformed into 2H-azirines **150** (Scheme 97).[145] The latter can be subjected to thermal isomerization into the corresponding indoles **125** (EWG = CN, CO$_2$Et) or isoxazoles **151** [EWG = C(O)Me].

Scheme 97

(EWG = CN, 85% – 92%;
EWG = CO$_2$Et, X = H, R = Bn, 42%)

151 (80% – 92%)
(EWG = C(O)Me; R = Me: X = H, 4-MeO, 4-O$_2$N)

III.2. Cyclization of enamines to form fused six-membered azaheterocycles

This section deals with the cyclization of push-pull enamines giving fused six-membered azaheterocycles. In most cases, we consider the cyclization of β-(*o*-haloaroyl)enamines **152** resulting in the formation of 4-quinolones and other fused 4-pyridones (Scheme 98). This approach to the construction of such heterocyclic systems has gained considerable attention in recent years. It has important advantages over the conventional thermal cyclization of β-(arylamino)acrylic esters **153**. Being more laborious, this approach, first, employs milder conditions (25 – 100 °C instead of 250 °C), second, is suitable also for the cyclization of π-deficient arenes and, third, allows for varying the nature of the substituent at the nitrogen atom of the resulting heterocycle over a wide range.

Scheme 98
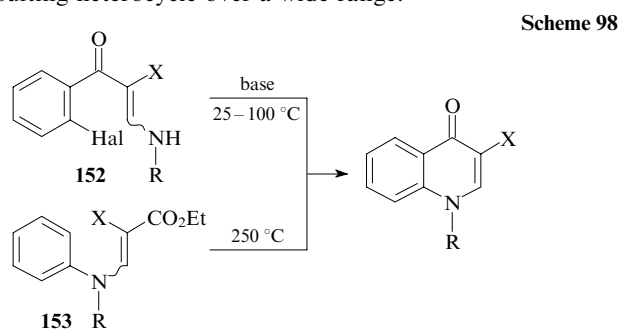
X = H, EWG

4-Oxoquinoline-3-carboxylic acid derivatives have attracted attention of pharmacologists for a long time due to a broad spectrum of biological activities. Many representatives of this class of compounds serve as effective antibiotics. These structures are actively, and not unsuccessfully, screened for antibacterial, antimicrobial, antiviral and antitumour activities. The approach based on the cyclization of β-(*o*-haloaroyl)enamines **152**, which are easily available from the corresponding aroylacetic esters, is efficiently used in the synthesis of a wide range of quinolone derivatives **154** (Scheme 99).[146 – 162] The cyclization is usually performed under heating in DMF in the presence of a base (most often, K$_2$CO$_3$). In most cases, the fluorine atom is rather easily replaced and no additional electron-withdraw-

Scheme 99
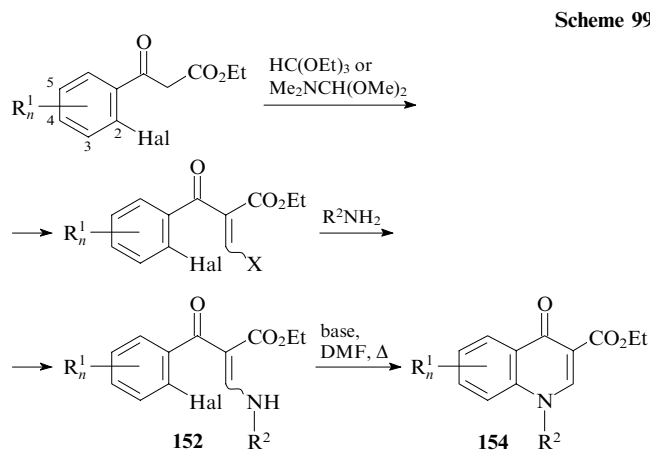
Hal = F: R_n^1 = H, 4-F, 5-I, 5-Alk, 5-OMe, 3,4-F$_2$, 4,5-F$_2$, 3,4,5-F$_3$; Hal = Cl: R_n^1 = 3-NO$_2$, 5-NO$_2$; X = OEt, NMe$_2$; R^2 = Alk, Ar

ing substituents in the ring are required.[146–158] To the contrary, the chlorine atom can be replaced only in the rings with pronounced π-deficiency.[159–162]

A similar procedure is advantageously employed to prepare aza analogues of quinolones **154** (Scheme 100).[163–169] These compounds are of great interest for pharmacology. Examples of the cyclization involving the thiophene ring and giving thienopyridones **155** (see Scheme 100) were reported.[170–173]

Scheme 100
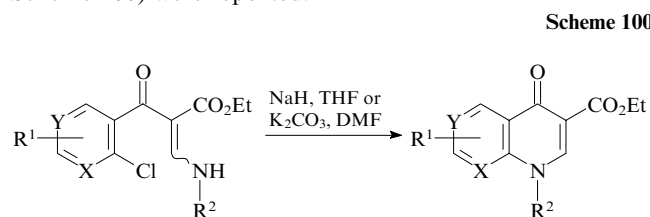
X = N, Y = CH: R^1 = H, 6-Cl, 5-F, 4-CF$_3$, 6-Me, 6-OMe; X = CH, Y = N: R^1 = H, 2-Cl; R^2 = Alk, Ar

R = Alk, Ar

The synthesis of 4-oxoquinolines and 4-oxo-1,8-naphthyridines based on the cyclization of the corresponding

Scheme 101

Ar = 2,4-F$_2$C$_6$H$_3$; (*a*) (for R = H) DMF, 80 °C, 30 min (38%); (*b*) (for R = Me) DMSO, 90 °C, 1 h (98%)

enaminones **156** and **157** has been described.[174] This cyclization reaction occurs *via* the intramolecular nucleophilic aromatic substitution of an activated halogen atom (Scheme 101). The reaction takes place under moderate heating in the presence of a base.

A similar cyclization reaction affords 2-trifluoromethyl-quinolones **158** (Scheme 102).[175] The starting enaminones are generated from acetophenone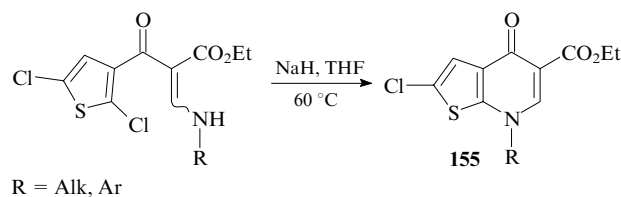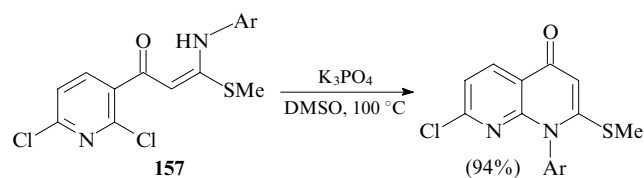s in the reactions with *N*-(aryl)imidoyl chlorides. In this case, it is possible to replace the chlorine atom, which is substantially less active than the fluorine atom, in the benzene ring containing no additional strong electron-withdrawing substituents.

Scheme 102
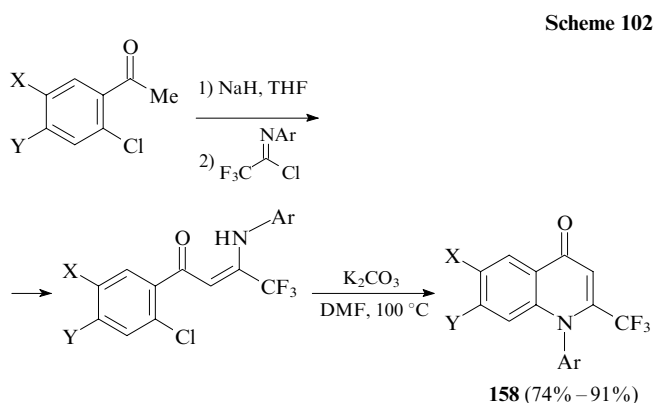
X = H, Y = Cl; X = Cl, Y = H; Ar = 3-MeOC$_6$H$_4$, 4-MeOC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-FC$_6$H$_4$

Bernini *et al.*[176] synthesized enaminones **159** by the reaction of primary amines with the corresponding benzoyl-alkynes, which are easily accessible under Sonogashira reaction conditions starting from *o*-halobenzoyl chlorides and terminal alkynes (Scheme 103). 1,2-Disubstituted quinolones **160** produced by the Cu-catalyzed cyclization were isolated in high yields. It should be noted that the bulkiness of the alkyl substituent at the enamine nitrogen atom has a crucial effect on the cyclization step. Thus, the yield for the N-cyclohexyl derivative was rather low (36%) and N-*tert*-butyl-substituted quinolone was not isolated at all. The chloro-substituted derivatives were cyclized under the same conditions as bromides. The reaction rate was substantially lower but the yields of quinolones remained high. The possibility of performing cyclization without the isolation and purification of enamine was demonstrated by one example.

Scheme 103
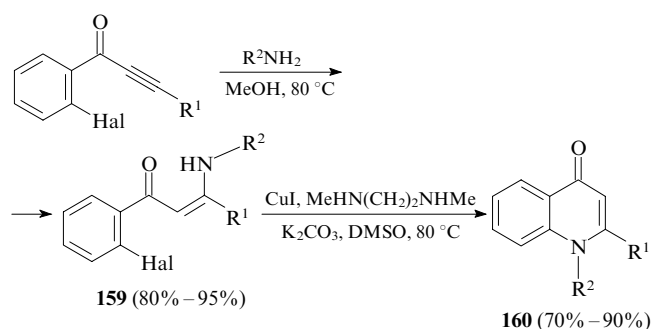
Hal = Br, Cl; R^1, R^2 = Ar, Alk

A similar approach was used in a number of studies,[177–179] where the cyclization was performed without the isolation of β-aroyl enamines. The cyclization step

producing *N*-alkyl-4-quinolones **161** was conducted [177] by refluxing with sodium hydride in dimethoxyethane (DME) (Scheme 104). Good yields were achieved not only for fluoro- but also for bromo-substituted substrates.

Scheme 104
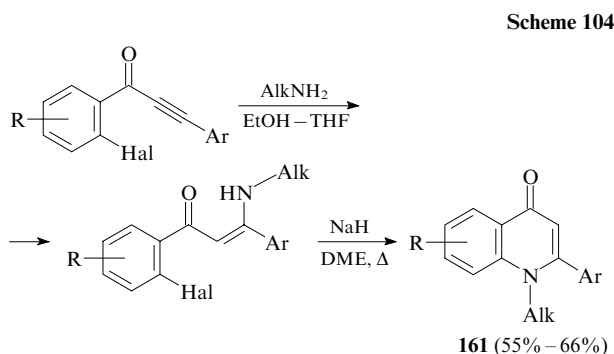
R = 5-Cl, 5-Me, 5-MeO, 6-MeO; Hal = F, Br; Ar = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-MeOC$_6$H$_4$, 3-ClC$_6$H$_4$, 3-Th, 3-Py; Alk = Me, Et, cyclo-C$_3$H$_5$

Zhao and Xu [178] synthesized *N*-aryl-4-quinolones from *o*-bromobenzoylalkynes *via* the successive 1,4-addition of arylamines and the Pd-catalyzed cyclization (Scheme 105). It was noted that the use of alkylamines in the synthesis leads to a substantial decrease in the yields of the final products. In the further study of this research group, a simplified version of the cyclization of *o*-chloro-substituted substrates (without using Pd) under the action of K$_3$PO$_4$ was proposed for the preparation of N-alkyl derivatives.[179]

Scheme 105

R^1 = Ph, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 2-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 3-Py, n-C$_5$H$_{11}$; (*a*) Pd$_2$(dba)$_3$, PPh$_3$, K$_2$CO$_3$, 1,4-dioxane, reflux (yield 60% – 85%); (*b*) K$_3$PO$_4$ DMSO, 140 °C (80% – 98%)

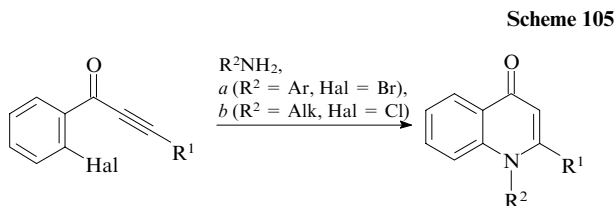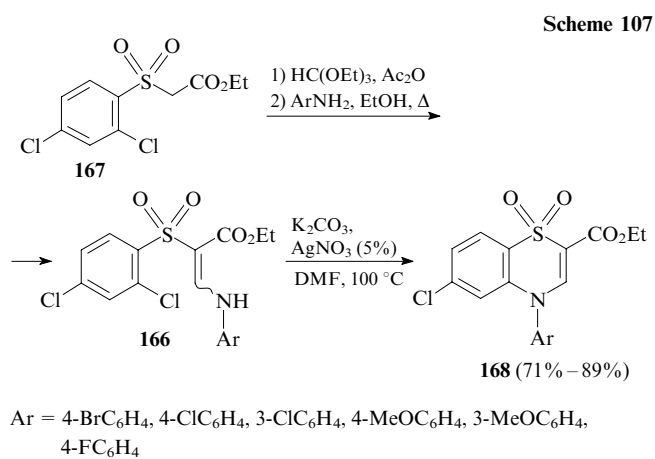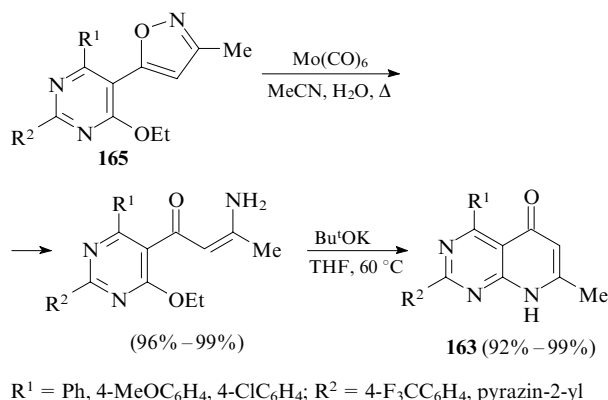The synthesis of 1,6-naphthyridin-4-ones **162** and pyrido[2,3-*d*]pyrimidin-5-ones **163** through the cyclization of enaminones, which are generated *via* the reductive ring opening of isoxazoles **164** and **165**, was documented (Scheme 106).[180, 181] Both steps are characterized by high yields of the target products. In the former case, a perfluoroalkyl substituent acts as a leaving group.

The cyclization of β-(arylsulfonyl)-substituted enamines affords 1,4-benzothiazine 1,1-dioxides. Lopez *et al.*[182] synthesized enamines **166** from (arylsulfonyl)acetic ester **167** by a method considered above for benzoylacetic esters. The cyclization produced *N*-aryl-1,4-benzothiazines **168** in high yields (Scheme 107).

Tsui *et al.*[183] prepared enamines **169** by the Rh-catalyzed addition of arylboronic acids to (*o*-fluorophenylsulfonyl)-acetonitrile (**170**) (Scheme 108). The subsequent intramolecular nucleophilic substitution gave N-unsubstituted 2-aryl-1,4-benzothiazine *S,S*-dioxides **171**.

A synthetic route to N-substituted 1,4-benzoxazines and 1,4-benzothiazines based on the Cu-catalyzed cyclization of enamines **172** was described by Melkonyan *et al.*[184] (Scheme 109).

Scheme 106

R = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-Me$_2$NC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 2-Py, 4-Py, Et, MeOCH$_2$

R^1 = Ph, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$; R^2 = 4-F$_3$CC$_6$H$_4$, pyrazin-2-yl

Scheme 107

Ar = 4-BrC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-FC$_6$H$_4$
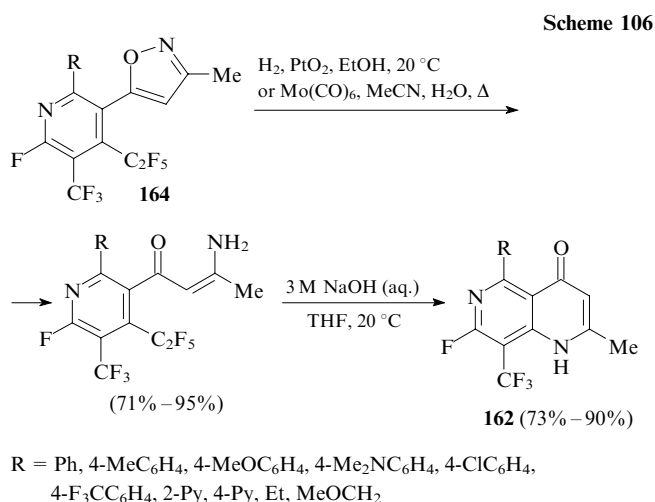
The synthesis can be performed without the isolation of enamines (one-pot process) to obtain target compounds in high yields. A decrease in the yields of cyclization products was observed only if substituents at the nitrogen atom create steric hindrance [R^2 = CHMePh (55%), Cy (53%), Bu^t (0%)]. Evidently, the cyclization of substrates **172** *via* the uncatalyzed nucleophilic aromatic substitution is hindered due to the π-excessive rather than π-deficient (as in the above-considered examples) character of the aromatic ring.

In a cycle of studies,[185–190] a methodology was proposed for the construction of polycyclic systems — benzofused tetrahydroimidazo-1,8-napthyridines — based on the reaction of cyclic enediaminones **19** (Scheme 110) with electrophilic reagents to form tetrahydroimidazopyridines

Scheme 108

170

169

171 (73% – 94%)
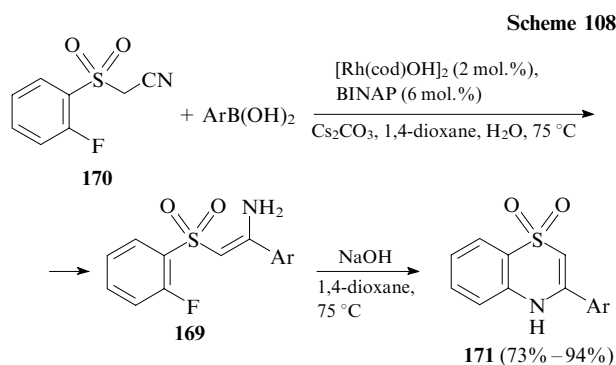
Ar = 4-MeOC₆H₄, 3-MeOC₆H₄, 2-MeC₆H₄, 4-ClC₆H₄, 3-F₃CC₆H₄,
4-AcC₆H₄, 3-AcC₆H₄, 4-FC₆H₄, 4-MeSC₆H₄, 3-Th, 1-Naph;
cod is cycloocta-1,5-diene; Naph is naphthyl;

BINAP =
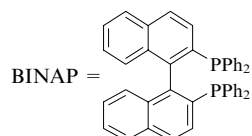
173. In the presence of a halogen atom in the position 2' of the benzoyl moiety, the latter compounds undergo cyclization.

Scheme 110

19

173 (80% – 90%)   (83% – 88%)
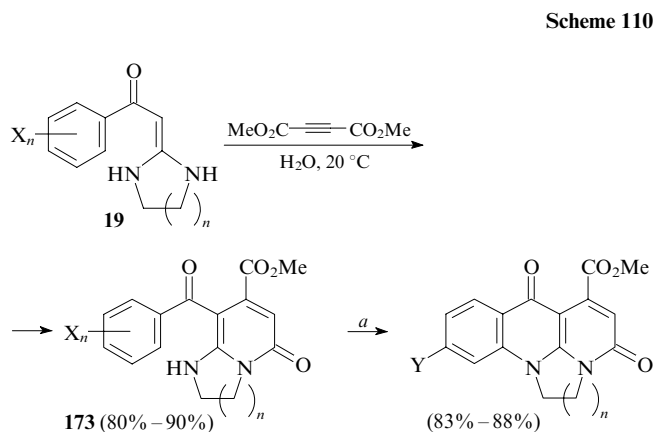
X_n = 2-Cl or 2,4-Cl₂, Y = H, Cl; (a) K₂CO₃, DMF, 80 °C

Scheme 109

172
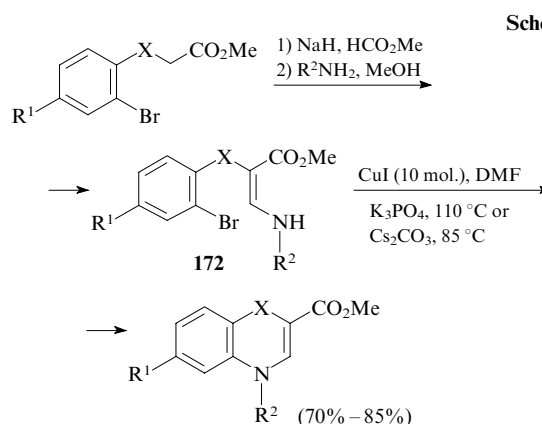
X = O, S; R¹ = H, Me, CO₂Me; R² = Alk, Ar

The pyridine ring in compounds **173 – 175** is formed through the cyclocondensation of enediamine with 1,3-dielectrophiles — acetylenecarboxylic acid diester[185] (see Scheme 110), substituted but-2,3-dienoic acid esters[186] and β-substituted α-bromoacroleins[187] (Scheme 111).

The multicomponent synthesis similar to the Biginelli reaction involving enediamines **19**, aldehydes and compounds containing an active methylene group also affords tetrahydroimidazopyridines, which are cyclized upon heating in DMF with K₂CO₃ *via* the intramolecular nucleophilic aromatic substitution of the chlorine atom (Scheme 112).[188, 189]

The four-component domino reaction providing tetrahydroimidazo-1,8-naphthyridine derivatives has been described[190] (Scheme 113). The synthesis can be performed without the isolation of the initially formed dihydropyridines.

The cyclization of β-arylaminocinnamic esters **176** *via* the alkynyl group to form 4-acylquinoline derivatives occurs through the Cu-catalyzed nucleophilic addition of the nucleophilic carbon centre of enamine at the carbon–carbon triple bond followed by the oxidation of the exocyclic carbon atom to the carbonyl group (Scheme 114).[191] The reaction takes place in an oxygen atmosphere, oxygen being involved in the oxidation step, as was demonstrated in an experiment with labelled oxygen (¹⁸O₂).

Scheme 111

174 (50% – 90%)   (95% – 99%)

175   (60% – 65%)
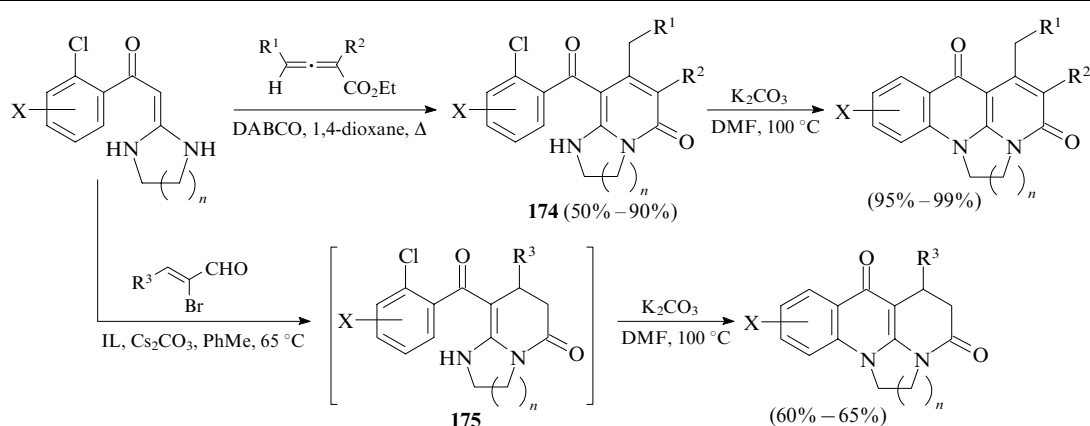
X = H, 4-Cl, 5-Cl, 4-Br; R¹ = H, Prⁿ, Buⁿ, Ph; R² = H, Bn; n = 1, 2;
R³ = Ph, 4-ClC₆H₄, 3-ClC₆H₄, 4-MeOC₆H₄, Me; IL is 1,3-dimesitylimidazolium chloride

Scheme 112

X = H, 4-Cl, 5-Cl

X = H, 4-Cl

Scheme 113

(65% – 80%)
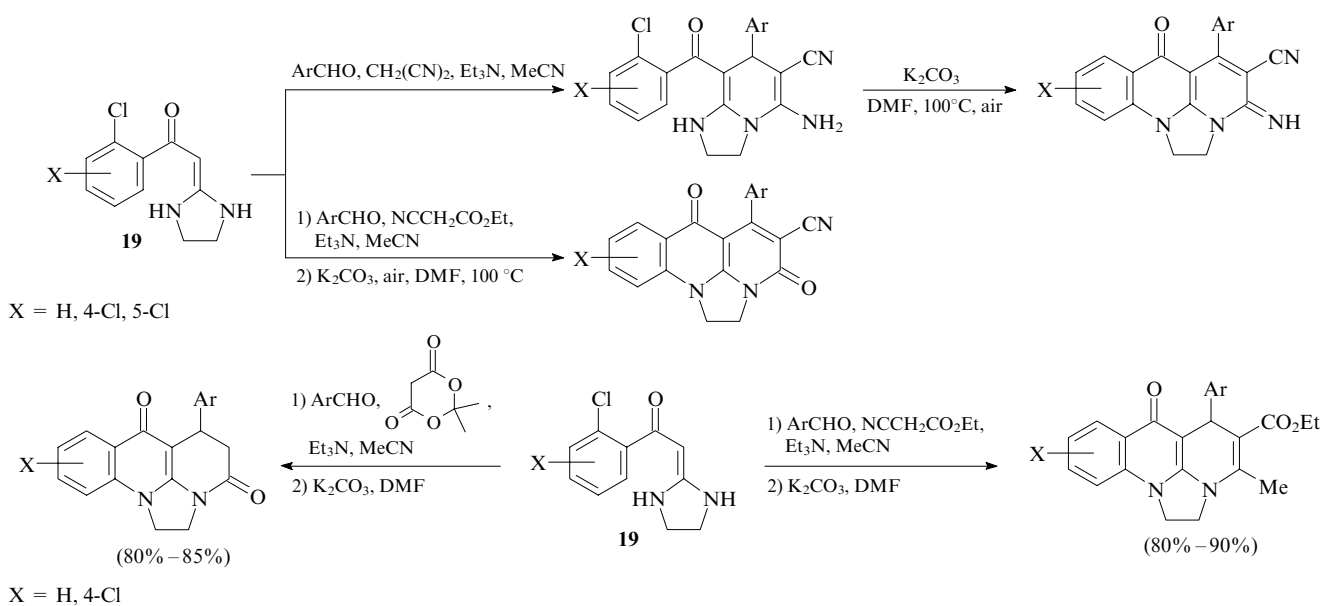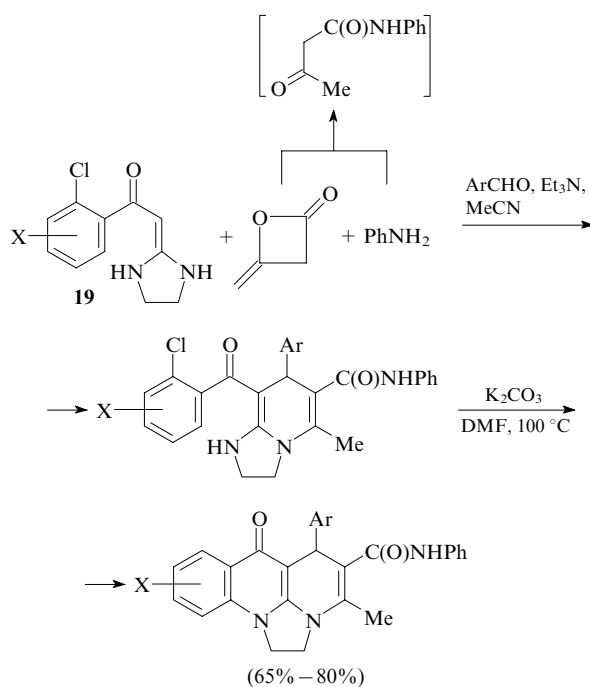
X = H, Cl, 5-Cl

Scheme 114
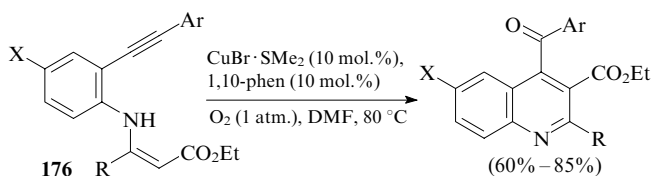
X = H, Cl, Br, Me, CN; R = Me, Pr^i, cyclo-C$_3$H$_5$, Ph, 2-BrC$_6$H$_4$, 3-BrC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-Naph, CO$_2$Me; Ar = Ph, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-MeC$_6$H$_4$

IV. Conclusion

Push-pull enamines are 1,3-dinucleophiles containing nucleophilic nitrogen and carbon centres. Due to the ability of such enamines to bind to two electrophilic centres in the same molecule, these compounds have a great potential in the synthesis of nitrogen-containing heterocycles (Scheme 115).

Scheme 115
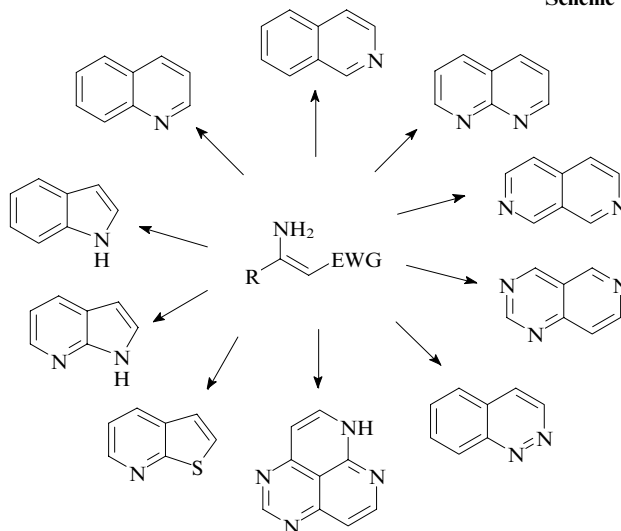
The cyclocondensation of push-pull enamines with cyclic 1,2-dielectrophiles affords fused pyrroles; with cyclic 1,3-dielectrophiles, fused pyridines are formed. The cyclization of aryl-substituted enamines also can give both types of heterocyclic systems. Electrophilic centres can be of diverse nature. Carbonyl and nitrile carbon atoms, carbon atoms of π-deficient aromatic rings, which often, but not always, bear a leaving group (mostly a halogen atom), and carbon atoms of multiple bonds conjugated to electron-withdrawing groups easily undergo nucleophilic attack of enamines. Examples of the nucleophilic attack on the nitrogen atom of the nitro group and sp^3-hybridized carbon atoms bearing the hydroxy group or a halogen atom were also reported. Besides, catalysts based on transition metals can be used to

form a bond between one of the nucleophilic centres of enamine and the nonactivated aromatic ring through the replacement of a halogen atom or the oxidative replacement of a hydrogen atom. Due to such a great diversity of the starting compounds and the reactions used, as well as the synthetic accessibility of push-pull enamines, the latter are useful building blocks in the synthesis of various fused heterocyclic systems.

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