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SYNTHESIS OF 1(2H)-ISOQUINOLONES. (REVIEW)

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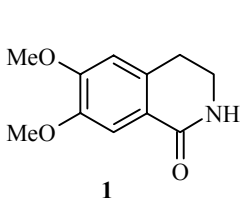
Methods published over the last 10 years for the production of substituted 1(2H-isoquinolones, including those involving the use of organometallic compounds, are discussed.

Keywords: isoquinolones.

Derivatives of 1(2H)-isoquinolone (isocarbostyril) are found among natural compounds [the alkaloids coryaldine (**1**), N-methylcoryaldine [1], dorianine (**2**) [2] and its 3,4-dihydro analog hydroxyhydrastinine, thalflavine (**3**) [3] and others] and compounds contained in more complex isoquinoline alkaloids and their oxidation products [2-6].



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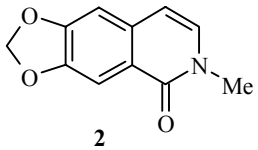

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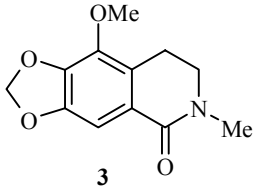

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By virtue of their chemical stability and relative accessibility substituted 1(2H)-isoquinolones are often used as building blocks in organic synthesis.

The unique structure of the isoquinolone ring, reminiscent of the rigidly fixed skeleton of phenyl-containing amino acids, gives it biomimetic characteristics [7]. It is not surprising, therefore, that antagonists of receptors 5-HT_3 [8], 5-6T_3 [9], glycoprotein IIb [10], and tachykinin receptors [11] have been found among the derivatives of 1(2H)-isoquinolones. Substituted isocarbostyrils exhibiting antidepressant [12], anti-inflammatory [13], analgesic [14], hypolipidemic [15], and analeptic [16] characteristics have also been described; there are also agents that act on the central nervous system [17], inhibitors of lipoxygenase [18] and poly(ADP-ribose)polymerase (19), inhibitors of cholesterol biosynthesis [20, 21], and agents for the treatment of stomach tumors [22, 23] and diseases of human brain cells [24].

Numerous papers have been devoted to alkaloids of the licorane group [(+)-licoricidine (**4**), pancratistatin (**5**), etc.], having a phenanthridone skeleton and clearly defined anticancer activity [25]. A total synthesis of (+)-licoricidine was achieved by Ogawa in 1991 [26], by Gudlitskii in 1992 [27-29], and by Weinreb in 1993 [30] and Trost in 1995 [31]. In the present review we will touch upon the production of alkaloids of the licorane group, phenanthridones, and certain other heterocyclic compounds condensed with the isocarbostyril nucleus only in so far as it is associated with the most recent approaches to the synthesis of 1(2H)-isoquinolones.

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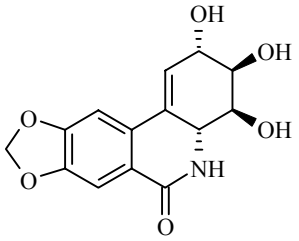
Traditional methods for the production of isocarbostyrils have been described in sufficient detail up to 1988 inclusive [32]. Since that time new methods for the synthesis of 1(2H)-isoquinolones, based on the reactions of organometallic compounds and metal-complex catalysts, have appeared. The present review is devoted to examination of these new methods and also traditional methods of synthesis published since 1988. With the exception of certain papers of historical or fundamental significance papers beginning with 1989 are included.



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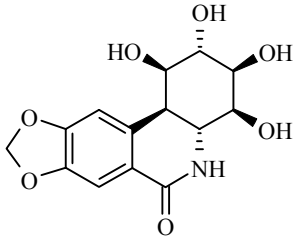

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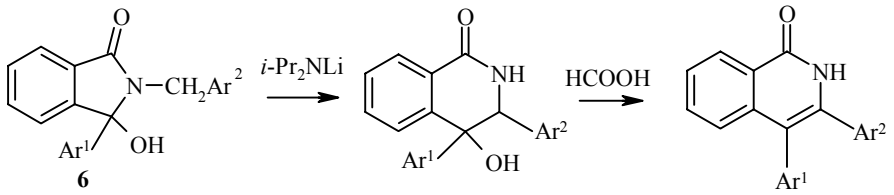
In view of the fact that according to UV and NMR spectroscopy 1-hydroxyisoquinolines exist predominantly in the tautomeric oxo form in solutions in deuterochloroform and ethanol [32], in this review this form is adopted as the main form, and the compounds are described as 1(2H)-isoquinolones even in cases where the possibility of tautomerism exists.

The methods for the production of 1(2H)-isoquinolones are grouped according to the type of bond formed at the key stage of the reaction (e.g., the $C_{(1)}$–$C_{(2)}$, $C_{(1)}$–$C_{(8a)}$, etc. bonds).

1. Syntheses with Substitution of the Heteroatom [O → N]

The Gabriel–Coleman synthesis of isoquinolones, known since the beginning of the century [33] and involving ring enlargement in phthalimides of type **6**, is still in wide use at the present time [34].



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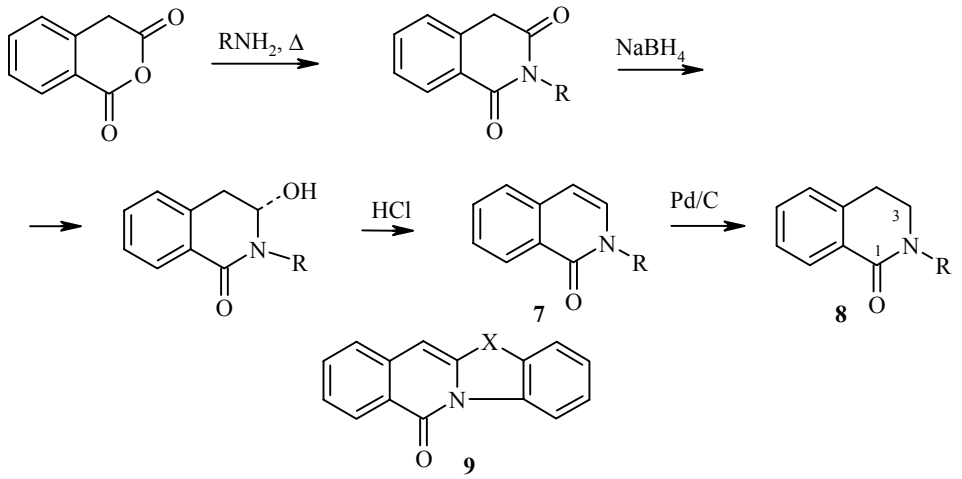
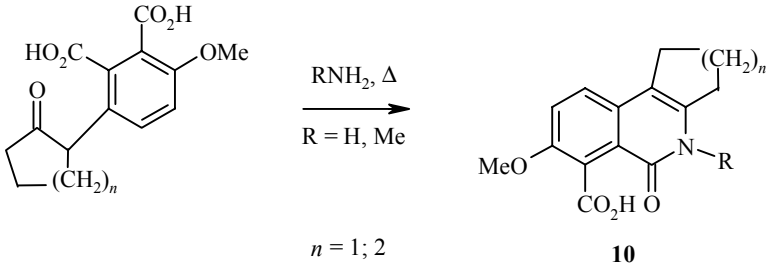
Ar^1, Ar^2 = Ph, 4-$MeOC_6H_4$

The condensation of amines with homophthalic anhydrides leads to 1,3-dioxo-3,4-dihydroisoquinolones [35], which can be reduced [36] to the 3-hydroxy derivatives capable of dehydration with the formation of the isoquinolones **7** and subsequent reduction to the 3,4-dihydroisoquinolones **8**:

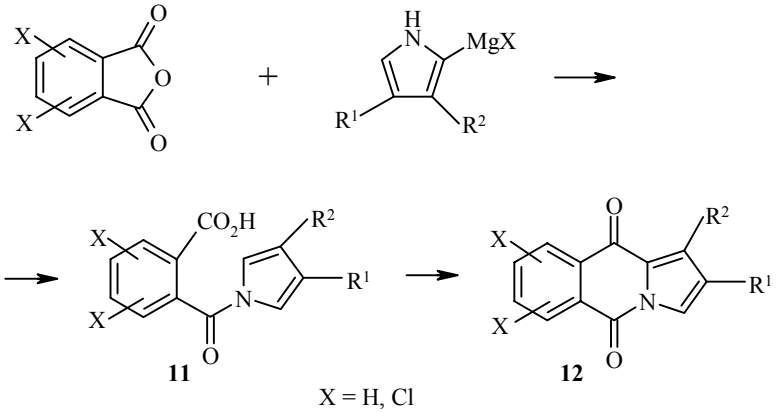


R = Ar [33]. $PhCH_2$, C_3H_7 [34, 37]; X = NH, O, S

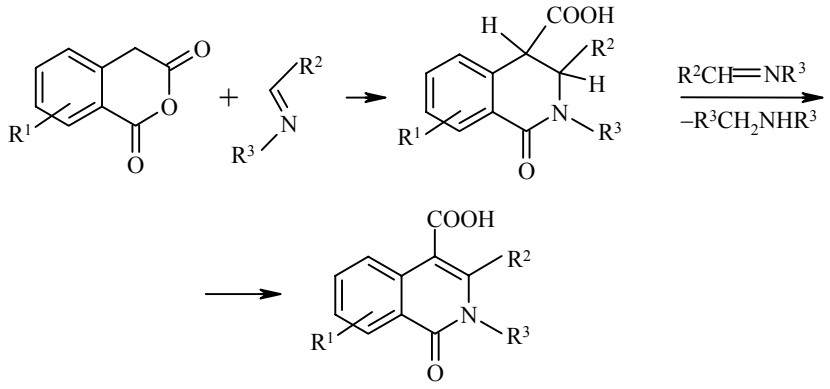
An excess of sodium $NaBH_4$ leads to opening of the $N_{(2)}$–$C_{(3)}$ bond of the ring. In the case of *o*-phenylenediamine, *o*-aminophenol, and *o*-aminothiophenol condensation products of type **9** are formed [38]. The intermediate formation of an enamine with its subsequent cyclization to the tricyclic product **10** was proposed in a similar reaction [39]. Ammonium acetate was used as source of ammonia.



The reaction of pyrrole-2-magnesium halides with substituted phthalic anhydrides [40] gave the amides **11**, capable of cyclization to pyrrolo[1,2-*b*]isoquinolinediones **12** (when boiled in a 5-10% aqueous solution of sodium acetate).

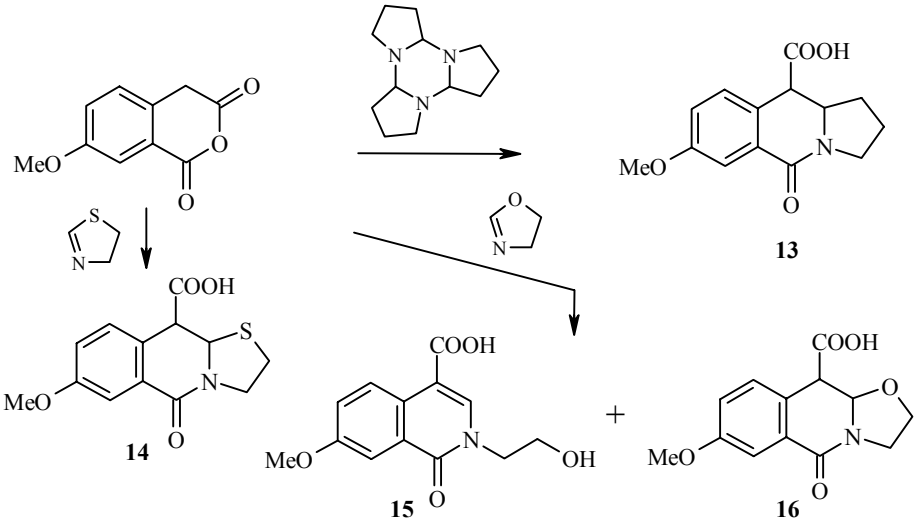


New approaches to 4-carboxy-substituted 1(2H)-isoquinolones appeared in the familiar condensation of homophthalic anhydrides with azomethines [41-43]. The reaction takes place on heating in benzene, chloroform, or dichloromethane with [44] or without [45] the presence of tertiary amines; an excess of the azomethine at the second stage of the process serves as oxidant for the intermediately formed 3,4-dihydroisoquinoline:

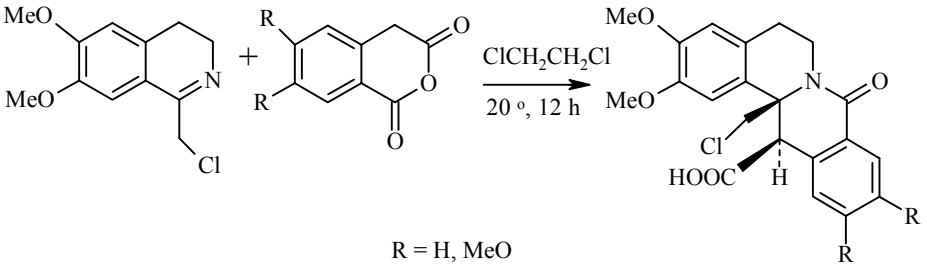


R^1 = H, MeO; R^2 = Ar; R^3 = Alk, CH_2=$CHCH_2$, $PhCH_2$

With the use of cyclic imines it is possible in this way to obtain 1(2H)-isoquinolones annellated with pyrrolidine, oxazolidine, and thiazolidine rings [46]. Whereas the yields of compounds **13** and **14** are practically quantitative in the form of 1:1 and 1:2 mixtures of the *cis* and *trans* isomers respectively, 2-oxazolidine forms the 2-hydroxyethyl derivative **15** with a yield of 55%, and the product **16** analogous with compounds **13** and **14** is isolated with a low yield.

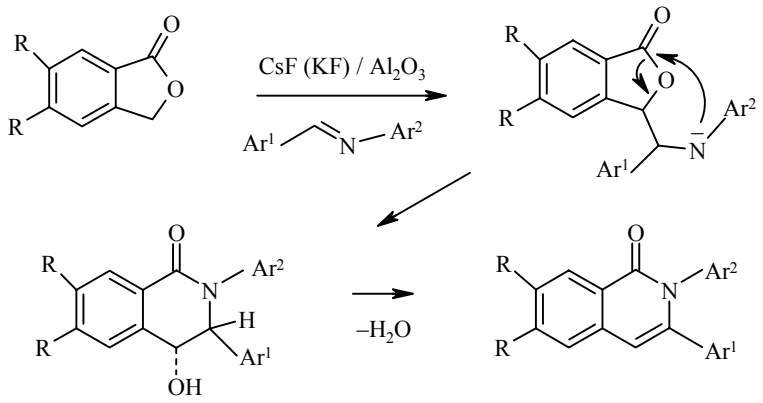


The condensation of homophthalic anhydrides with 1-chloromethyl-3,4-dihydroisoquinoline leads to protoberberine systems, containing an isoquinolone fragment (yields 70-89%) [47]:



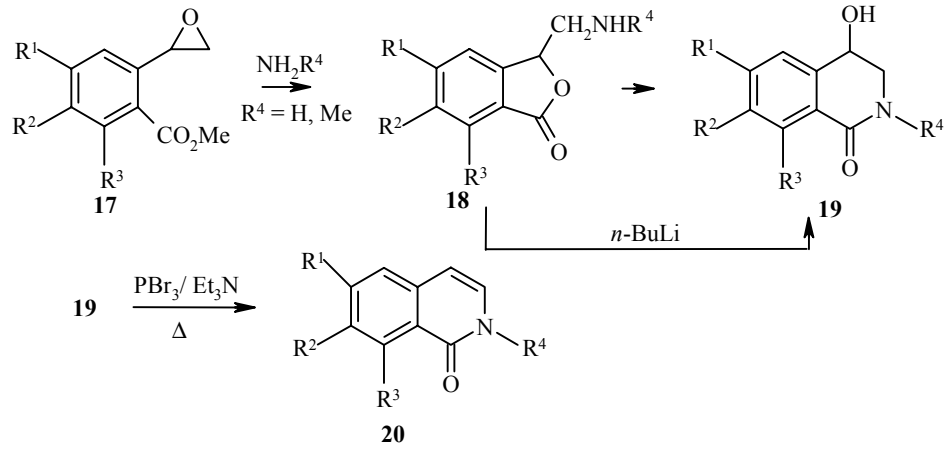
R = H, MeO

2,3-Diaryl-1(2H)-isoquinolones were synthesized with yields of 37-72% by the reaction of phthalides with the anils of aromatic aldehydes in the presence of the catalytic system CsF/Al_2O_3 [48]; with KF the yields were rather lower.

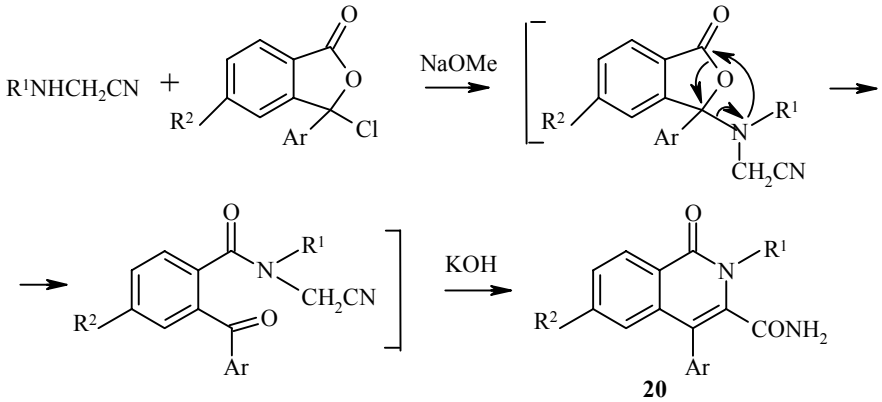


R = H, MeO; Ar^1 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3-FC_6H_4, 4-$Et_2NSO_2C_6H_4$; Ar^2 = Ph, 4-pyridyl, 2-thienyl

An original method was developed for the synthesis of 4-hydroxy-1(2H)-isoquinolones substituted in the aromatic ring by electron-withdrawing substituents [49]. The reaction of 2-methoxycarbonylstyrene oxide **17** with ammonia or methylamine with $R^1 = R^3 = H$, $R^2 = H$, NO_2 leads directly to 4-hydroxy-1(2H)-isoquinolone **19**. With $R^1 = R^3 = Me$ and $R^2 = CO_2Et$, however, the intermediate aminomethylphthalide is formed, and this changes into the isoquinolones (**19**) after treatment with a strong base; subsequent dehydration leads to the 1(2H)-isoquinolones **20** (yields 33-82%).

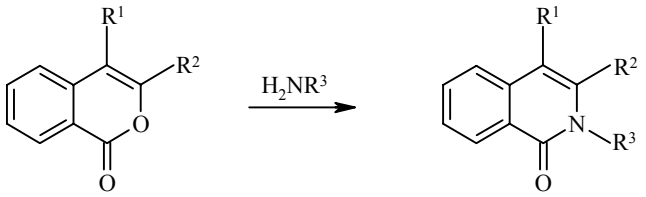


In reaction with α-amino nitriles the halogenophthalides form substituted 3-carbamoyl-1(2H)-isoquinolones **20** [50]:



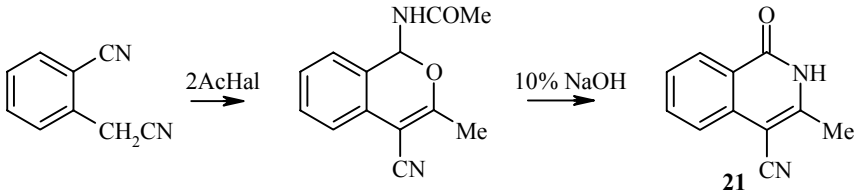
R^1 = Me, *i*-Pr, Bu, $PhCH_2$; R^2 = H, Cl; Ar = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-BrC_6H_4

Derivatives of coumarin and isocoumarin [51], including those annellated at positions 3,4 [53], react with ammonia and amines like the phthalides:

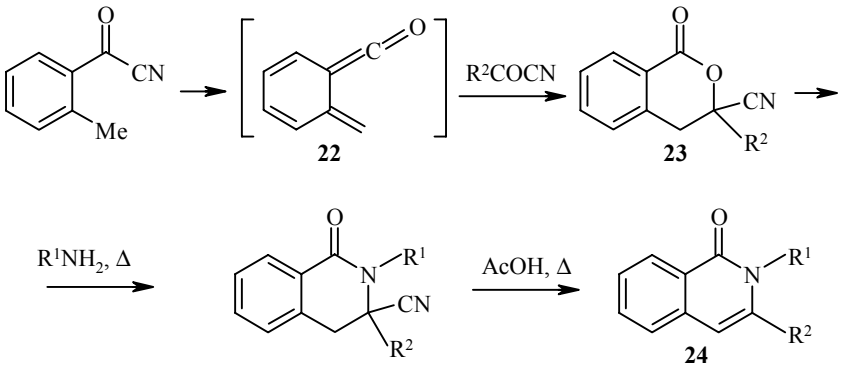


The indicated approach was used in the synthesis of (±)-licoricidine [37, 53], the enantiomer of narciclasine [54], (+)-deoxypancratistatin [55], and also the benzophenanthridine alkaloid nitidine [56].

The acetylation of α-cyano-*o*-tolunitrile followed by treatment with sodium hydroxide led to 4-cyano-3-methyl-1(2H)-isoquinolone (**21**) (yield 92%) [57].



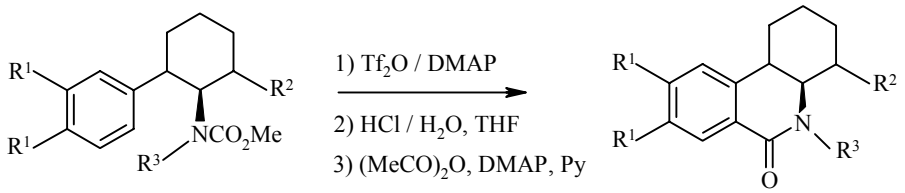
The [4+2]-cycloaddition of the ketene **22** to cyano ketones gave 3-cyanoisocoumarins **23**, which were converted by reaction with amines into the isoquinolones **24** with yields of 60-80% at the last stage [58].



R^1 = Bu, $PhCH_2$; R^2 = Me, Ph

2. Formation of $C_{(1)}$–$C_{(8a)}$ Bond

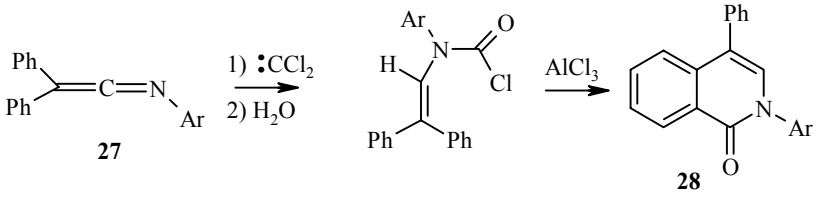
The group of reactions with the formation of a $C_{(1)}$–$C_{(8a)}$ bond is historically close to the classical methods for the synthesis of the isoquinoline nucleus, i.e., the Bischler–Napieralski and Pictet–Spengler reactions [59]. Thus, it was shown during the cyclization of the carbamates **25** in the synthesis of derivatives of licorane and licoricidine [60, 61] that as well as the traditional reagents of the $POCl_3$, $P_2O_5/POCl_3$ [62], or $P_2O_5/MeSO_3H$ [63] type it is possible to use the milder condensing agent Tf_2O/4-dimethylaminopyridine (DMAP) in methylene chloride [64-66] followed by hydrolysis to the 1(2H)-isoquinolones **26**.



(R)-**25** (R)-**26**

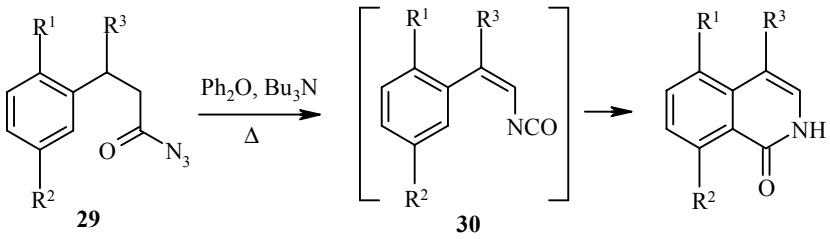
R^1 = H, MeO; R^2 = R^3 = H, $R^2 + R^3 = (CH_2)_3$

Acylation of the aromatic ring with the formation of the 1(2H)-isoquinolones **27** was observed in the reaction of the ketene imine **28** with dichlorocarbene [67]:



27 **28**

The previously developed thermal cyclization of the azides **29** [68] remains in use to this day, but the yields depend on the substituents in the aromatic ring [31].

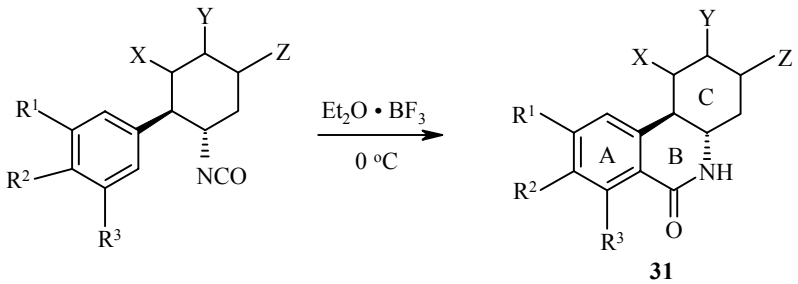


29 **30**

R^1 = Me, R^2 = R^3 = H, yield 61% [69-71];
R^1 = R^2 = OMe, R^3 = Me, yield 10% [72]

This method is only effective for the azides of α,β-unsaturated acids; substituted 3,4-dihydro-1(2H)-isoquinolones cannot be synthesized by this method. Benzo[*h*]-1(2H)-isoquinolones are obtained in a similar way [73]. The intermediate isocyanates [30] can be generated photochemically [74].

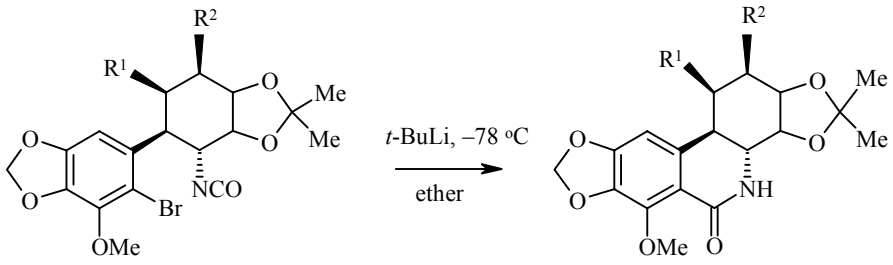
Phenanthridines of the **31** type were synthesized successfully by the cyclization of the isocyanates in the presence of boron trifluoride etherate [75]. The yields amount to 98% but depend on the presence and position of the double bond in ring C. None of the previously described methods for the cyclization of carbamates (e.g., [64]) is suitable for the production of compounds **31** with acceptable yields.



31

X, Y, Z = H, or X = H, Y + Z = bond, or X + Y = bond, Z = H

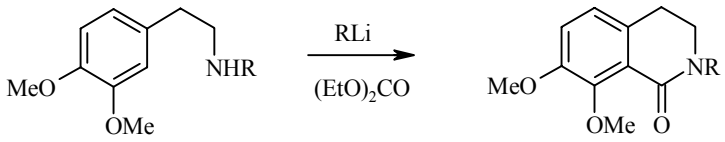
The unique "carbanion" variant of the Bischler–Napieralski reaction was carried out by Trost in the synthesis of (+)-pancratistatin, the yield of which amounted to 65% [31]:



The success of this reaction is explained by the fact that halogen–metal exchange takes place more quickly than the reaction of *t*-butyllithium with isocyanate.

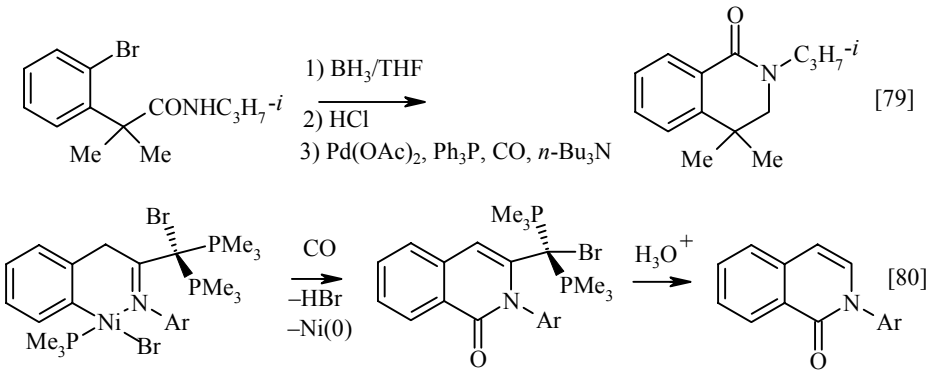
3. Formation of $C_{(1)}$–$C_{(8a)}$ and $C_{(1)}$–$N_{(2)}$ Bonds

During lithiation by the method of Simig [76, 77] the $C_{(1)}$–$C_{(8a)}$ and $C_{(1)}$–$N_{(2)}$ bonds are formed simultaneously. This reaction is widely used in the synthesis of 1(2H)-isoquinolones, e.g., [78]:



R = H, Et

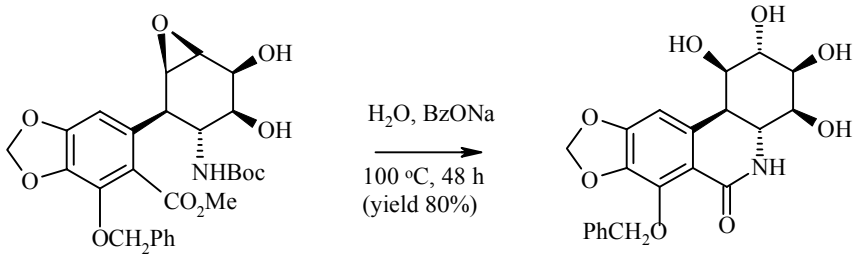
Notable examples of carbonylation with complexes of Pd(II) and Ni(II) were published simultaneously in 1993 by two groups of investigators:



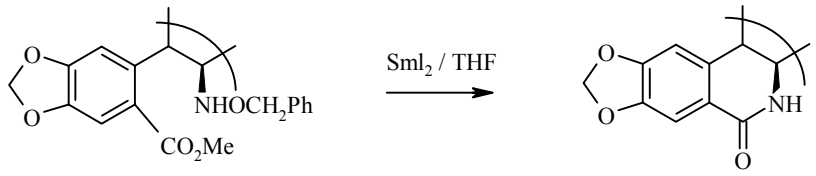
Ar = 2,6-$Me_2C_6H_3$

4. Formation of $C_{(1)}$–$N_{(2)}$ Bond

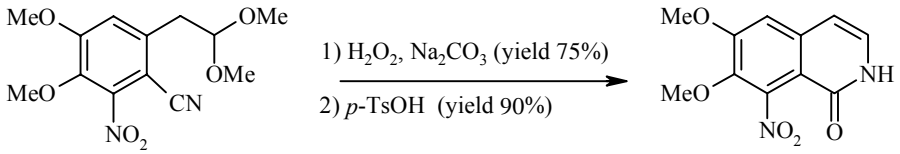
An interesting example of the formation of a $C_{(1)}$–$N_{(2)}$ bond in the synthesis of (+)-pancratistatin was presented in [81]; under comparatively mild conditions an amide bond is formed together with cleavage of an epoxide ring:



In another case such a bond is formed in the reduction of substituted hydroxylamine with SmI_2 [82]:



Hydrolysis of the nitrile **32** followed by cyclization gave the intermediate 1(2H)-isoquinolone in the synthesis of aaptamine [83]:



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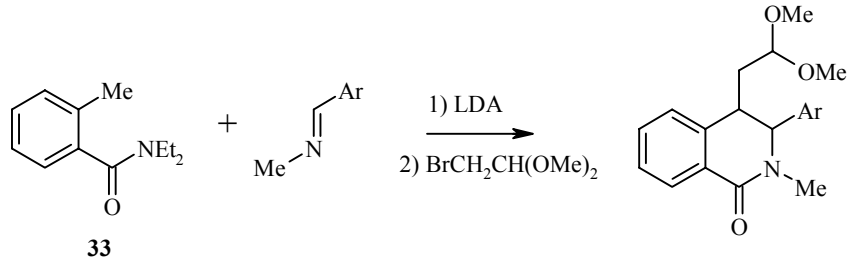
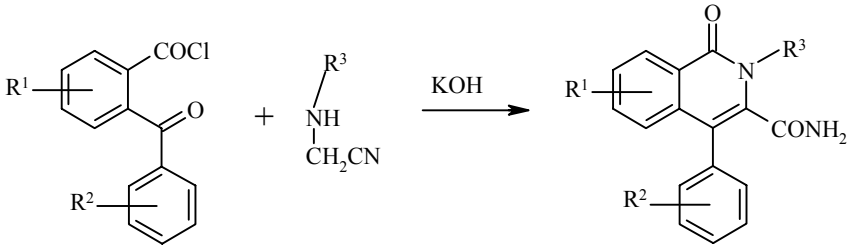
5. Formation of $C_{(1)}$–$N_{(2)}$ and $C_{(3)}$–$C_{(4)}$ Bonds

The synthesis of the benzo[*c*]phenanthridine alkaloid hydroxynitidine was achieved in [84]. One of the stages was the condensation of the lithiated *o*-toluamide **33** with a Schiff base, accompanied by the formation of $C_{(1)}$–$N_{(2)}$ and $C_{(3)}$–$C_{(4)}$ bonds.



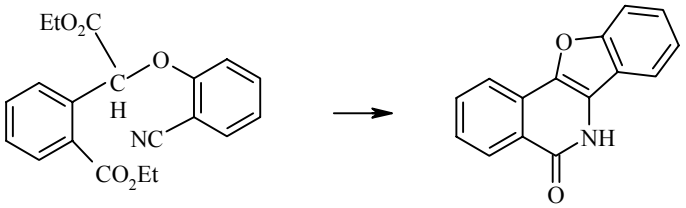
33

The latter are also formed during the production of 4-aryl-3-carbamoyl-1(2H)-isoquinolones **34** [85]:



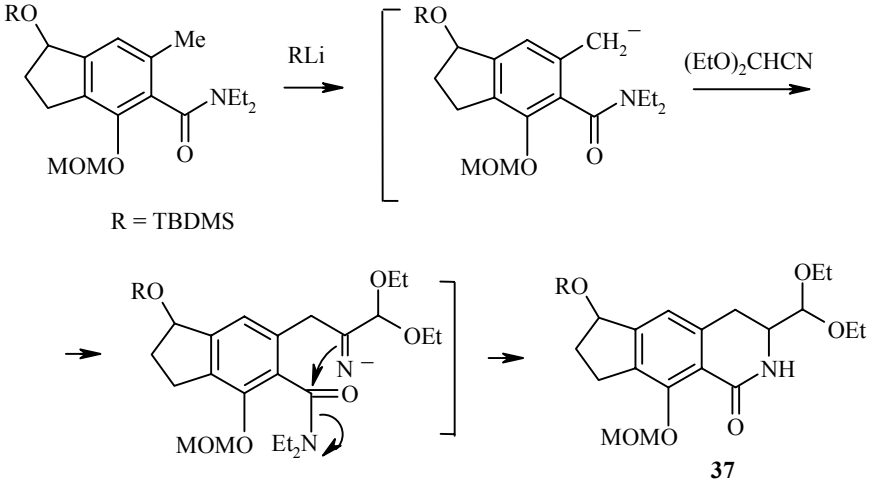
34

When boiled with sodium hydride in toluene (20 h) the cyano ester **35** gives the benzofuro[3,2-*c*]-isoquinolone **36** [86]:



35 **36**

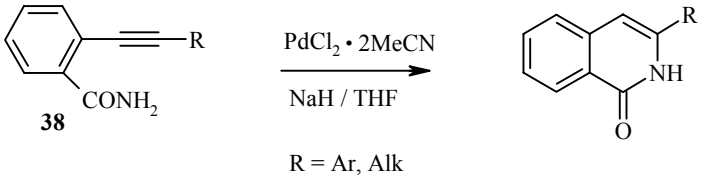
As already mentioned [31, 76-78, 84], lithiation reactions are widely used for the production of 1(2H)-isoquinolones, and various authors have used different approaches. As example it is possible to cite the synthesis of the isoquinolone fragment **37** of the antibiotic (±)-fredericamycin [87].



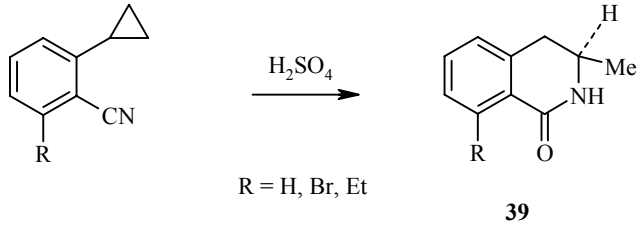
37

6. Formation of $N_{(2)}$–$C_{(3)}$ Bond

Cyclization with the formation of a $N_{(2)}$–$C_{(3)}$ bond is rarely encountered. One example is intramolecular cyclization of the amides **38**, catalyzed by the $PdCl_2 \cdot 2CH_3CN$ complex (yields 57-66%) [88]:



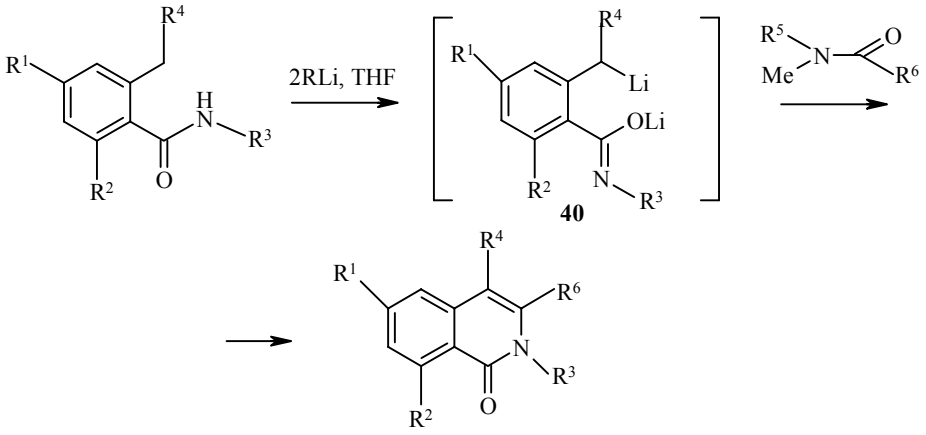
An original method for the production of the quinolones **39** (as mixtures of enantiomers) is also known [89]:



39

7. Formation of $N_{(2)}$–$C_{(3)}$ and $C_{(3)}$–$C_{(4)}$ Bonds

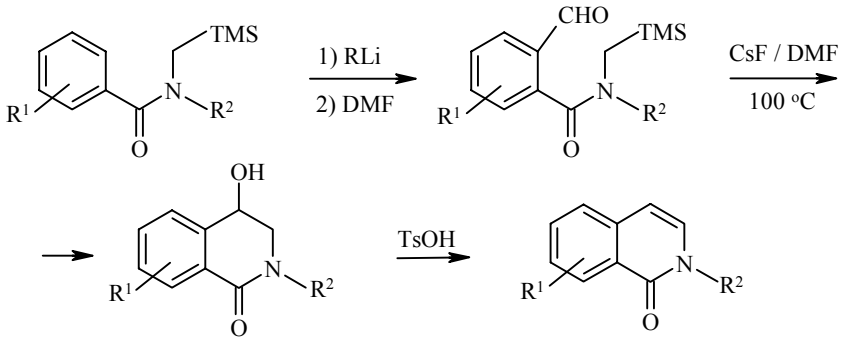
Metallation proved particularly fruitful for cyclization with the formation of $N_{(2)}$–$C_{(3)}$ and $C_{(3)}$–$C_{(4)}$ bonds. On the basis of work on the *o*-lithiation of benzamides [90, 91] preparative methods were developed for the production of various isoquinolines and 1(2H)-isoquinolones. In general the methodology of lithiation can be representation by the following scheme:



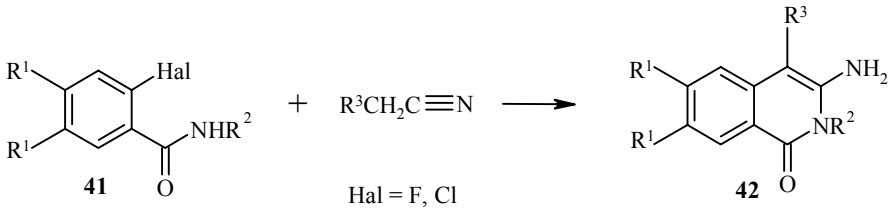
R^1 = H, Cl, OMe; R^2 = H, Alk; R^3 = 2-methylallyl [92], Me [93], MeO [94], EtOC(O)NH [95]; R^4 = H, Ph; R^5 = H, Me; R^6 = H, Bu, Ar, $Cl(CH_2)_3$

As seen from the scheme, two equivalents of the organolithium compound *n*-BuLi, *s*-BuLi, (*i*-Pr)$_2$NLi are used at the first stage; the intermediate **40** is then condensed with DMF [92, 93], the N-methoxy-N-methylamides of ω-chlorine-substituted carboxylic acids [94], or the methyl esters of substituted benzoic acids [95].

A somewhat different method was used in [96]. An electrophilic aldehyde group was introduced by *o*-lithiation of substituted benzene, while the nucleophile in latent form was already present in the molecule:

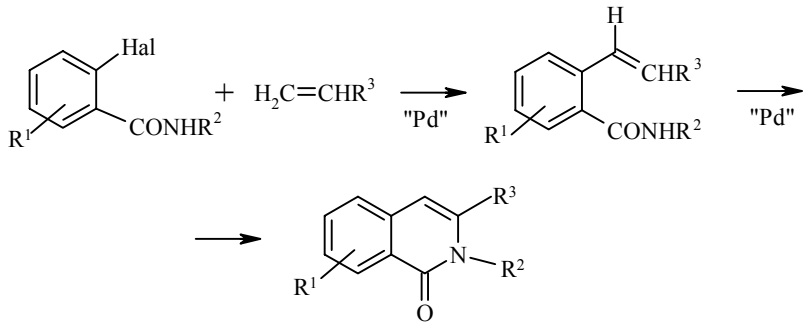


3-Amino-1(2H)-isoquinolones **42** were obtained by the condensation of *o*-halogenobenzamides **41** with substituted nitriles [97-100]:



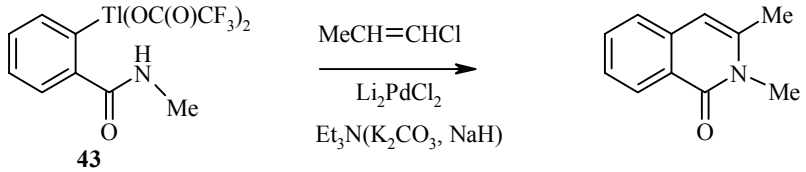
8. Formation of $N_{(2)}$–$C_{(3)}$ and $C_{(3)}$–$C_{(4)}$ Bonds

In this section three groups of methods must be mentioned. First, there is metal-complex catalysis by palladium compounds [101, 102], which takes place according to the following scheme:

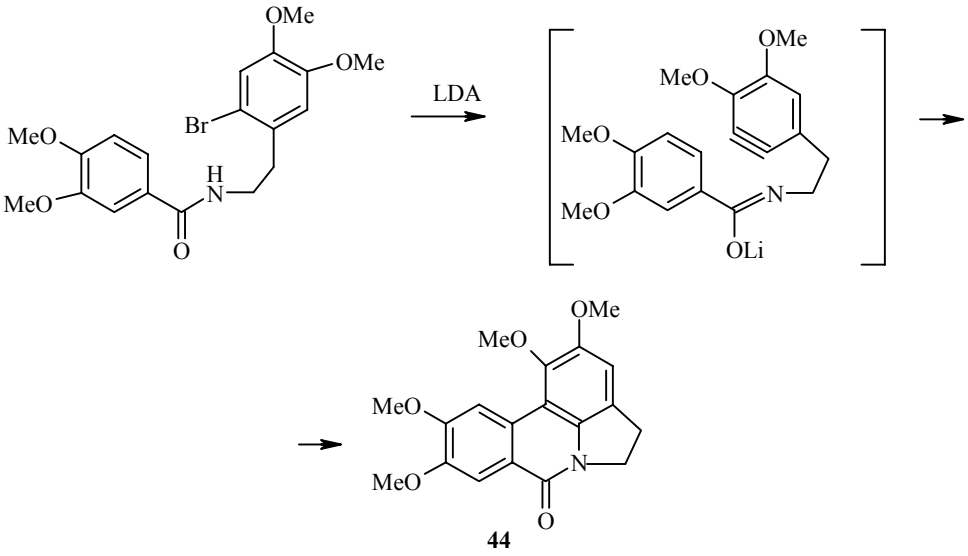


R^1 = H, Me, MeO; R^2 = H, Alk; R^3 = H, MeOCO; Hal = Br, I

The catalysts are $PdCl_2/CuCl_2$ and $Pd(Ph_3P)_2Cl_2/Et_3N$ in DMF etc. In some cases the formation of 1,2,3,4-tetrahydro derivatives is possible [102]. The palladium-catalyzed condensation of the thalliation product **43**, leading to 2,3-dimethyl-1(2H)-isoquinolone, is known [103]:

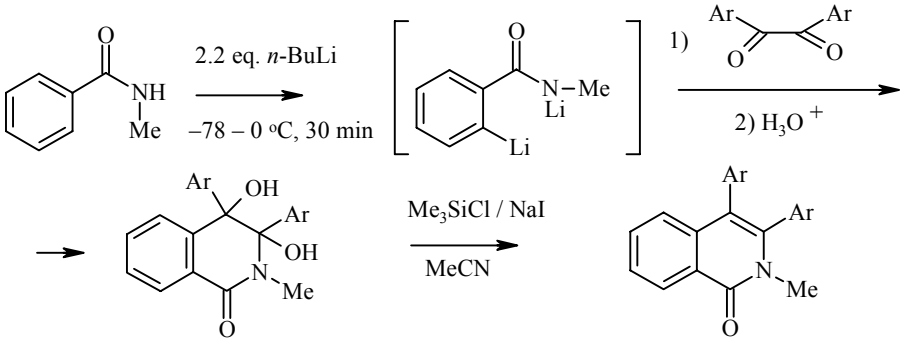


Second, there are syntheses through dehydrobenzene [104, 105]. An alkaloid **44** of the *Amaryllidaceae* family was obtained in this way:



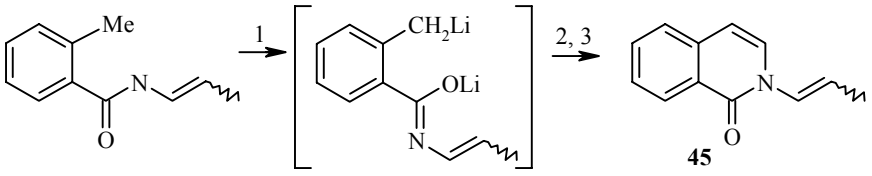
44

Finally, there is the metallation of benzamides (yields of final products 60-80%) [106]:



9. Formation of $C_{(3)}$–$C_{(4)}$ Bond

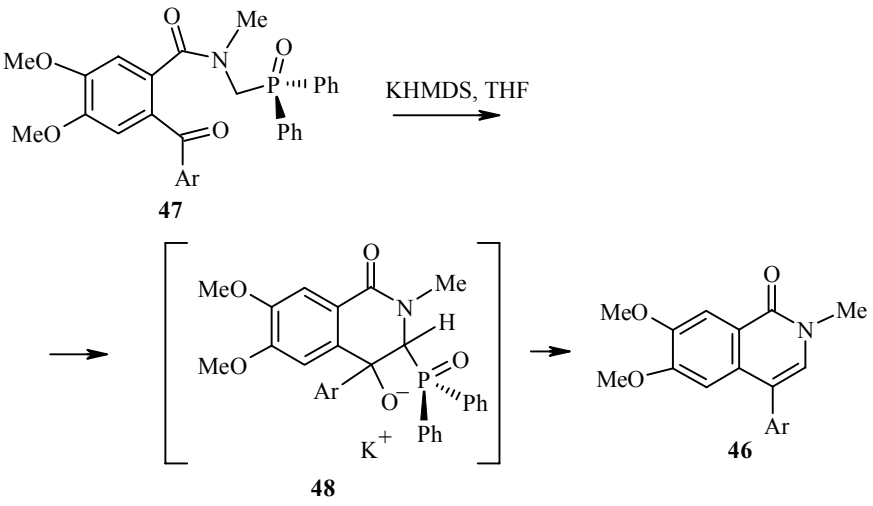
In this section it is necessary to mention the double metallation of an amide with the formation of compound **45** [107]:



45

1: 2.2 eq. *s*-BuLi, -70° C, THF; 2: excess DMF; 3: 1 M HCl

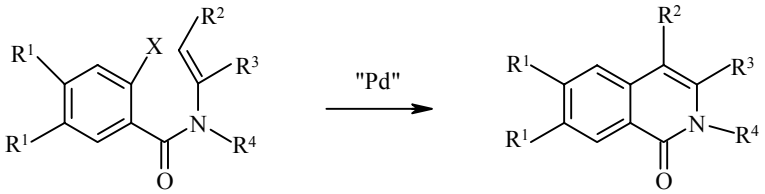
An original method for the production of 1(2H)-isoquinolones of type **46** from phosphorylated carboxamides **47** was developed in a series of papers [108-110]. The reaction takes place through the intermediate adducts **48**:



This method was used in the synthesis of the alkaloids (±)-cherylline and (±)-latifine [111].

10. Formation of $C_{(4)}$–$C_{(4a)}$ Bonds

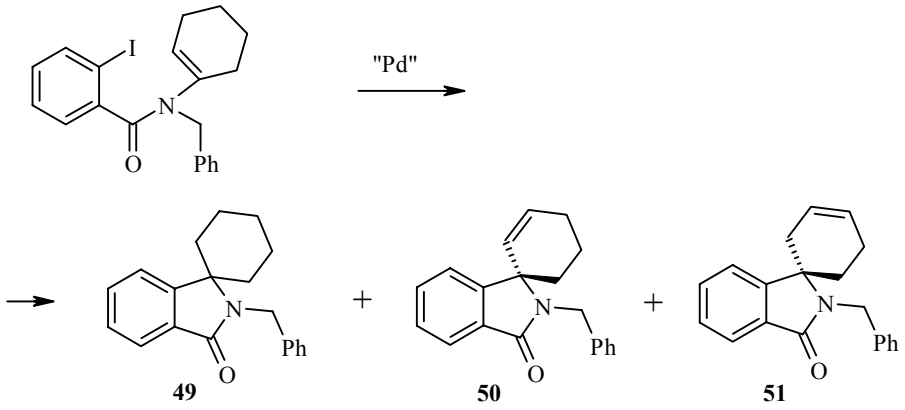
An approach based on an intramolecular Heck reaction proved particularly useful for the formation of the $C_{(4)}$–$C_{(4a)}$ bond. The scheme of transformations in general form is as follows:



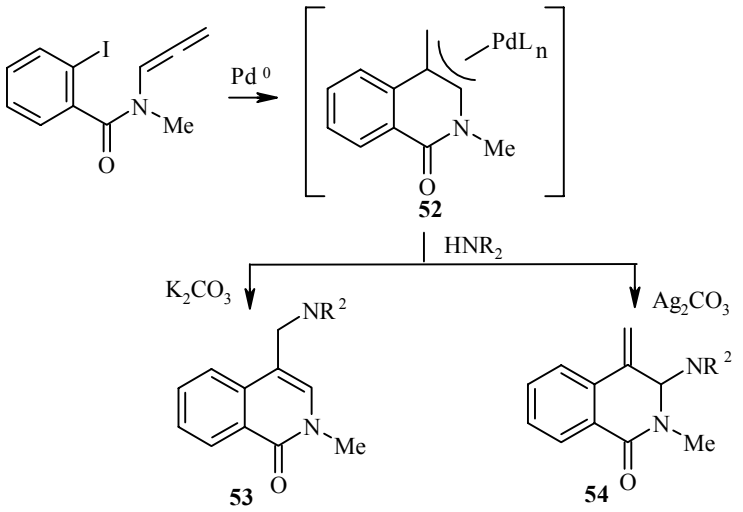
R^1 = H, Hal, MeO; X = Br, I; R^2 = R^3 = Alk, R^2+R^3 = $(CH_2)_4$; R^4 = Me, $PhCH_2$

The method was used successfully in the synthesis of (+)-licoricidine [26-30], where the catalyst was $Pd(OAc)_2$ (up to 20 mole %), the complexing agents were various bisphosphines (up to 40 mole %), and the necessary base in all cases was up to two equivalents of TlOAc, the role of which was to prevent isomerization of the alkene [112]. The nature of the counterion (Tl^+, Ag^+, $Bu4N^+$), like the nature of the base, is important for attaining the optimum yields [30].

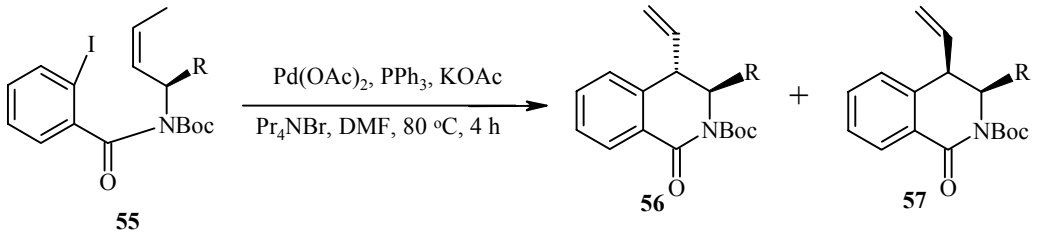
With two different olefinic substituents at the nitrogen atom the reaction takes place at the most sterically accessible of them [113]; a side reaction in the absence of TlOAc is the formation of the isoindolones **49-51** [112, 113]:



In the case of allene substituents at the nitrogen atom during catalysis by the $Pd(OAc)_2/PPh_3$ system in acetonitrile (80°C) two different products are formed, depending on the chosen base [114]; this is explained by the fact that in the case of the use of silver carbonate as base the transitional complex (**52**) has carbocationic character, and stabilization by the amine takes place at the most electrophilic carbon atom of the allylic system, adjacent to the nitrogen atom (yield of product **53** 91% after 28 h; yield of product **54** 77% after 6 h).



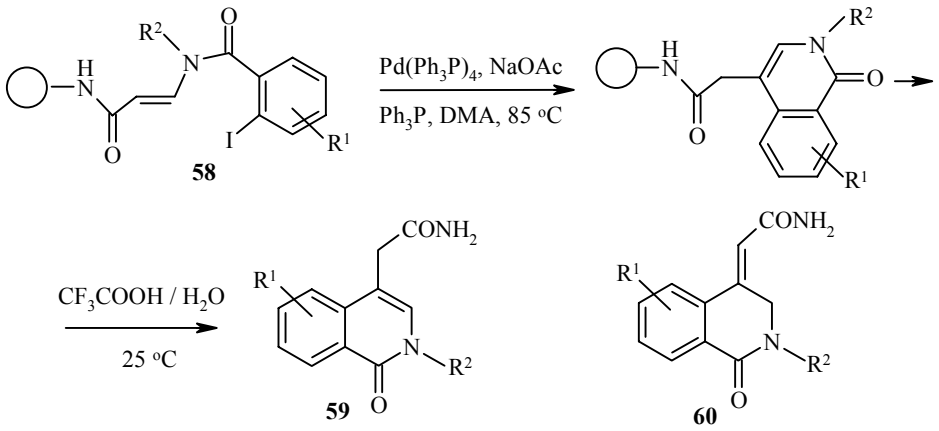
The intermediate palladium complexes can be isolated [115]. Although the Heck reaction usually has certain limitations in regio- and stereoselectivity, due to the β-elimination of the palladium compound and hydride ion at the last stage of the process, the reaction with the enantiomerically pure amides **55** takes place with a considerable degree of regioselectivity and is practically stereoselective (**56**/**57** ratio 12-20/1, total product yield 65-82%) [116]:



R = Me, Et, *i*-Pr, $PhCH_2$

Since the degree of stereoselectivity increases with increase in the size of the substituent, the authors conclude that the success of the synthesis is brought about by the presence of the substituent at the α-carbon atom of the stereogenic center. An important role is played by the optimum choice of base and complexing agent. Thus, replacement of Ph_3P by $(o\text{-}MeC_6H_4)_3P$ leads to a marked decrease in regioselectivity and to the formation of a large amount of 4-ethylidene derivatives.

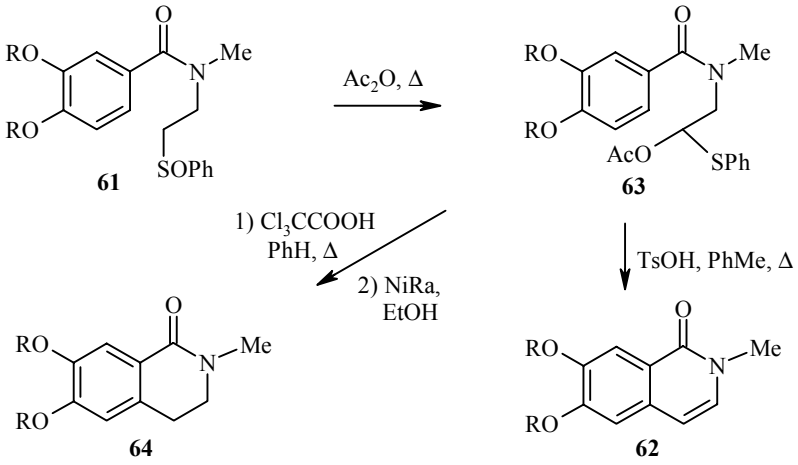
A solid-phase synthesis of "libraries" of 2-substituted 4-carbamoylmethyl-1(2H)-isoquinolones based on the Heck reaction of the amides **58** combined with a polymer has been described [117]. The products **59** with an endocyclic double bond are mostly formed, although in the presence of a substituent at position 5 mixtures of compounds **59** and **60** are obtained.



R^1 = H, 5-Me, 7-Cl, 8-F, 6,7-$(MeO)_2$; R^2 = *i*-Bu, Ph, $PhCH_2CH_2$

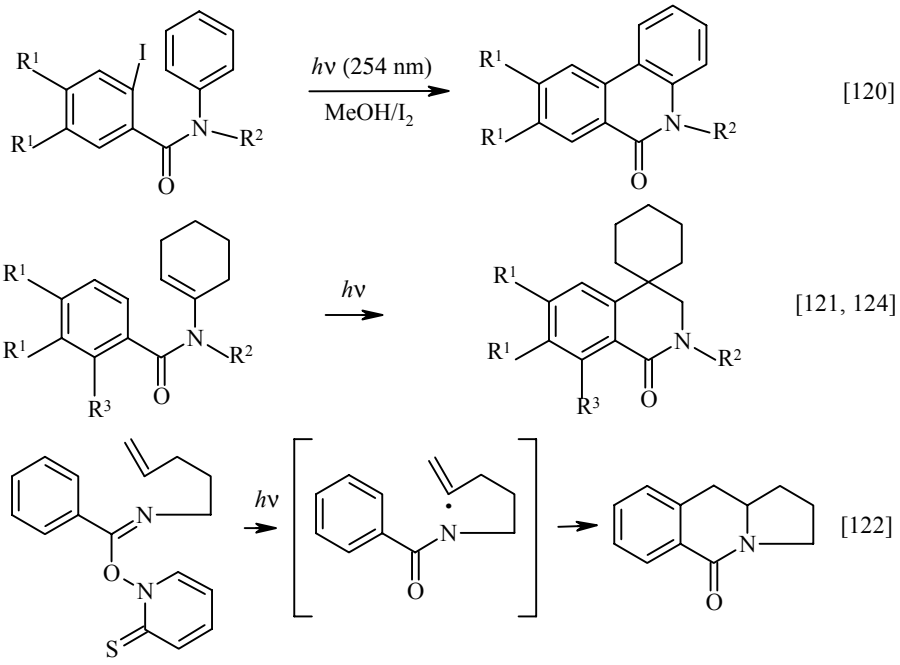
In one case radical cyclization with AIBN/Bu_3SnH in boiling benzene was used for the formation of the (+)-1-deoxylicorine system [118].

An original method was based on the Pummerer rearrangement of sulfoxides **61** [119]. The isoquinolones **62** are formed with 75-93% yields during the cyclization of the acetoxy sulfide **63** in toluene by the action of TsOH, whereas the production of the 3,4-dihydro derivatives **64** requires milder conditions – cyclization by the action of trichloroacetic acid in benzene followed by desulfurization with Raney nickel in ethanol.



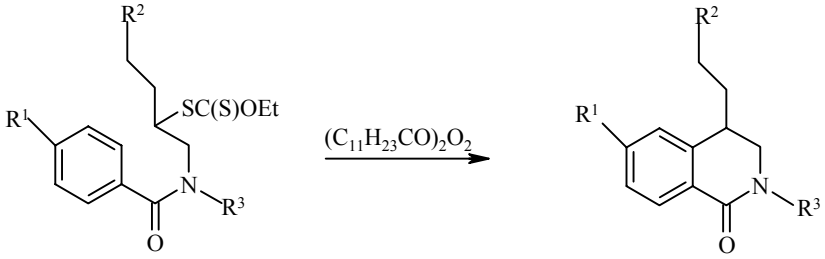
R = Me; R + R = CH_2

The second large group of reactions used for the creation of a $C_{(4)}$–$C_{(4a)}$ bond is photochemical cyclization [120-125]. Some examples are given below:



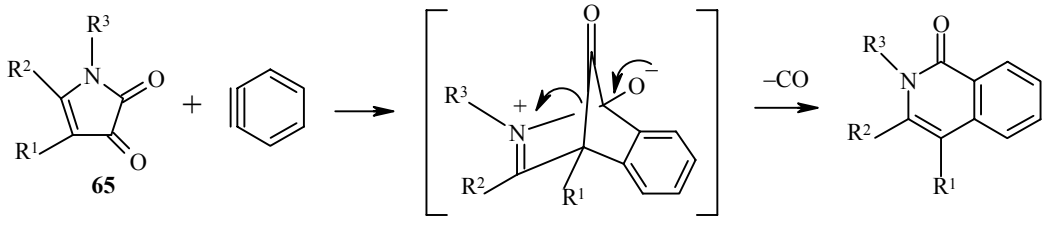
The reactions are promoted by electron-donating substituents R^1, R^2, and R^3.

Intramolecular radical cyclization of xanthates by the action of lauryl peroxide leads to derivatives of 1(2H)-isoquinolone [126]:



R^1 = H, MeO, Br, F; R^2 = CN, Acyl; R^3 = Me, Et, MeOCO

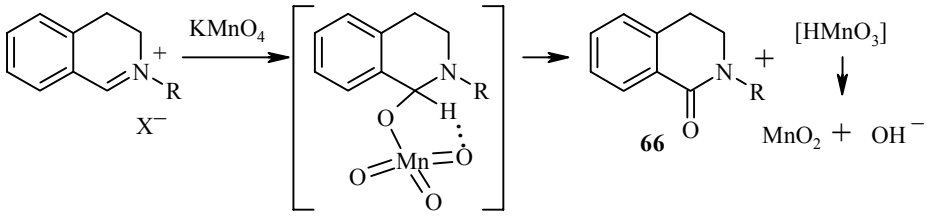
The synthesis of 1(2H)-isoquinolones from pyrrolidinediones **65** and dehydrobenzene with the simultaneous formation of $C_{(4)}$–$C_{(4a)}$ and $C_{(1)}$–$C_{(8a)}$ bonds has been described [127]:



R^1 = H, Cl, Ph; R^2 = Ph; R^3 = Alk

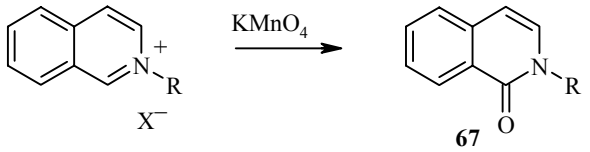
11. Oxidation at the $C_{(1)}$ Atom

Various oxidizing agents have been used to convert derivatives of isoquinoline into isocarbostyrils: $KMnO_4$ [128], $K_3Fe(CN)_6$ and $RuO_2 \cdot H_2O$ [129, 130], bromosuccinimide and CrO_3 [131], *m*-chloroperbenzoic acid [132], $Pb(OAc)_4$ [133], and atmospheric oxygen [134]. The formation of 1(2H)-isoquinolones **66** during the oxidation of 3,4-dihydroisoquinolones, 2-alkyl(acyl)-1(2H)-3,4-dihydroisoquinolones, and 1- and 2-alkyl-1(2H)-isoquinolines by potassium permanganate was studied in [128]:



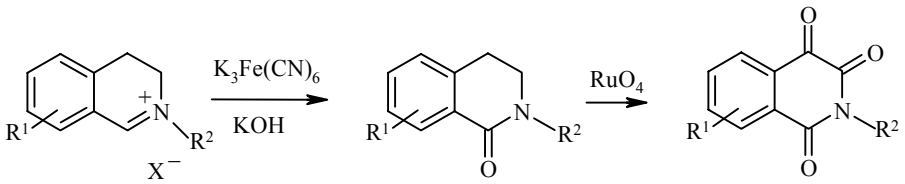
X = Cl, I; R = Me, Et, $PhCH_2$, acyl

Isoquinolinium salts are oxidized in a similarly way, but their N-acyl derivatives are completely unstable to hydrolysis in an aqueous medium, and the substituted isocarbostyrils **67** are therefore isolated:

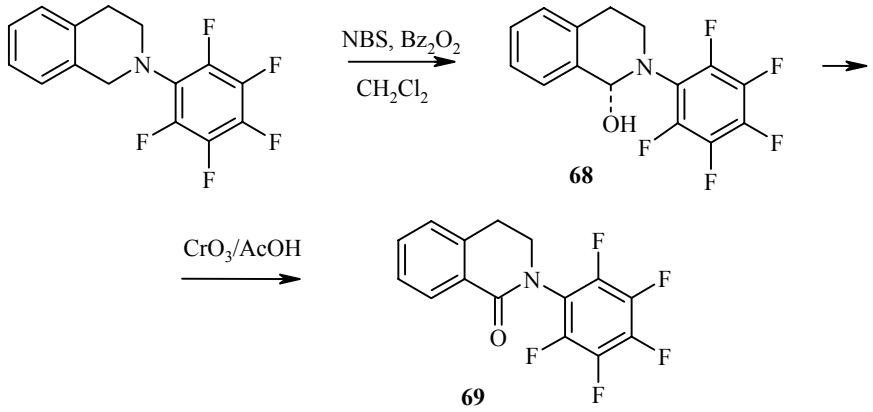


The oxidation was conducted in acetone or acetonitrile, but better yields were obtained with the addition of 18-crown-6 in methylene chloride. N-Substituted 1,2,3,4-tetrahydroisoquinolines are also converted under the reaction conditions into 1(2H)-isoquinolones through a stage involving oxidation to the 3,4-dihydro derivatives. With R = acyl the isoquinolones **66** and particularly compounds **67** are unstable to hydrolysis and are converted into unsubstituted isocarbostyril.

The oxidation of a N-alkylisoquinolinium salt to 1(2H)-isoquinolones was realized with $K_3Fe(CN)_6$ in an alkaline solution; further oxidation with ruthenium tetroxide leads to 1,3,4-triketo-1,2,3,4-tetrahydroisoquinolines [130]:

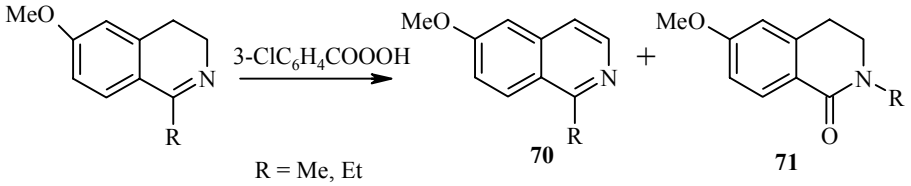


N-Pentafluorophenyl-1,2,3,4-tetrahydroisoquinoline reacts with bromosuccinimide in methylene chloride in the presence of benzoyl peroxide with the formation of a mixture of products, in which the 1-hydroxy derivative **68** predominates; treatment of the mixture with CrO_3 in acetic acid leads to the isoquinolone **69** with a yield of 91% [131]:

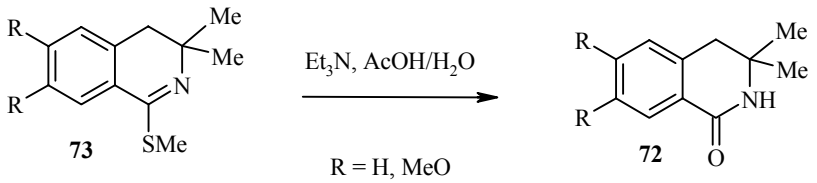


It is interesting that N-(tetrafluoro-4-pyridyl)-1,2,3,4-tetrahydroisoquinoline, like the nitrophenyl derivatives, undergoes ring opening under the same conditions [132].

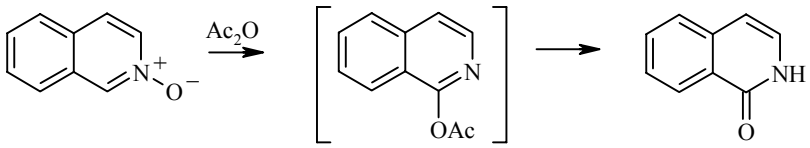
During the oxidation of 3,4-dihydroisoquinolines with *m*-chloroperbenzoic acid isocarbostyrils **71** are formed with yields of 14-15% in addition to the isoquinolines **70** (yields 61-65%) [135]:



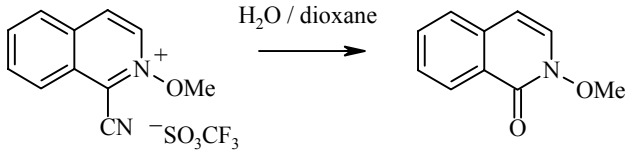
The authors of the present review developed a preparative method for the production of 3,3-dialkyl-3,4-dihydro-1(2H)-isoquinolones **72** (yields 71-80%) by the hydrolysis of methyl sulfides **73** in acetic acid in the presence of a tertiary amine [136]:



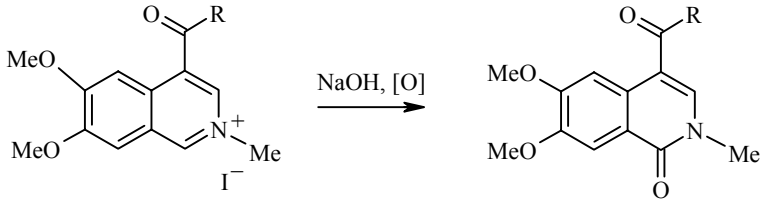
The addition of sodium acetate to the reaction mixture accelerates the reaction. Hydrolysis probably takes place through the corresponding 1-acetoxy derivative, as in the previously described transformation of isoquinolinium N-oxide [137]:



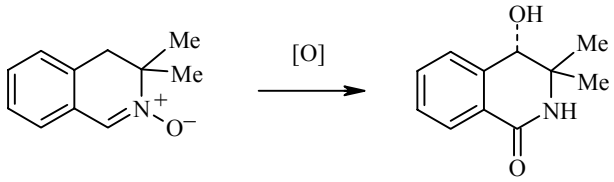
Substituted 1-(2H)-isoquinolones are often formed during the hydrolysis of isoquinolinium salts, for example [138]:



The methiodides of substituted isoquinolinium salts undergo oxidative hydrolysis in air [139]:

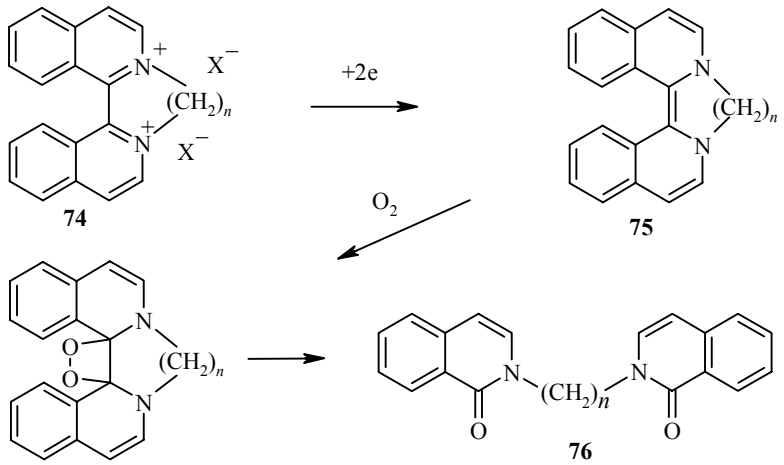


1(2H)-isoquinolone metabolites are formed *in vitro* during the oxidation of cyclic nitrones – free-radical traps [140]:



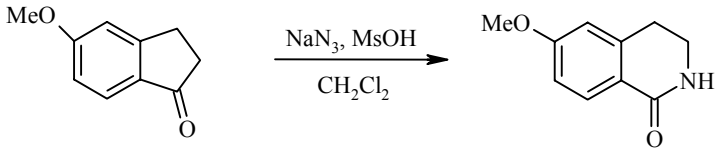
The oxidation of 2-acyl-1-carboxy-1,2,3,4-tetrahydroisoquinolines by atmospheric oxygen in the presence of dicyclohexylcarbodiimide leads to 2-acyl-1(2H)-isoquinolones with yields of 80-99% [141].

The chemiluminescence of bisisoquinolinium salts **74**, discovered in 1967 [142], was studied in detail in [134]. This oxidation–reduction process takes place in protic solvents in the presence of alkali; the electron-rich diisoquinolyl **75** is formed at the first stage and is then oxidized by atmospheric oxygen to the corresponding bisisoquinolone **76**:

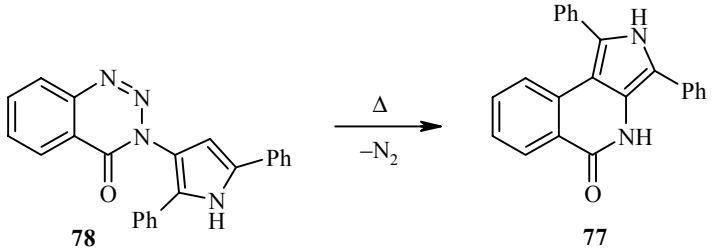


12. Other Examples of the Synthesis of Derivatives of 1(2H)-Isoquinolones

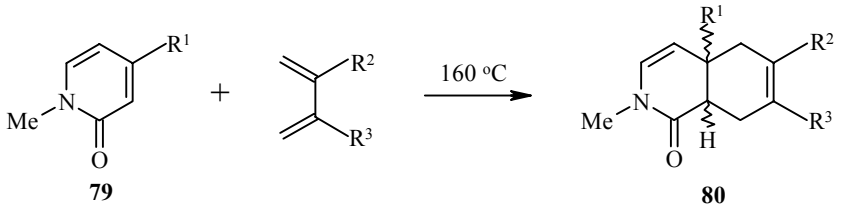
A method for the production of 7-methoxy-3,4-dihydro-1(2H)-isoquinolone based on the Schmidt reaction has been published [143]:



Pyrrolo[3,4-*c*]isoquinolinones **77** are formed as a result of the thermal rearrangement of compounds **78** [144]:



The pyridones **79**, which act as dienophiles, form the partially hydrogenated 1(2H)-isoquinolones **80** [145]:



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