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NUCLEOPHILIC AROMATIC SUBSTITUTION OF HYDROGEN AS A TOOL FOR THE SYNTHESIS OF INDOLE AND QUINOLINE DERIVATIVES[#]

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[#]*This paper is dedicated to Professor Sho Ito on the occasion of his 77th birthday.*

Abstract - Indole and quinoline belong to the most important heterocyclic systems. Although there are numerous methods of syntheses of these heterocycles, new processes leading to these systems have still attracted considerable attention. Nucleophilic Aromatic Substitution of Hydrogen in nitroarenes and other electrophilic arenes opens new rich possibilities for synthesis of indole and quinoline derivatives. In this review a variety of methods for synthesis of these heterocycles based on the initial nucleophilic substitution of hydrogen are discussed.

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6. REFERENCES AND NOTES

1. INTRODUCTION

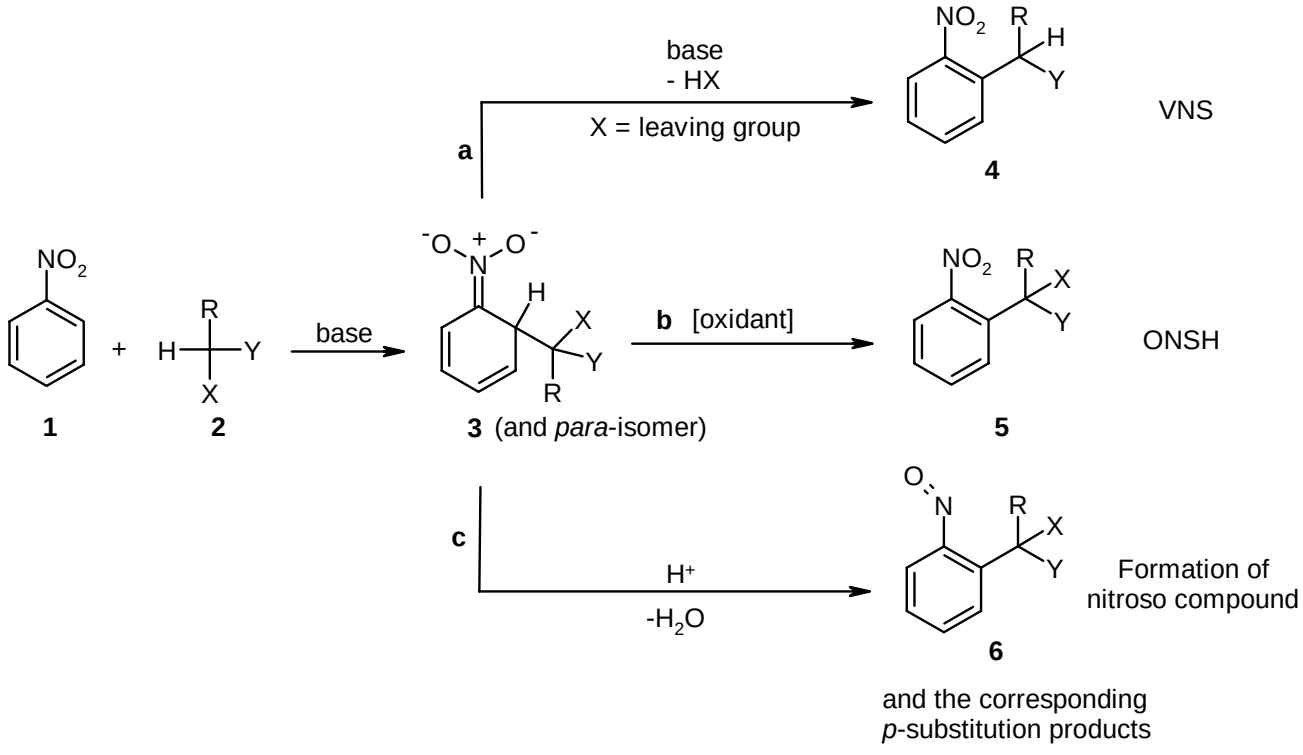
Due to electron-withdrawing effect the nitro group in nitroarene activates positions *ortho* and *para* for addition of nucleophilic agents.[1-4] Thus, the first step in reactions of nitroarenes with nucleophiles is the formation of σ-adducts in these positions. The well-known process of nucleophilic aromatic substitution (S_NAr) of halogen X located in the *ortho* and/or *para* positions to the nitro group in nitroarenes proceeds *via* the formation of the corresponding σ^X-adducts. However, addition of nucleophiles to these positions occupied with hydrogen, leading to the formation of σ^H-adducts (**3**), is usually a faster reaction. These σ^H-adducts can be transformed into final products of nucleophilic substitution of hydrogen *via* a variety of ways.[4,5] The most important of these ways for carbon nucleophiles are shown in Scheme 1:

a - vicarious nucleophilic substituton of hydrogen (VNS): addition of the nucleophile containing a leaving group X, followed by base-induced β-elimination of HX from the σ^H-adduct

b - oxidation of the σ^H-adducts with external oxidants;

c - protonation of the nitronate oxygen followed by elimination of water leading to the formation of nitrosoarene.

Scheme 1



1.1. Vicarious Nucleophilic Substitution of Hydrogen (VNS)

Of the ways shown in Scheme 1, VNS of hydrogen[6-9] seems to be the most general and practically important reaction. The process is of general character with respect to the both components: nucleophiles and nitroarenes. Practically any carbanion $RXYC^-$ (**2**$^-$) containing a leaving group X such as halogens, alkoxy, aryloxy, arylthio at the carbanionic center, which can be eliminated as HX from the σ^H-adducts (**3**), can undergo the VNS reaction. There are practically no limitations concerning other substituents R and Y. It is desirable for Y to stabilize carbanions moderately, as in the case of arenesulfonyl, alkoxycarbonyl or cyano group, so the formation of the carbanions is facilitated, while they show sufficient nucleophilicity. Examples of such carbanion precursors are $ClCH_2SO_2Ph$,[10-15] $ClCH_2CO_2R$,[16,17] Cl_2CHCO_2R,[18] $ArOCH_2CN$,[19-21] $CHCl_3$,[22] $CH_2(SPh)_2$,[23] *etc*. The process has also a wide scope concerning nitroarenes; practically any nitrobenzene derivative containing at least one hydrogen in the *ortho*- or *para*-position with respect to the nitro group can undergo the VNS reaction. Usually the VNS proceeds faster than the conventional S_NAr of halogen located at similarly activated positions.[5,24,25] Since the products of the VNS reaction are formed and remain in the reaction mixture as nitrobenzylic carbanions, they cannot behave as electrophilic species towards the carbanions and, consequently, the reaction proceeds selectively to give the *mono*-substituted product. As expected, substituents in the aromatic rings affect the reaction course, i.e. its rate and orientation, and in some cases can inhibit the reaction totally.

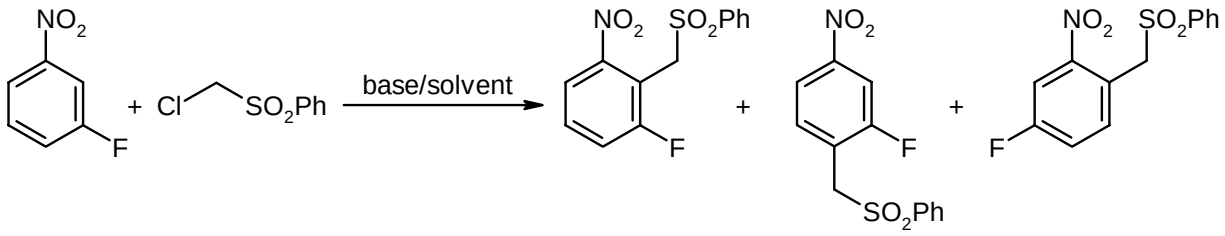
The reaction is not limited to nitrobenzene derivatives. Nitronaphthalenes,[15] nitro[10]annulenes[26,27] and a wide range of nitro derivatives of aromatic heterocycles such as furan,[28,29] thiophene,[28,29] pyrrole,[28,29] pyrazole,[30] imidazole,[22,31,32] thiazole,[33] pyridine,[11,34] indole,[35,36] benzoxazole,[37] quinoline,[38] benzofuroxan[39,40] also undergo VNS reactions, usually in excellent yields. The VNS proceeds also in pyridine,[41] pyridazine,[42] and 1,2,3-triazine[43,44] rings activated *via* conversion into dicyanomethylene ylides. Some nonbenzenoid aromatic carbocycles, such as azulene[45] and tropylium salts,[46] or heterocycles, such as 1,2,4-triazine,[10,47] pteridines,[48] benzoxazole,[10] benzothiazole,[10] naphthyridines,[49] and acridine,[10] which exhibit electrophilic character *per se*, react with carbanions bearing leaving groups following the VNS pathway, even without additional activation by the nitro group.

Basic mechanistic features of the VNS are at present well clarified.[5,24,25,50] On the basis of numerous qualitative observations, and recent, more exact studies, it was shown that this reaction proceeds *via* the reversible addition of carbanions to nitroarenes and the subsequent irreversible base-induced β-elimination of HX from the formed σ^H-adducts.[24,50] Relation of rates of these two steps depends on kind of educts and the reaction conditions.[24,25] In fact it was shown that the overall rate of process can be determined by the rate of addition or β-elimination, depending on the strength and concentration of

base.[25,50]

In nitroaromatic rings there is usually more than one position (*ortho* and *para*) in which the VNS can take place, thus the orientation of substitution is an important problem. It is governed by three major factors: the structure of the nitroarene, the nature of the nucleophile and the reaction conditions.[25] From many observations we can conclude that the formation of the *ortho* σ^H-adduct occurs faster than the corresponding *para*-isomer, although the latter is usually more thermodynamically stable.[25] The reaction conditions which assure rapid β-elimination, i.e. high concentration of a strong base, favor *ortho*-substitution.[12,51]

Scheme 2



7 **8** **9** **10** **11**

NaOH/DMSO	27%	49%	9%
t-BuOK/THF	84%	0%	6%

In some cases this effect is so strong that just by changing the nature or even the concentration of base it is possible to execute the *ortho*- or *para*-substitution selectively.[52] Usually VNS reactions are performed in dimethyl sulfoxide, dimethylformamide, or liquid ammonia in which carbanions form loose ion-pairs with the counterions. Replacing these solvents with tetrahydrofuran markedly affects the orientation of the VNS due to ion-pairing and chelation of counterion by the nitro group, hence strong tendency for the substitution of hydrogen *ortho* to the nitro group is observed (Scheme 2).[12,19]

Orientation of the VNS reaction is highly sensitive to the electronic effects and steric environment of substituents present in the ring, and is also strongly affected by the size of the nucleophile. Bulky nucleophiles such as tertiary carbanions, tend to react in the *para*-position, although under certain conditions (low temperature) these carbanions can react at the *ortho*-position satisfactorily.[51]

1.2. Oxidative Nucleophilic Substitution of Hydrogen (ONSH)

In spite of numerous reports on ONSH with carbon nucleophiles much less is known about the characteristic features of this reaction. While carbon nucleophiles are usually very sensitive to oxidation, one can afford ONSH with external oxidants when addition giving σ^H-adducts proceeds to the completion and the amount of the free nucleophile in the system is negligible. Very little is known about mechanism

of the oxidation process and selection of the oxidants. Often it is even not clear what is the oxidant: atmospheric oxygen or nitroarene.[53-55] In numerous papers it was reported that the oxidation of σ^H-adducts was accelerated by oxygen.[2,56-58] In some cases it was shown that oxidation of σ^H-adducts of secondary carbanions with oxygen is accelerated by an excess of base, suggesting that actually deprotonated σ^H-adducts are oxidized.[59] More defined are oxidation processes with potassium permanganate,[60-63] bromine in the presence of triethylamine,[64,65] 2,3-dichloro-5,6-dicyanoquinone (DDQ),[60,64,66] cerium ammonium nitrate (CAN),[67,68] and 9-fluorenone.[58] In oxidations of σ^H-adducts with hypochlorites the competing process of chlorodenitration resulting in a replacement of the nitro group with chlorine was observed.[69] Recently discovered oxidation of σ^H-adducts with dimethyldioxirane results in replacement of the nitro group by hydroxy substituent.[70]

ONSH often competes with other processes such as VNS or S_NAr and factors controlling the reaction course are generally not clear.[59]

1.3. Nucleophilic substitutions proceedings according to intramolecular redox stoichiometry resulting in formation of nitrosoarenes

Not much is known about transformations of the σ^H-adducts into nitroso compounds. Carbanions of arylacetonitriles react with nitroarenes in protic media to form nitrosoarenes substituted *para* or *ortho* with the carbanion moiety.[71-74] Since reactivity of the nitroso group is higher than that of the nitro group, the nitrosoarenes are often not isolated but postulated as intermediates in multistep transformations of σ^H-adducts into the final products.[54,75-81] On the basis of known examples one can not recognize which structural features of nucleophiles are necessary for this process. It usually takes place in protic solvents so the supposition that it proceeds *via* protonation - elimination of water appears reasonable.

In this review methods of synthesis of indole and quinoline derivatives involving nucleophilic substitution of hydrogen such as VNS, ONSH and others will be presented, mostly on the basis of research in our group. A preceding short review on the application of VNS to synthesis of heterocyclic compounds was published in 1997.[82]

Nucleophilic substitution of hydrogen can be applied to synthesis of indole and quinoline derivatives in many ways: direct cyclization *via* substitution of hydrogen or single or multistep transformations of the VNS or ONSH products. In two subsequent parts synthesis of indoles and quinolines will be discussed and in the last part examples of synthesis of natural and biologically active compounds using nucleophilic substitution of hydrogen will be presented.

2. SYNTHESIS OF INDOLES

2.1. Direct synthesis of indole ring system from derivatives of *m*-nitroaniline

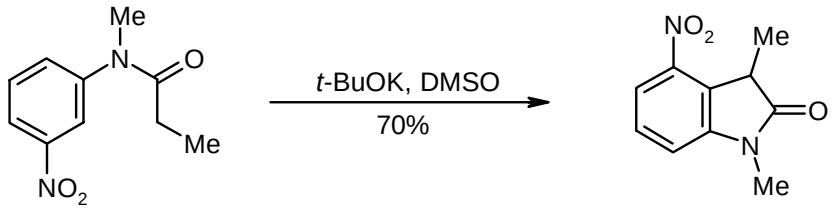
Direct synthesis of the indole ring system can be accomplished by the intramolecular VNS of the *m*-nitro substituted chloroacetanilides (**12**) giving substituted nitrooxindoles (**13**) as exemplified in Scheme 3.[83]

Scheme 3

12 **13**

Oxidative nucleophilic substitution of hydrogen in *m*-nitro-propionanilides (**14**) gives also access to nitrooxindoles (**15**).[84] In both of these reactions the strong preference for substitution of the hydrogen *ortho* to the nitro group was observed giving mainly 4-nitrooxindole derivatives (Scheme 4).

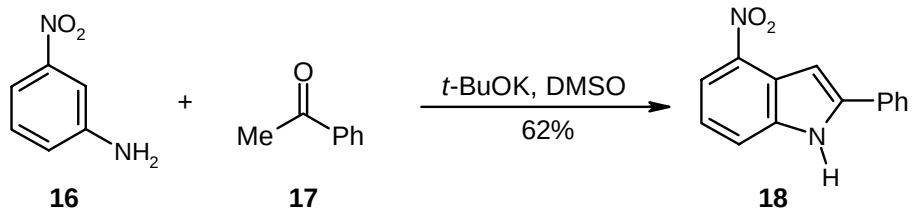
Scheme 4



14 **15**

Perhaps the simplest synthesis of 4- and 6-nitroindole derivatives consists in base-promoted oxidative substitution of hydrogen in 3-nitroanilines by enolate anions derived from dialkyl, cycloalkyl, and alkyl aryl ketones.[85] For example, the reaction of acetophenone (**17**) and 3-nitroaniline (**16**) in the presence of potassium *tert*-butoxide in dimethyl sulfoxide affords 2-phenyl-4-nitroindole (**18**) in good yield (Scheme 5). It appears that in this reaction the σ^H-adducts of the enolate anion to the nitroarene are additionally stabilized by the interaction of the amino and carbonyl group. Subsequent oxidation of the σ^H-adducts and the intramolecular formation of an imine followed by hydrogen shift give nitroindoles.

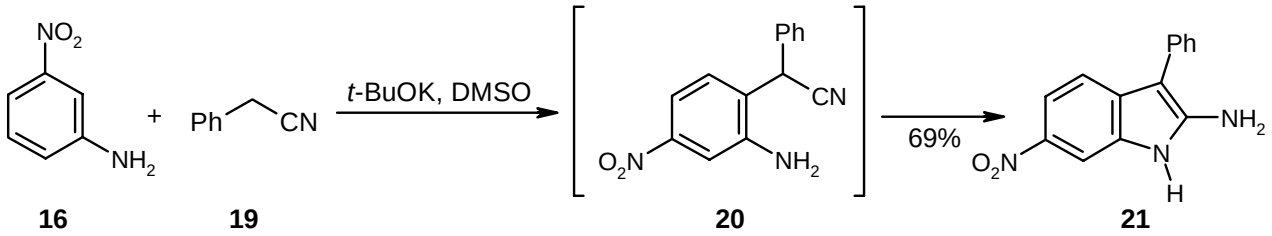
Scheme 5



16 **17** **18**

Somehow similar is the reaction between *m*-nitroaniline (**16**) and phenylacetonitrile (**19**). Oxidative nucleophilic substitution of hydrogen *para* to the nitro group and the subsequent addition of the amino to the cyano group gave 2-amino-6-nitro-3-phenylindole (**21**) (Scheme 6).[86]

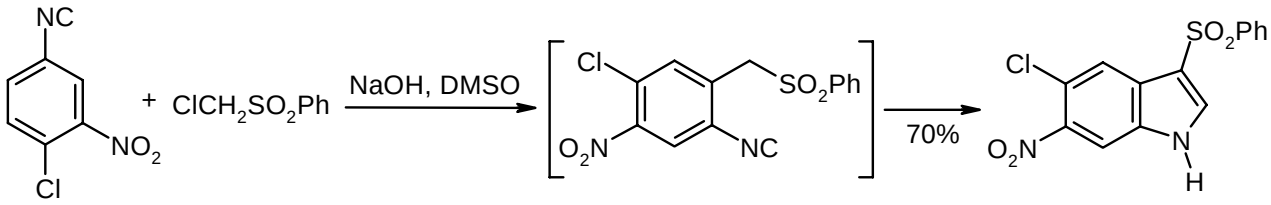
Scheme 6



16 **19** **20** **21**

Electrophilic properties of the isocyano group were utilized in the direct synthesis of 3-substituted nitroindoles (**24**) *via* the VNS reaction of 3-nitrobenzisonitriles (**22**), readily available from *m*-nitroanilines, with chloromethyl phenyl sulfone (**8**). Under the reaction conditions the initial VNS product (**23**) cyclizes to nitroindole (**24**) (Scheme 7).[87]

Scheme 7



22 **8** **23** **24**

2.2. Indoles *via* reductive cyclization of *o*-nitrobenzylic compounds

2.2.1. *Indoles from o-nitrobenzyl ketones*

o-Nitrobenzyl derivatives of aldehydes, ketones, esters and nitriles readily form indoles upon reduction of the nitro group. Of particular interest should be reduction of the nitro group in *o*-nitrobenzyl ketones because the initially formed *o*-aminobenzyl ketones cyclize directly to indoles.[88] In fact *o*-aminobenzyl ketones produced *via* $S_{RN}1$ reaction of the halogen in *o*-iodoanilines with enolates readily cyclize to indoles in good yields.[89-92]

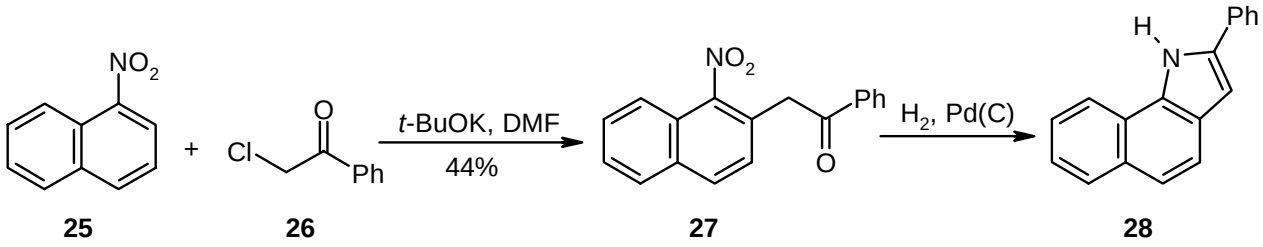
This attractive approach to indole ring construction *via* reduction of *o*-nitroarylmethyl ketones was of minor practical use because the starting materials were not readily availabile.[93-95] An exception is the Reissert procedure[96] in which the *o*-nitrotoluenes are condensed with diethyl oxalate to give *o*-nitroarylpyruvates, which are catalytically hydrogenated to ethyl esters of indole-2-carboxylic acids.[97] Other *o*-nitrobenzyl ketones are usually prepared by multistep procedures involving diverse processes such as

acylation of active methylene compounds with the corresponding *o*-nitroarylacetyl chlorides,[93] Meerwein arylation of vinyl acetate with 2-nitroaryldiazonium salts,[94] or nitration of alkyl benzyl ketones.[98]

In recent years new processes of direct introduction of carbonylalkyl substituents into nitroaromatic rings *via* nucleophilic substitution of hydrogen in nitroarenes were developed. Thus, *via* VNS and ONSH reactions of nitroarenes with enolate anions a variety of α-(2-nitroaryl)alkyl ketones can be prepared.

VNS of hydrogen in nitroarenes with enolate anions of α-chloroalkyl ketones (**26**) proceeds in moderate yields (Scheme 8).[99] Thus, the above-mentioned disadvantage is compensated by enhanced availability of these starting materials. The usual reduction of the obtained nitroaryl ketones furnishes indole derivatives generally in quantitative yields.[93-95,100]

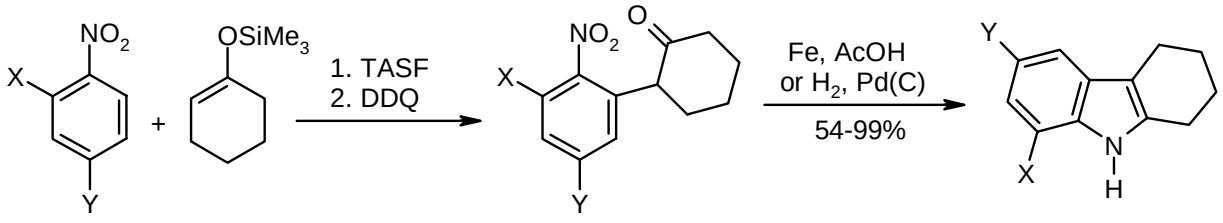
Scheme 8



25 **26** **27** **28**

An attractive procedure for synthesis of nitroarylated alkyl ketones *via* ONSH was developed by RajanBabu.[65,66,101] Silyl ethers of enols activated with fluoride anion behave as strong C-nucleophiles and add to nitroarenes in the *ortho*- and *para*-positions to the nitro group giving σ-adducts stabilized by the *O*-silyl function. Oxidation of these σ-adducts with DDQ leads to α-(2-nitroaryl)alkyl ketones.[66,101] For example, oxidation of the σ^H-adducts formed in the reaction of substituted nitrobenzenes with 1-trimethylsilyloxycyclohexene (**30**) activated with tris(dimethylamino)sulfonium difluorotrimethylsiliconate (TASF) furnishes 2-(2-nitrophenyl)cyclohexanones (**31**) which in turn can be reduced to 1,2,3,4-tetrahydrocarbazole derivatives (**32**).[101]

Scheme 9

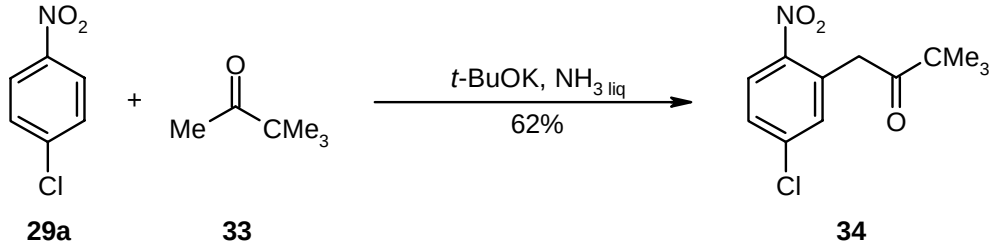


29 **30** **31** **32**

a, X = H, Y = Cl; **b**, X = Cl, Y = H; **c**, X = Y = Cl; **d**, X= MeO, Y = Cl.

5-Chloro-2-nitrobenzyl ketones (**34**) can be also prepared by direct oxidative substitution of hydrogen in the *ortho* position of *p*-chloronitrobenzene (**29a**) with enolates of methyl ketones, for example pinacolone (**34**) (Scheme 10).[56,102] Reduction of produced **34** to indole was not reported.

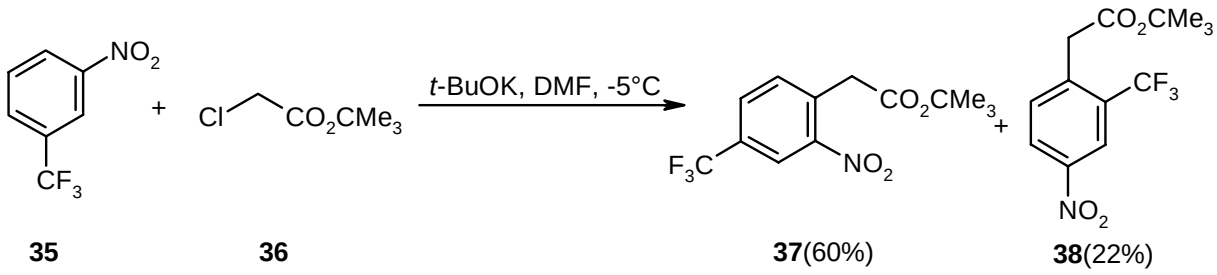
Scheme 10



2.2.2. *Indoles from esters of α-(2-nitroaryl)alkanoic acids*

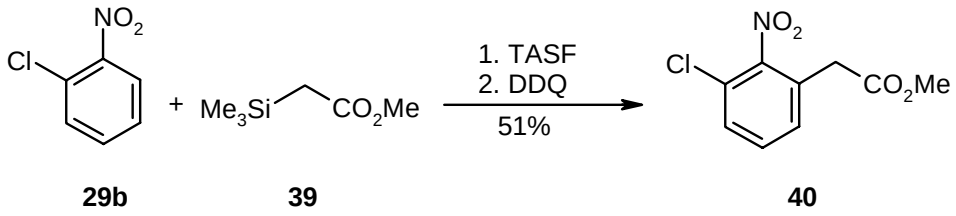
Reductive cyclization of 2-nitrophenylacetic acids and its derivatives is one of versatile methods of synthesis of oxindoles. In older procedures the required starting materials were prepared by nucleophilic replacement of halogen in 2-chloro- or 2-fluoronitrobenzenes with carbanions of dialkyl malonates followed by hydrolysis and decarboxylation. More general and efficient is synthesis of 2-nitroarylacetic acid esters *via* VNS of hydrogen in nitroarenes by carbanions of alkyl chloroacetates (**36**) (Scheme 11).[17]

Scheme 11.



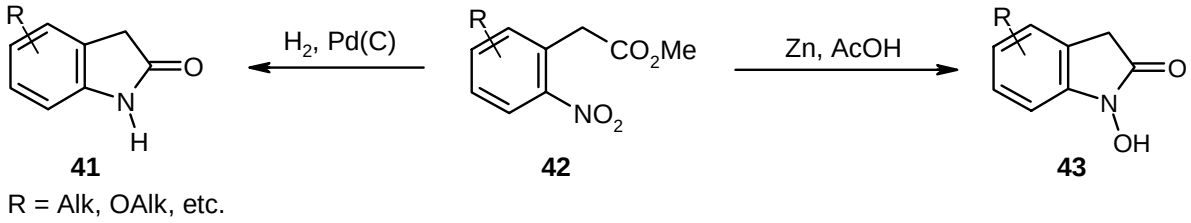
Fluoride ion induced reaction of methyl trimethylsilylacetate (**39**) with nitroarenes gives σ-adducts which after oxidation with DDQ also provide (2-nitroaryl)acetates (**40**) (Scheme 12).[65,66,101]

Scheme 12



Reduction of 2-nitroarylacetates (**42**) gives various products depending on the reaction conditions. Catalytic reduction with hydrogen over palladium gives oxindole (**41**),[103] while with zinc in acetic acid 1-hydroxyoxindoles (**43**) can be formed.[104,105]

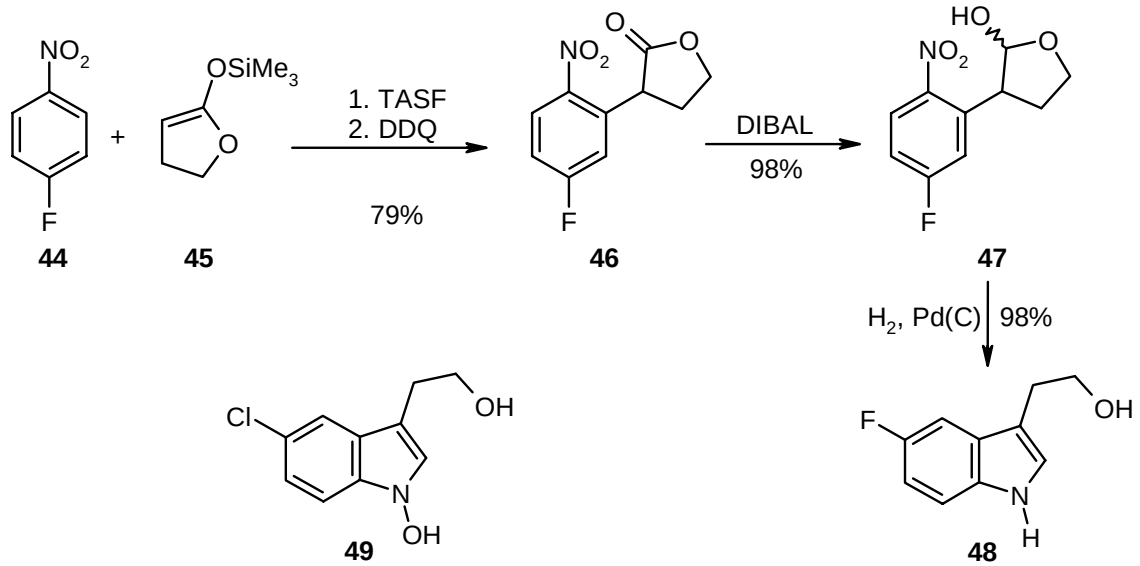
Scheme 13.



Ketene silyl acetals, *e.g.* **45**, react with aromatic nitro compounds in the presence of fluoride ion similarly to silyl enol ethers to give the expected σ^H-adducts. Oxidation of the σ^H-adducts with DDQ or bromine gives nitroarylacetic acid derivatives (Scheme 14).[65,66,101]

An interesting example of such process is fluoride ion-induced addition of 2,3-dihydro-5-(trimethylsilyl-oxy)furan (**45**) to *p*-fluoronitrobenzene (**44**), followed by oxidation with DDQ to arylbutyrolactone (**46**).[101] Two-step reduction of the lactone (**46**) with diisobutylaluminum hydride (DIBAL) followed by catalytic hydrogenation leads to 5-fluorotryptophol (**48**) (Scheme 14). Interestingly, the analogous chloro derivative under these conditions is hydrogenated to 1-hydroxyindole derivative (**49**).

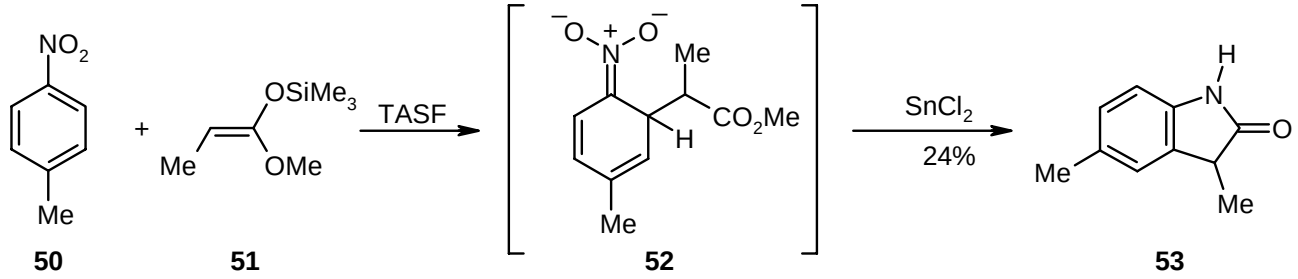
Scheme 14



In some instances the initially formed σ-adducts can be directly reduced to indolin-2-one derivatives (**53**). One example of such reaction, in which tin(II) chloride has been used as a reducing agent, is shown in

Scheme 15.[101] Similar procedures employing copper(I) iodide[106] and lithium aluminum hydride[107] were used for the synthesis of alkylanilines *via* direct reduction of σ-adducts of the Grignard reagents to nitroarenes.

Scheme 15



50 **51** **52** **53**

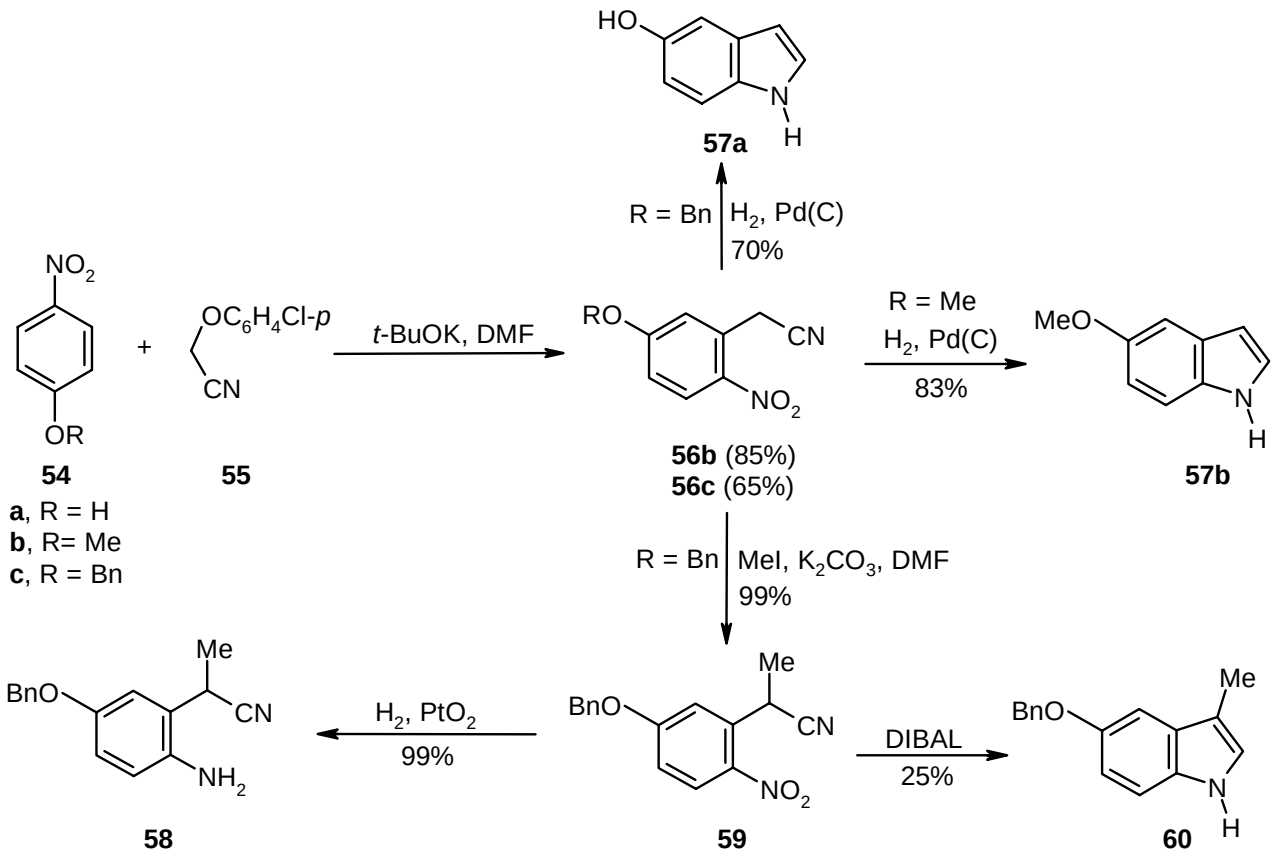
2.2.3. *Indole derivatives from α-(2-nitroaryl)alkanenitriles*

One of the most valuable methods for the synthesis of indole derivatives consists of the reductive cyclization of (2-aminoaryl)acetonitriles[108] and (2-nitroaryl)acetonitriles.[103,109] These reactions known for many years, has been of minor practical use because the required nitriles were not readily available. Thanks to the possibility of direct introduction of cyanomethyl group into a nitroarene moiety by vicarious nucleophilic aromatic substitutions of hydrogen, this process has become an attractive method for the synthesis of substituted indoles starting from easily available nitroarenes.[21] Reactions of nitroarenes with chloroacetonitrile,[19] aryloxyacetonitriles,[21] and arylthioacetonitriles[110,111] result in the direct introduction of cyanomethyl substituent. Introduction of cyanomethyl group into nitroarenes *via* ONSH [56,57] is also possible but perhaps less general and less practically useful.

The *o*-nitroarylacetonitriles readily available by this way, are widely used in further reductive transformations into indoles, as was exemplified by the synthesis of isomeric 4-, 5-, 6-, and 7-hydroxy- and -methoxyindoles (**57**, **63**, **67**, **70**) from isomeric nitrophenols (Schemes 16, 17, 18, and 19).[21] Since mononitrophenols (*e.g.* **54a**) exist in the form of the corresponding anions in basic media, and are not susceptible to a nucleophilic attack, it is necessary to protect the phenolic hydroxy group before the VNS reaction with acetonitrile derivatives. Employing various alkyl protecting groups and then various reduction procedures of the cyanomethylated nitroarenes one can obtain alkoxy- or hydroxyindoles.

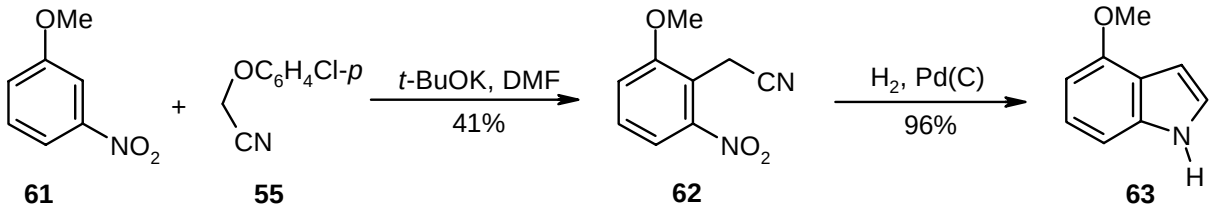
Ethers of *p*-nitrophenol were used as starting materials for the synthesis of 5-hydroxyindole derivatives. Vicarious nucleophilic substitution of hydrogen in 4-nitroanisole (**54b**) by the carbanion of (4-chlorophenoxy)acetonitrile (**55**) proceeds in good yield.[21] The catalytic hydrogenation over palladium gives 5-methoxyindole (**57b**) in good yield. When benzyl 4-nitrophenyl ether (**54c**) was used as the starting material the reduction of the obtained 5-benzyloxy-2-nitroarylacetonitrile (**56c**) leads to 5-hydroxyindole (**57a**).

Scheme 16



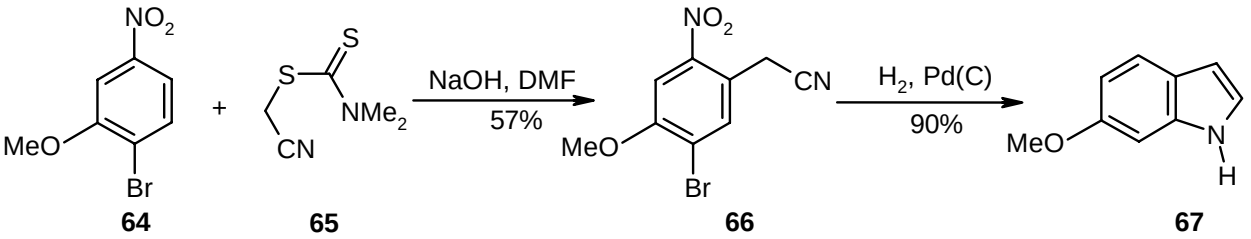
Interestingly, the analogous VNS reaction of 3-nitroanisole (**61**) occurs in the most hindered position 2 and furnishes **62**, the precursor of 4-methoxyindole (**63**) (Scheme 17).[21]

Scheme 17



2-Bromo-5-nitroanisole (**64**) was chosen as a starting material for the synthesis of 6-methoxyindole (**67**). The VNS reaction with the bulky carbanion of dimethyldithiocarbamoylacetonitrile (**65**) in the presence of powdered sodium hydroxide leads to the expected nitroarylactonitrile derivative (**66**).[21] Bromine atom protects the *para*-position to the nitro group and additonally the steric interaction of bromine and the methoxy substituent prevents the substitution in the 6-position. Catalytic hydrogenation of **66** results in the cyclization and removal of the bromine to give 6-methoxyindole (**67**) in very good yield (Scheme 18).

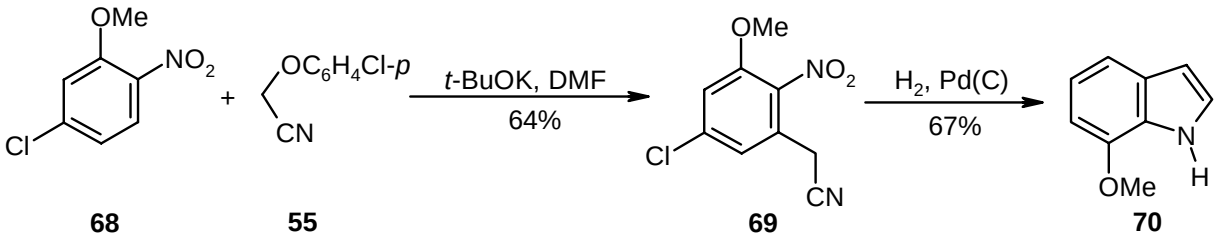
Scheme 18



Attempts to obtain (2-nitro-3-methoxyphenyl)acetonitrile, the precursor of 7-methoxyindole (**70**) by the direct reaction of 2-nitroanisole with aryloxyacetonitriles or the dithiocarbamoyl acetonitrile were unsuccesful. Due to low electrophilic activity of this nitroarene the formation of the σ^H-adduct occured only to a negligible extent and the competing Thorpe condensation of the C-H acid dominated, leading to 2,4-bis-(4-chlorophenoxy)-3-iminobutyronitrile.[21] On the other hand, with the more electrophilic 5-chloro-2-nitroanisole (**68**) the VNS reaction proceeded smoothly to give **69**,[21] and its further hydrogenation results in cyclization to 7-methoxyindole (**70**) with simultaneous removal of the auxiliary chlorine atom (Scheme 19).

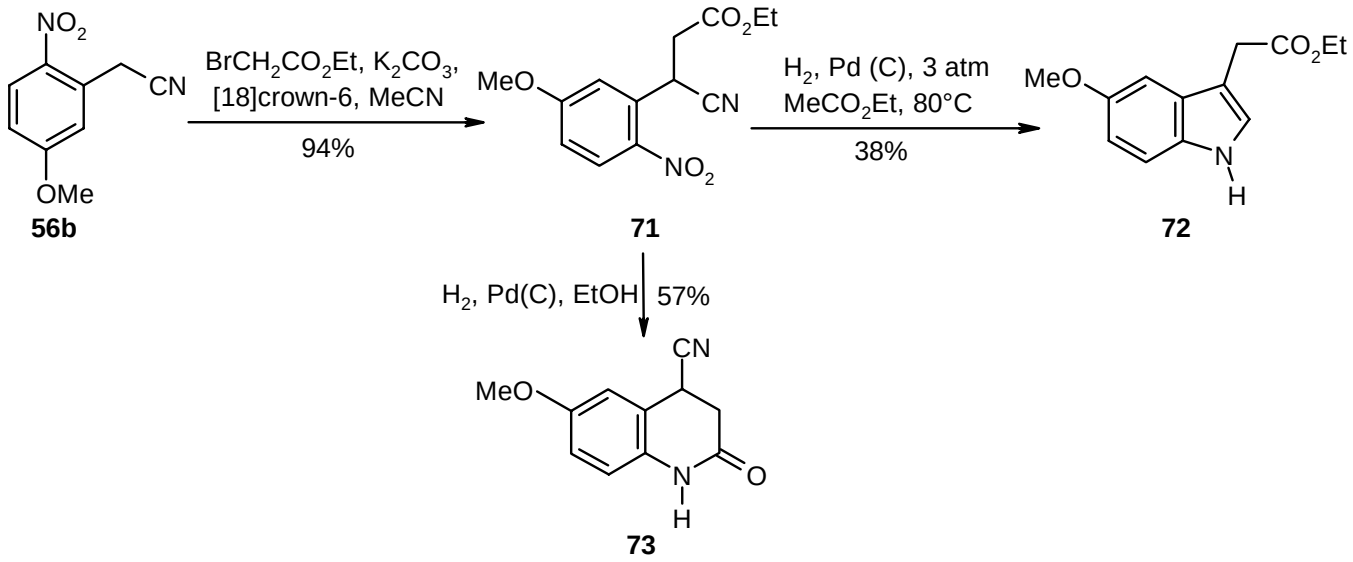
When benzyl ethers of the corresponding nitrophenols were used as starting materials for the VNS, the catalytic hydrogenation of the obtained 2-nitroarylacetonitriles gave corresponding hydroxyindoles.[21] On the other hand benzyloxyindole (**60**) can be obtained when diisobutylaluminum hydride (DIBAL) was used for simultaneous reduction of the cyano and nitro groups (Scheme 16).[112]

Scheme 19



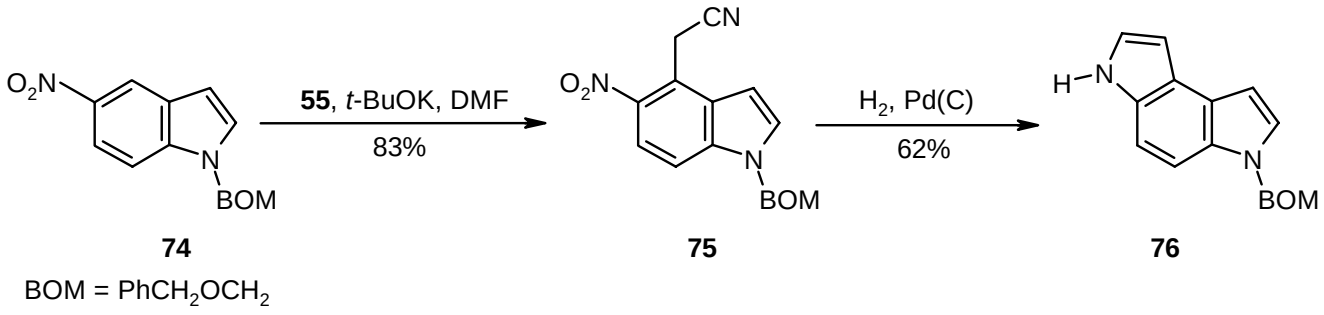
An additional value of this VNS cyanomethylation is connected with the possibility to alkylate the intermediate nitroarylacetonitriles with alkyl halides[21,113] or alcohols,[34,114] leading to precursors of 3-substituted indoles.[21,34,114] For example, alkylation of the *o*-nitroarylacetonitrile **56b** with ethyl bromooacetate gave ethyl 3-(*o*-nitroaryl)-3-cyanopropionate (**71**) which upon reduction can cyclize in two directions, giving indole (**72**) or quinoline (**73**) derivatives (Scheme 20).[21]

Scheme 20



The VNS cyanomethylation of protected 5-nitroindole (**74**) followed by a reduction of the obtained 5-nitroindol-4-ylacetonitrile (**75**) enables to prepare pyrrolo[3,2-*e*]indole derivative (**76**) (Scheme 21),[35] a parent heterocyclic fragment of an antitumor antibiotic CC-1065.[115]

Scheme 21

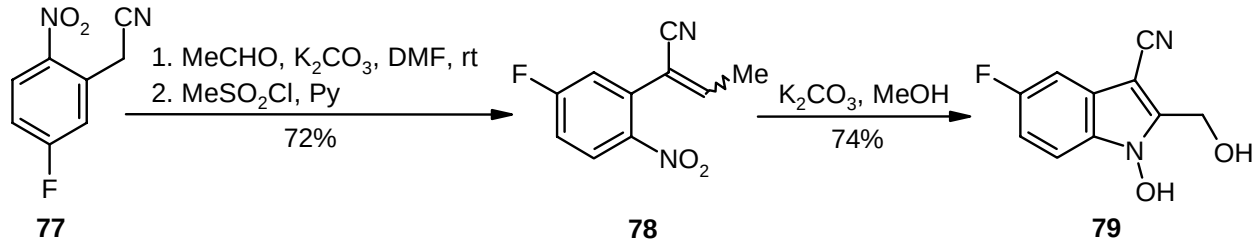


2.3. Formation of indoles *via* direct interaction of the nitro group with *ortho*-carbon substituents

Intermolecular reactions of carbanions with aromatic nitro group are seldom observed.[116-120] On the other hand, related intramolecular reactions are common processes. Older examples of these ractions of *ortho*-alkyl substituted nitroarenes leadnig to indole derivatives were reviewed by Preston and Tennant.[76]

o-Nitroarylacetonitriles react with aliphatic aldehydes under mild conditions giving the Knoevenagel condensation products of the active methylene group.[113] The unsaturated nitriles, *e.g.* **78** in the presence of potassium carbonate in methanol undergo intramolecular condensation giving 1-hydroxy-2-(hydroxymethyl)indole derivatives (**79**) (Scheme 22).[121]

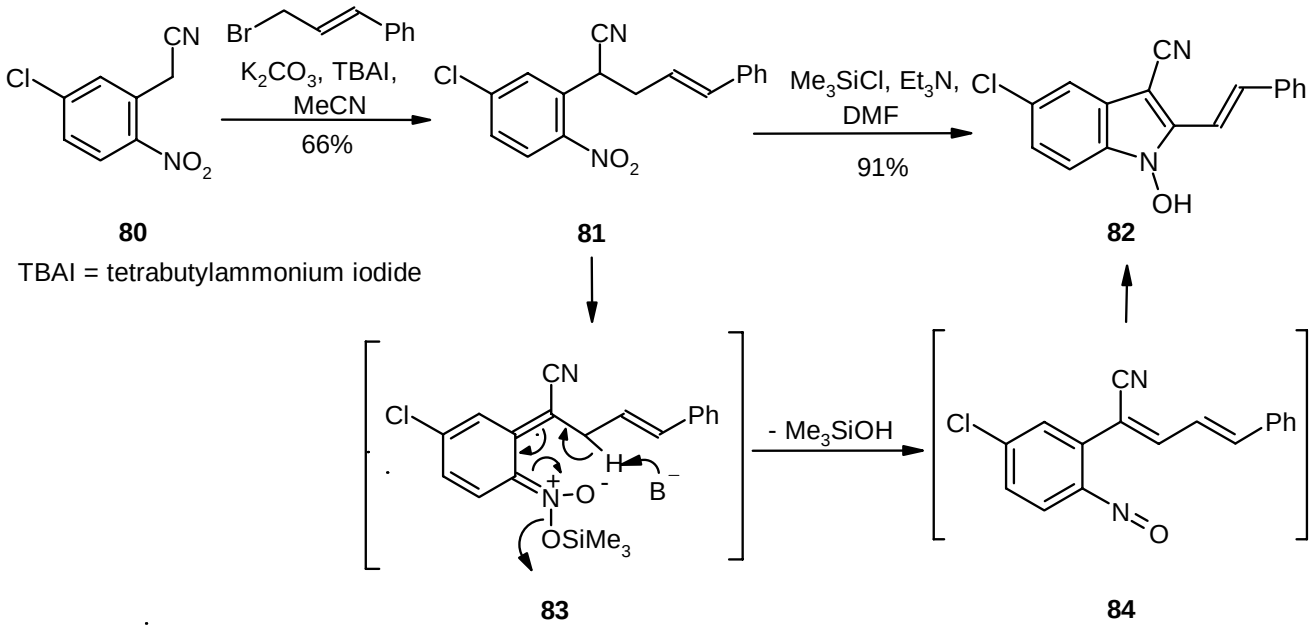
Scheme 22



77 78 79

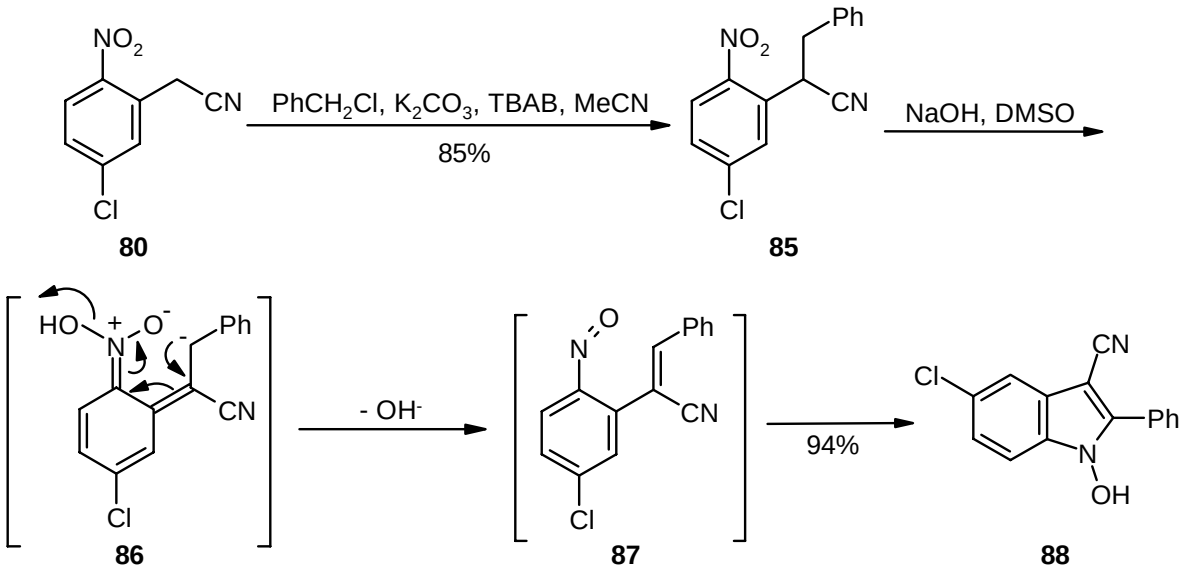
As it was mentioned earlier, *o*-nitroarylacetonitriles can be readily alkylated with various alkylating agents.[21,113] This process is particularly facile with allyl halides.[122] The allylated products in the presence of chlorotrimethylsilane and triethylamine undergo a cyclization leading to 3-cyano-1-hydroxy-2-vinylindoles (**82**) (Scheme 23).[122] The way these products are formed is unclear, but presumably it proceeds *via* 1,5-elimination of trimethylsilanol from the intermediate trimethylsilyl nitronate (**83**) followed by an electrocyclization of **84** and hydrogen shift.

Scheme 23



A similar process is presumably involved in the formation of *N*-hydroxyindole (**88**) from 2-(5-chloro-2-nitrophenyl)-3-phenylpropionitrile (**85**).[77] The crucial step of this transformation is a dehydration of **86** leading to the formation of the intermediate nitroso compound (**87**) (Scheme 24).

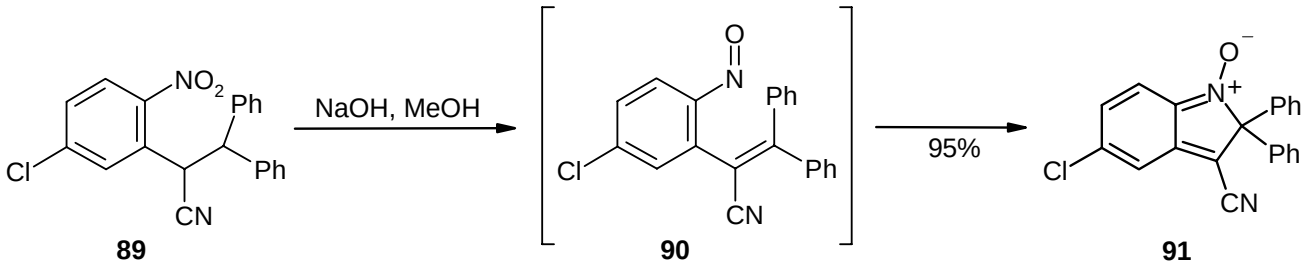
Scheme 24



TBAB = tetrabutylammonium bromide

The intermediate vinyl nitroso compound (**87**) undergoes an electrocyclization resulting in nitrone (2*H*-indole *N*-oxide), a tautomer of *N*-hydroxyindole (**88**). This supposition was supported by the cyclization reaction of the benzhydryl derivative (**89**) to 2,2-diphenyl-2*H*-indole *N*-oxide (**91**) in excellent yield (Scheme 25).[77]

Scheme 25



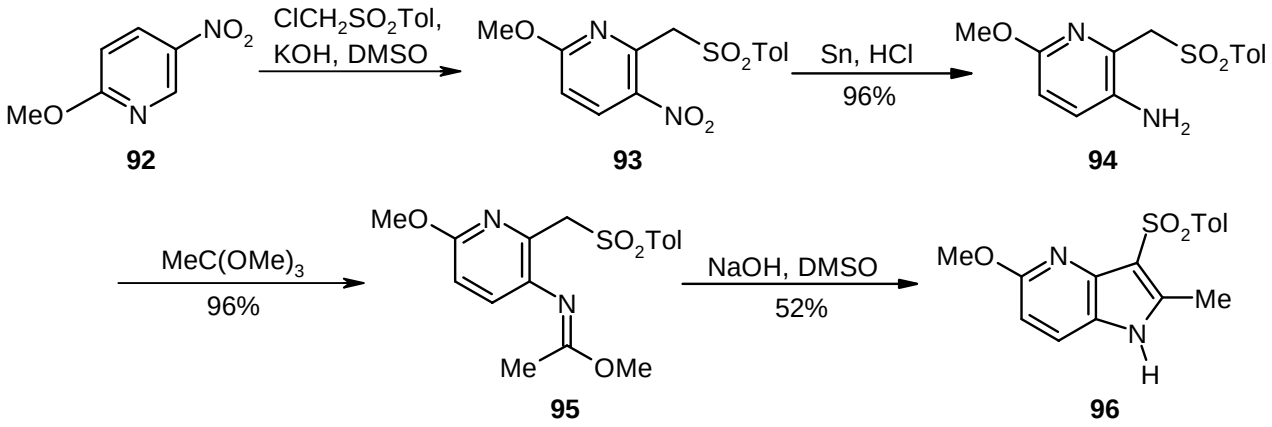
2.4. Indole derivatives from 2-aminobenzyl sulfones.

Reduction of the nitro group in *o*-nitroarylmethyl ketones, esters, and nitriles results in immediate cyclization to indole derivatives. Alternative attractive possibilites are provided by reduction of *o*-nitroarylmethyl aryl sulfones, *e.g.* **93**, readily obtained *via* VNS in nitroarenes with chloromethyl aryl sulfones.[11,13,15,123]

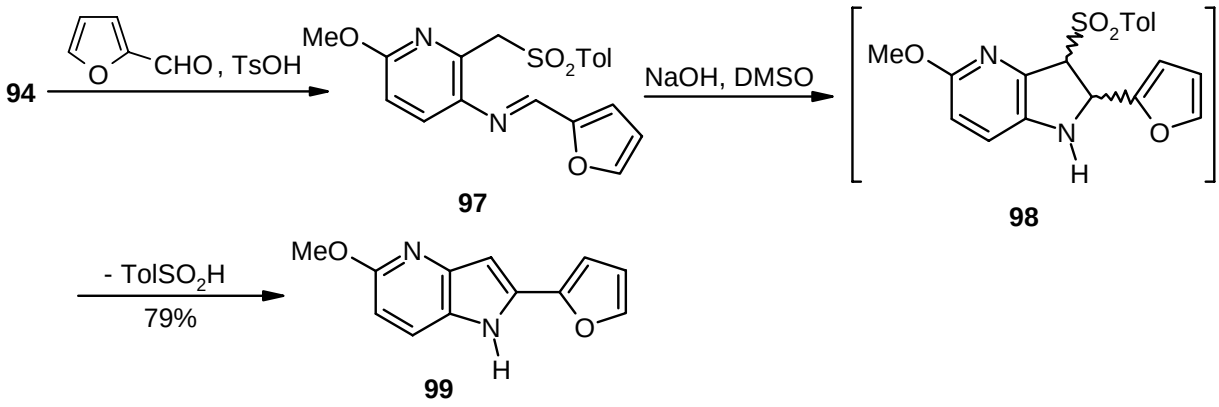
The reduction of sulfone (**93**) under mild conditions with tin in a hydrochloric acid-methanol mixture furnishes *o*-aminobenzyl sulfone (**94**), which, by various procedures (Schemes 26-28), can be

transformed into indole derivatives. Thus, the condensation of the amino compound (**94**) with methyl orthoacetate gives imidate **95**, which cyclizes under the basic conditions to give 3-sulfonylindole (**96**).[124]

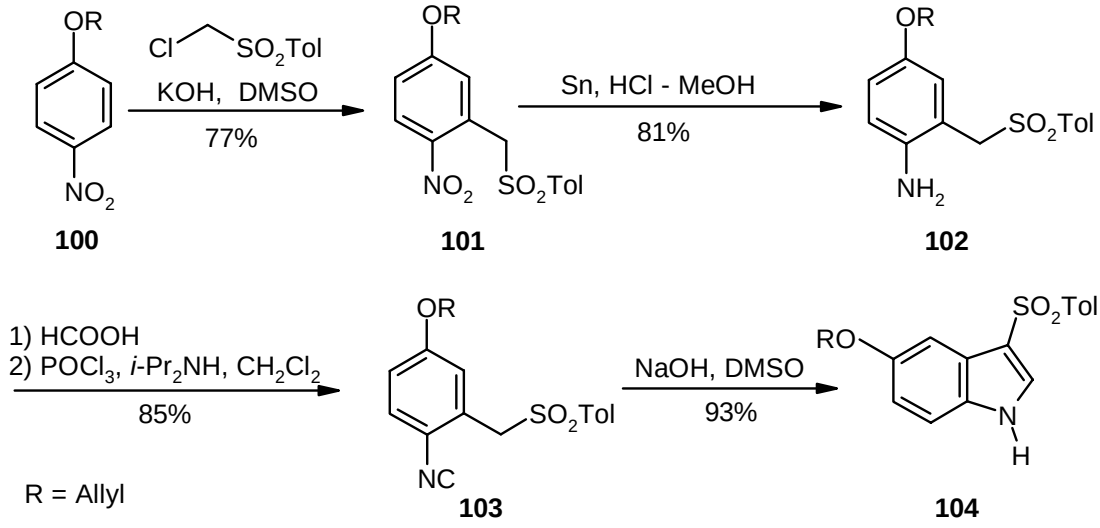
Scheme 26



Scheme 27



Scheme 28



The condensation of *o*-aminobenzyl sulfone (**94**) with aromatic or heteroaromatic aldehydes leads to the imine (**97)**, which in the presence of NaOH in DMSO cyclizes to 2-aryl substituted indole (**99**).[125]. This reaction proceeds *via* an intermediate 3-arylsulfonyl-2,3-dihydroindole (**98**) which undergoes further β-elimination of arenesulfinic acid (Scheme 27). Alternatively, the *o*-aminobenzyl sulfone (**102**) can be converted by a standard procedure into *o*-isocyanoarylmethyl sulfone (**103**) which also cyclizes to 3-sulfonylindole (**104**) upon treatment with a base (Scheme 28).[126]

3. QUINOLINES

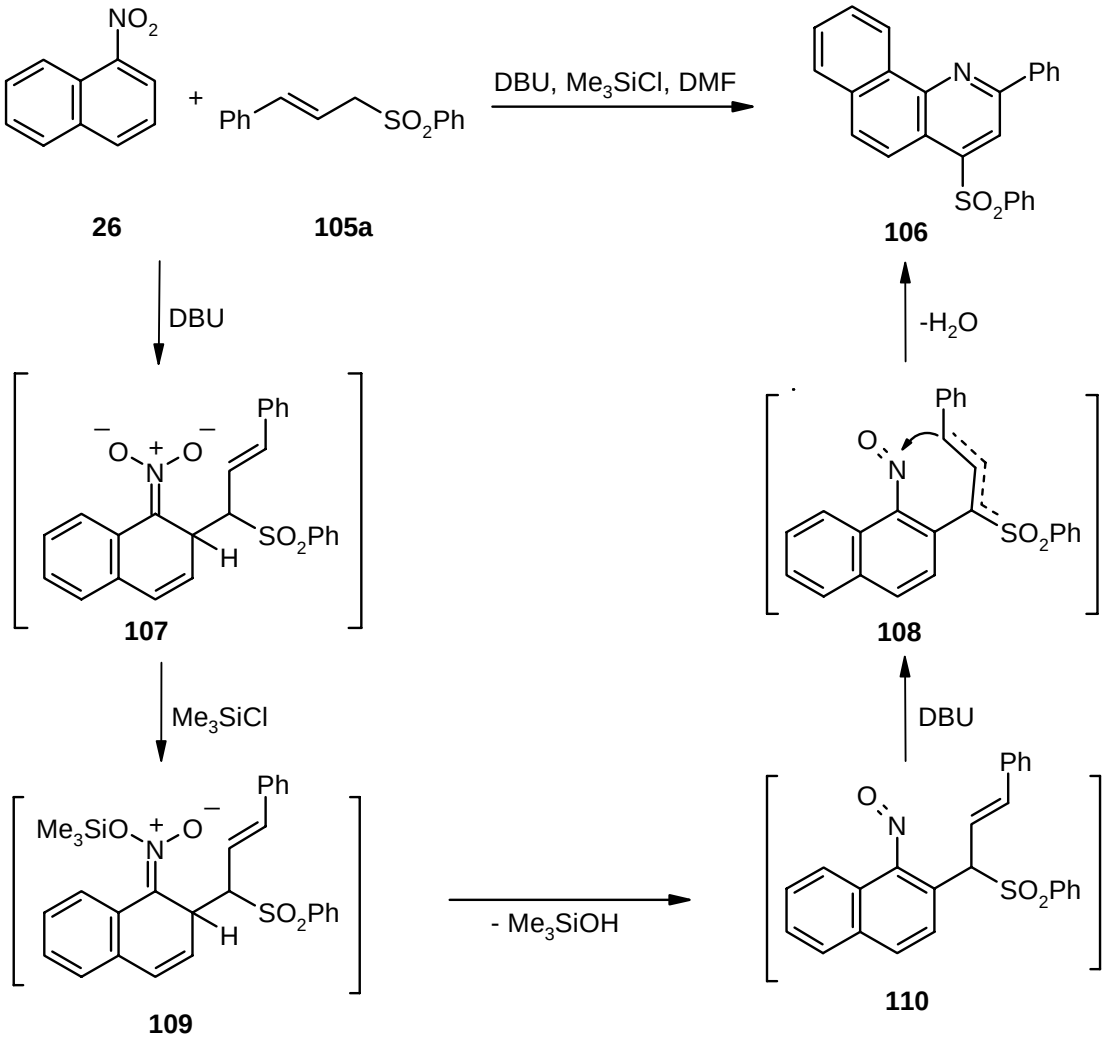
Nitroarenes bearing functionalized alkyl substituents in the *ortho*-positions are versatile starting materials also for synthesis of quinolines. Numerous older examples of such processes were reviewed by Preston and Tennant.[76] Since a variety of functionalized alkyl substituents can be introduced into the *ortho*-positions of nitroarenes *via* nucleophilic substitution of hydrogen (VNS, ONSH, etc), these reactions provide new attractive possibilities for synthesis of quinolines.

Quinoline ring systems can be obtained from the products of VNS of hydrogen in nitroarenes *via* reactions utilizing the nitro group as a predecessor of the quinoline ring nitrogen, or utilizing other substituents in the starting nitroarene for this purpose.

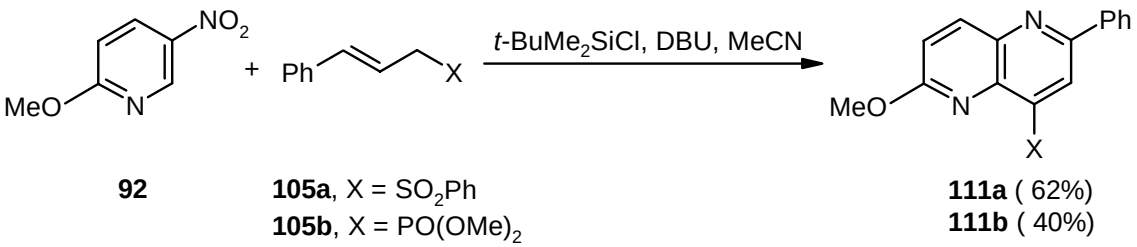
Particularly interesting is the formation of quinoline ring system by the direct reaction of some allylic carbanions with nitroarenes in which nucleophilic substitution of hydrogen and cyclization involving the nitro group proceeds in one operation (Scheme 29).[80] This reaction proceeds satisfactorily when relatively active nitro compounds such as 4-nitrochlorobenzene, 1-nitronaphthalene (**26**), 2-nitrothiophene, nitropyridines, 5- and 8-nitroquinolines, are treated with carbanions of cinnamyl phenyl sulfone (**105a**),[80,81] cinnamonitrile,[80] and dimethyl cinnamylphosphonate (**105b**).[80] Its speculative mechanism is presented in the Scheme 29. The initially formed σ-adduct (**107**) in the presence of silylating agent (Me_3SiCl, *t*-$BuMe_2SiCl$, or bis-(trimethylsilyl)acetamide (BTMSA)) undergoes conversion to the nitroso compound (**110**), and the consecutive intramolecular addition of the ambident carbanion (**108**) to the nitroso group results in formation of the quinoline ring.

For example, cinnamyl phenyl sulfone (**105a**) and dimethyl cinnamylphosphonate (**105b**) add to 2-methoxy-5-nitropyridine (**92**) in the presence of DBU and a silylating agent giving 4-sulfonyl- and 4-phosphonyl-6-methoxy-2-phenyl[1,5]naphthyridines (**111a**,**b**) (Scheme 30).[80] In the formed sulfonyl derivative (**111a**) the arenesulfonyl group can be easily replaced by a variety of nucleophiles (thiolates, azide, cyanide, and methylcyanoacetate anions) or even can be removed by reaction with sodium borohydride, giving access to a variety of functionalized quinoline derivatives.[80]

Scheme 29

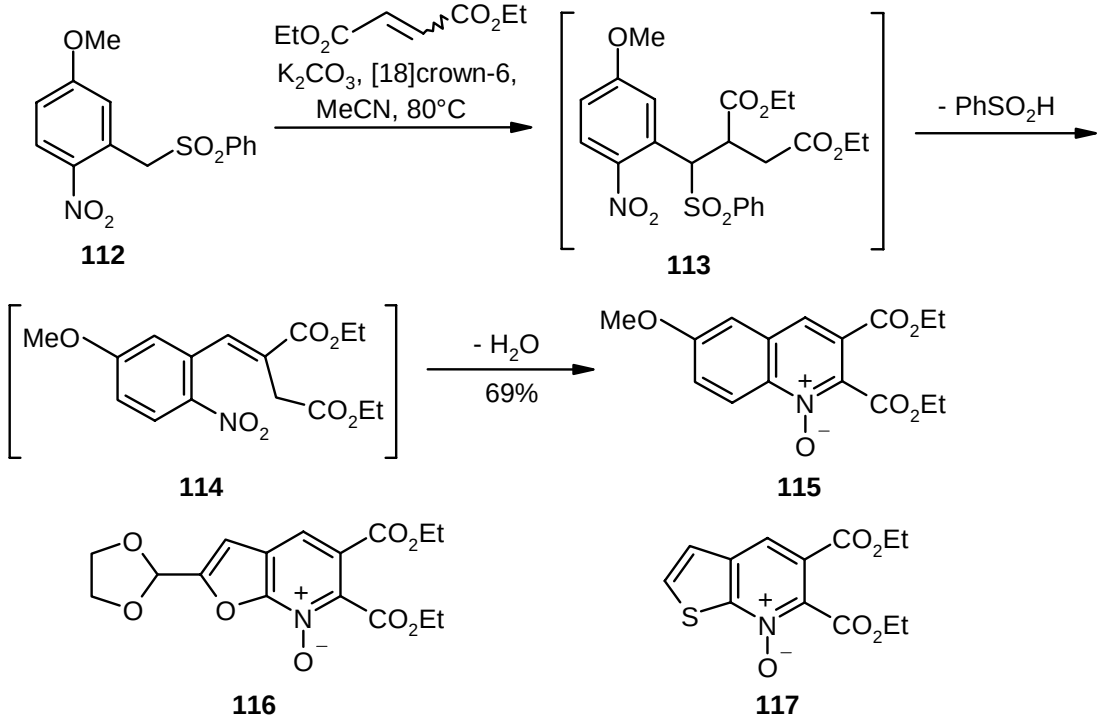


Scheme 30.

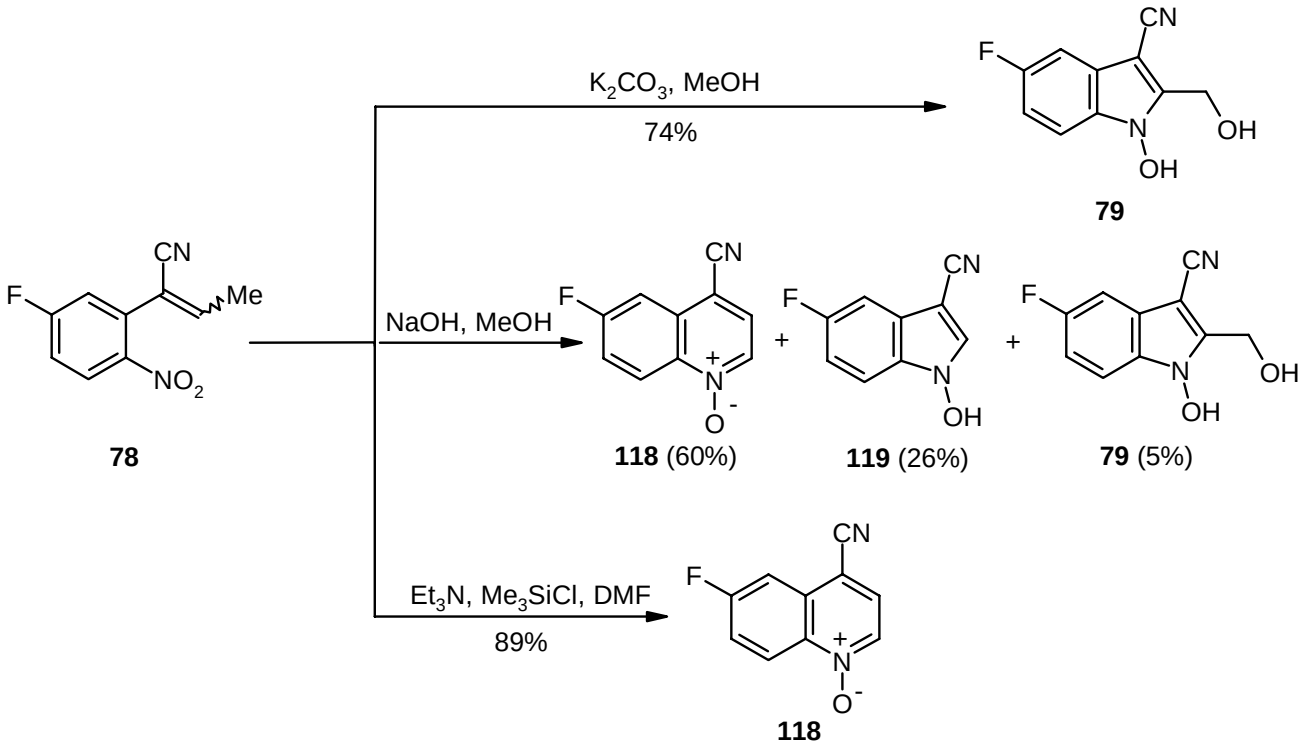


Base-catalyzed Michael addition of *o*-nitrobenzyl sulfone, *e.g.* **112**, and its heterocyclic analogues to diethyl maleate or fumarate initiates a series of transformations involving addition of the intermediate allylic carbanion of **114** to the nitro group which finally leads to diethyl 6-methoxyquinoline-1,2-dicarboxylate-*N*-oxide (**115**) or its analogues **116** and **117** (Scheme 31).[127]

Scheme 31



Scheme 32

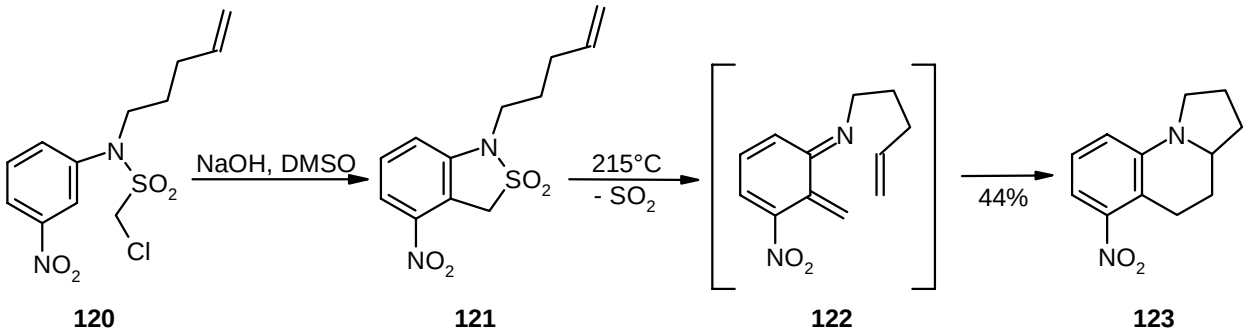


It was shown that alkylidene nitriles, the Knoevenagel condensation products of *o*-nitroarylacetonitriles and aliphatic aldehydes,[113] cyclize to 1-hydroxy-2-hydroxymethylindole derivatives in good yields upon treatment with potassium carbonate in methanol (Scheme 22)[121,128] The cyclization pathway of these alkylidene derivatives strongly depends on the reaction conditions. For example, the nitrile (**78**) in methanolic NaOH solution converts into a mixture of quinoline-*N*-oxide (**118**), *N*-hydroxyindole (**119**),

and *N*-hydroxy-2-(hydroxymethyl)indole (**79**), while in the presence of K_2CO_3 in methanol, the major product is indole (**79**),[121] and in the presence of trimethylamine and chlorotrimethylsilane quinoline *N*-oxide (**118**) is formed selectively (Scheme 32).

Intramolecular VNS in *N*-chloromethanesulfon(*m*-nitro)anilides,[129] and intramolecular oxidative substitution of hydrogen in *N*-metanesulfon(*m*-nitro)anilides[130] leads to benzosultams, which undergo thermal extrusion of SO_2 leading to aza-*o*-xylylenes.[131] These reactive 1-azadienes undergo an intramolecular [4+2] cycloaddition leading to 1,2,3,4-tetrahydroquinoline derivatives. For example, intramolecular reaction of aza-*o*-xylylene (**122**) generated from 1-(pent-4-enyl)benzosultam (**121**) provides condensed 1,2,3,4-tetrahydroquinoline derivative (**123**) (Scheme 33).[132]

Scheme 33

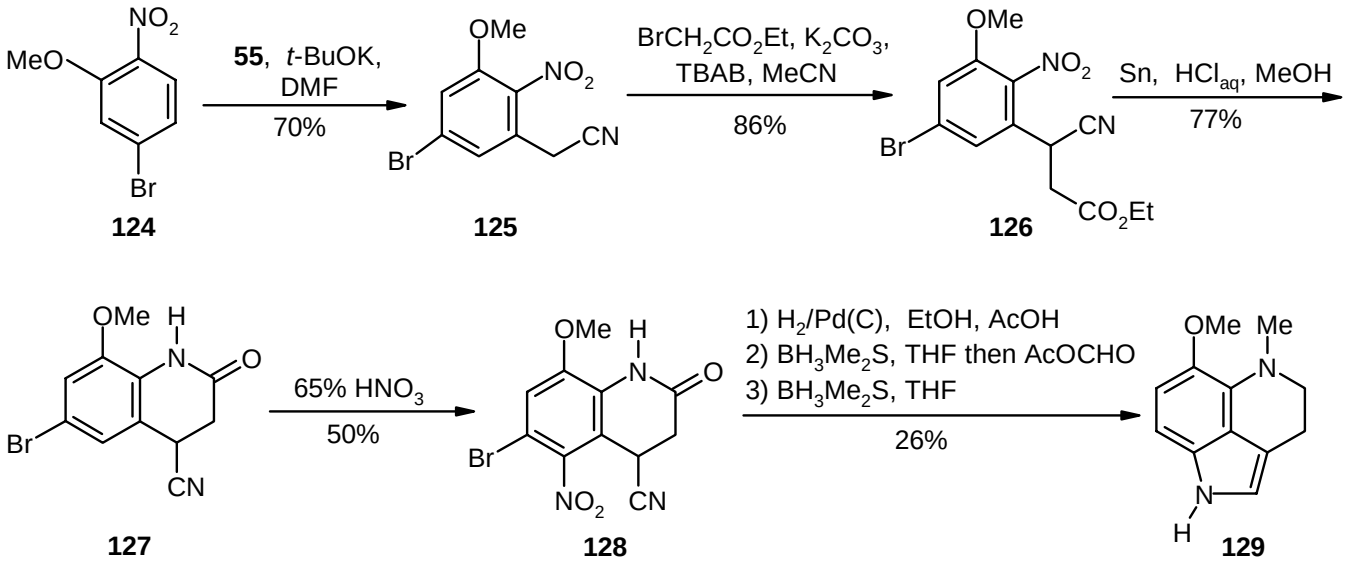


4. THE SYNTHESIS OF NATURAL PRODUCTS CONTAINING INDOLE AND QUINOLINE RINGS

Indole and quinoline ring systems are frequently present in natural products and biologically active compounds, thus the reactions presented above offer a valuable tool for their synthesis. However, to date there are not many examples of the application of the VNS or ONSH reactions in the synthesis of natural products. The following examples highlight the possibilities provided by these reactions for solving some synthetic problems in this field. In our laboratory syntheses of several natural products: *O*-methyl-nordehydrobufotenine (**129**)[133], an alkaloid of animal origin, 1,3,4,5-tetrahydrobenz[*cd*]indole[126] a serotonine antagonist, and eupolauramine[81,134] an alkaloid of plant origin, were executed.

The key step in synthesis of nordehydrobufotenine (**129**)[133] (Scheme 34) was the VNS cyanomethylation of 5-bromo-2-nitroanisole (**124**) furnishing nitrile (**125**). The nitrile was then alkylated with ethyl bromoacetate and the product (**126**) was subjected to catalytic hydrogenation leading to 1,2,3,4-tetrahydro-4-cyano-2-quinolinone (**127**), which was subsequently subjected to nitration. The obtained nitro derivative (**128**) was transformed into the target compound (**129**) *via* standard operations.

Scheme 34

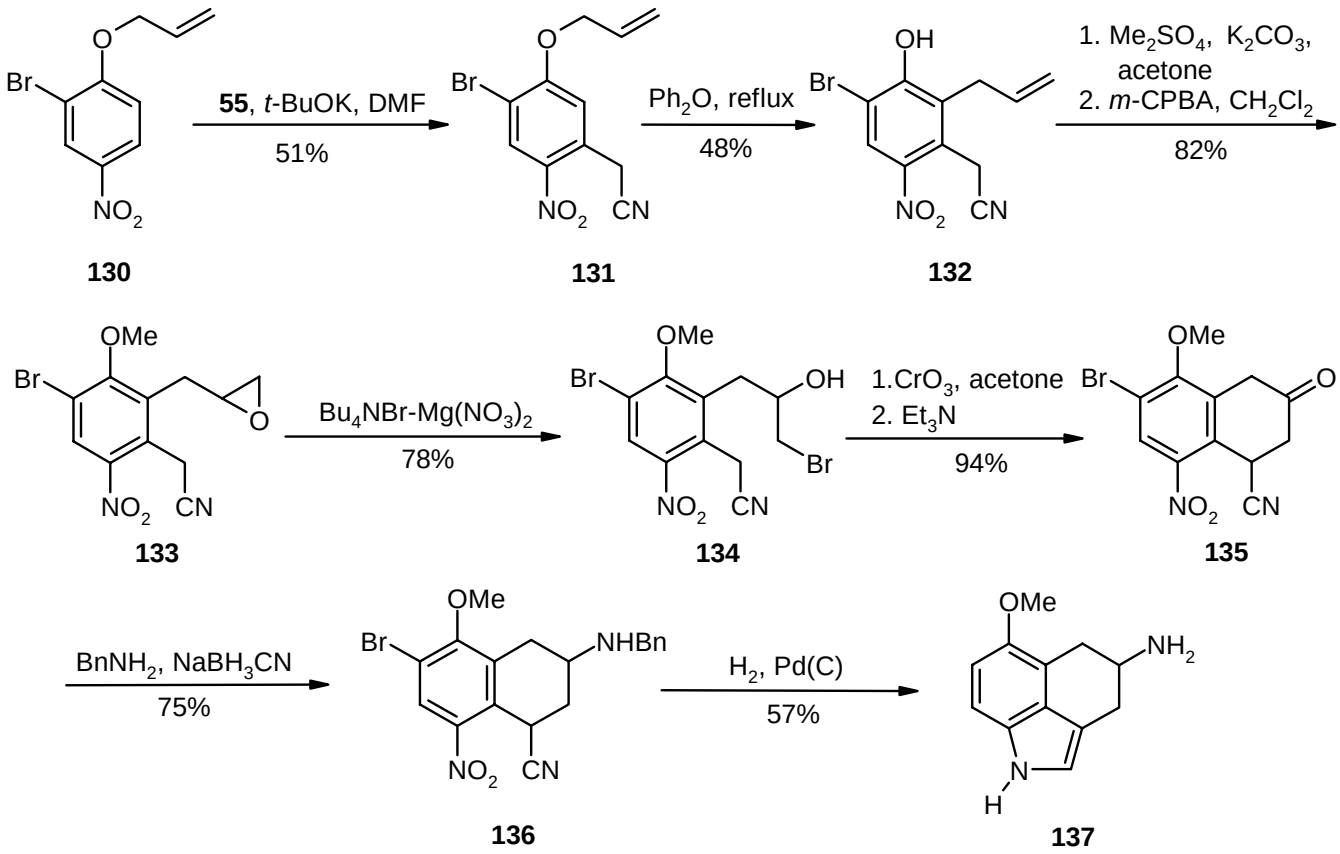


Similarly, the VNS cyanomethylation of allyl 2-bromo-4-nitrophenyl ether (**130**) was employed as the crucial step in the synthesis of benz[*cd*]indole derivative (**137**)[126] as shown in Scheme 35.

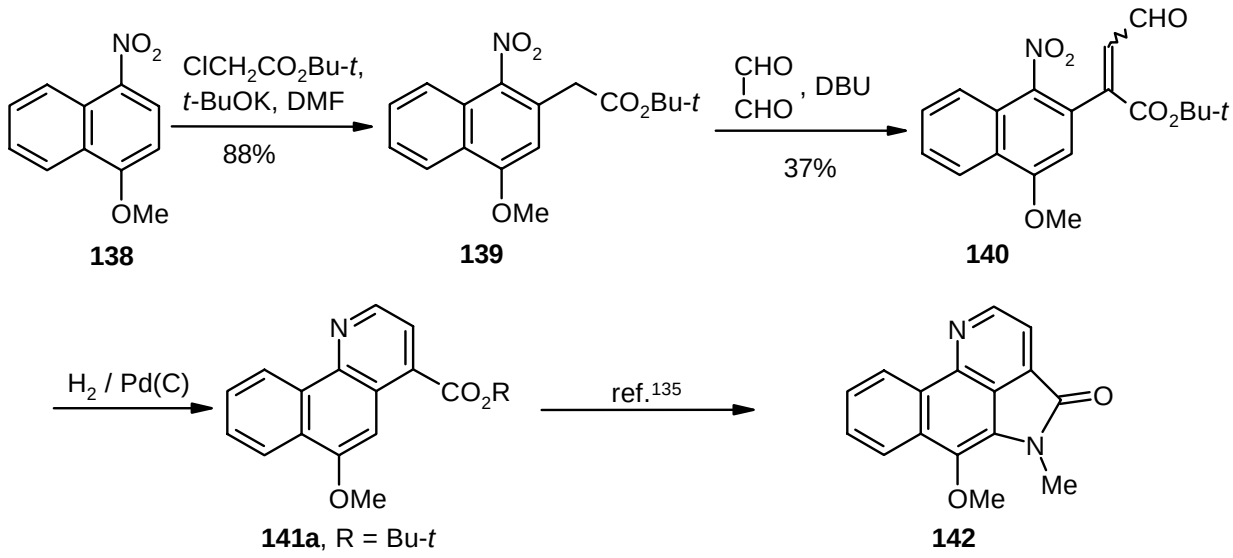
Another example of the application of VNS in natural product chemistry is the formal synthesis of eupolauramine (**142**), an azaphenanthrene alkaloid isolated from the bark of African plant *Eupomatia laurina.* In our approach[134] the ester (**139**), obtained *via* VNS in 1-methoxy-4-nitronaphthalene (**138**) with *tert*-butyl chloroacetate, was used as a starting material (Scheme 36). In a few steps this ester was transformed into azaphenanthrene (**141a**), from which the eupolauramine (**142**) can be obtained following the known procedure.[135]

Recently much simpler approach to eupolauramine was developed.[81] 1-Methoxy-4-nitronaphthalene (**138**) reacts with allyl phenyl sulfone (**105a**) in the presence of DBU, magnesium chloride, and bis(trimethyl-silyl)acetamide (BTMSA), leading to 6-methoxy-4-(phenylsulfonyl)benzo[*h*]quinoline (**143**, 49%), in which the sulfonyl group was then substituted by cyano group (Scheme 37). Further steps included hydrolysis, nitration and cyclization of oxindole ring according to the known procedure[135] led to **142**.

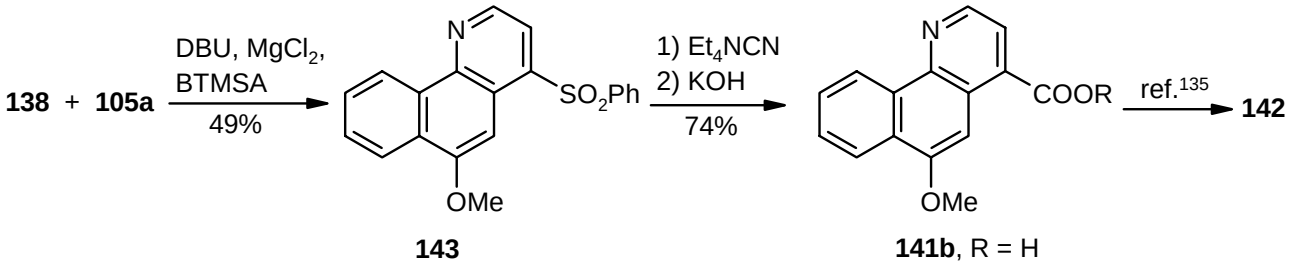
Scheme 35



Scheme 36



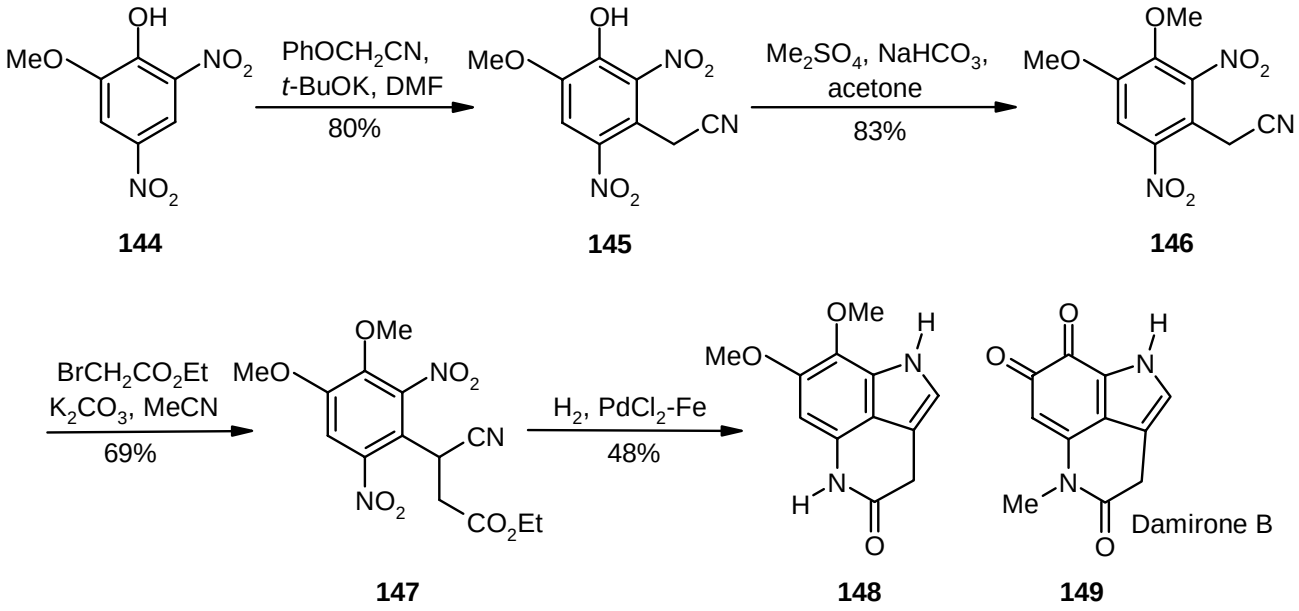
Scheme 37



143 141b, R = H

In the key step of the synthesis of damirone B precursor (**148**) specific orientation of VNS in 2,4-dinitrophenol was used.[136] Namely, 4,6-dinitroguaiacol (**144**) was cyanomethylated with phenoxyacetonitrile selectively in the 5-position. Subsequent standard transformations shown in Scheme 38 gave the desired compound (**148**).

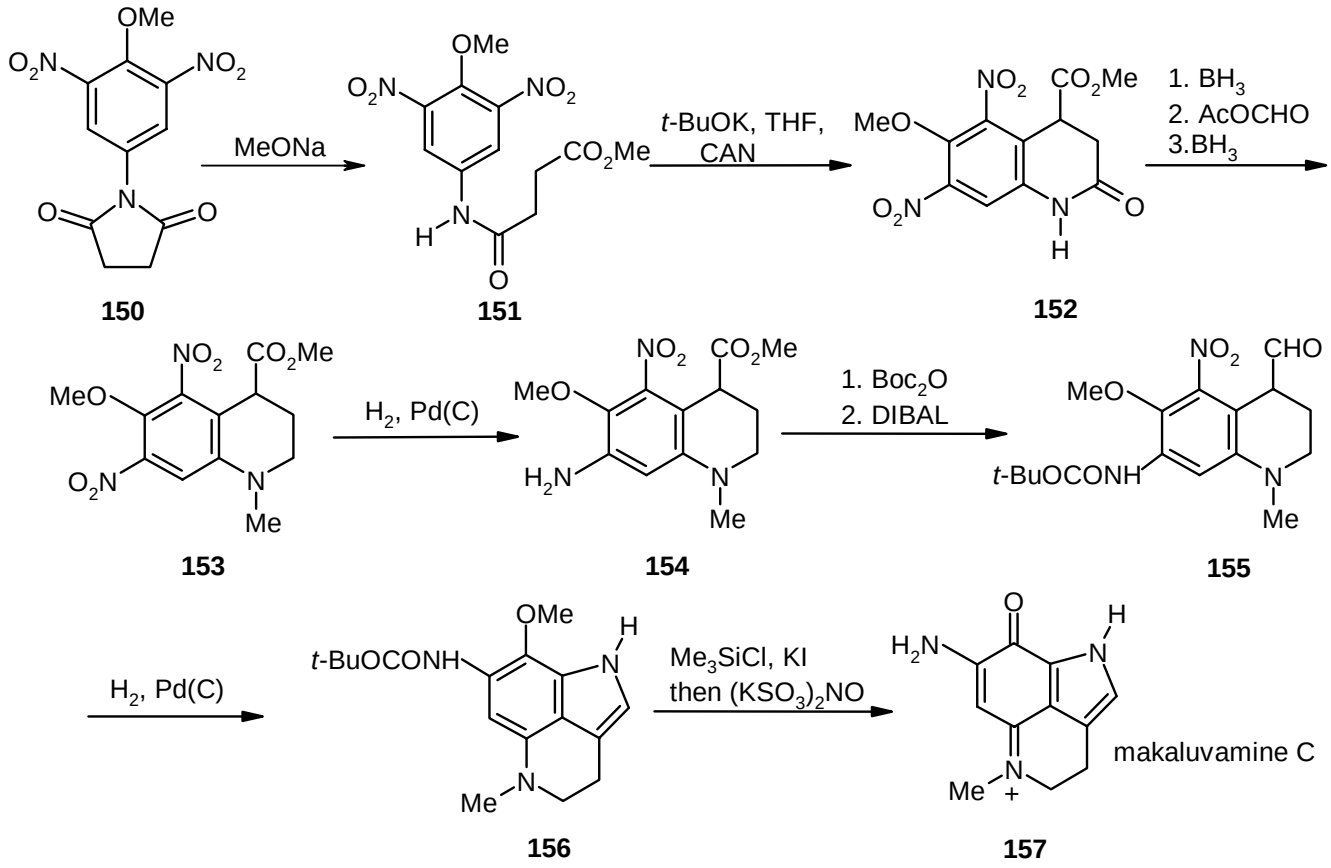
Scheme 38



144 145 146 147 148 149

Oxidative nucleophilic substitution of hydrogen was used as the key step in the synthesis of makaluvamine C (**157**), a neoplastic agent isolated from marine sponges.[67,68] The synthesis started from easily available *N*-(3,5-dinitro-4-methoxyphenyl)succinimide (**150**) which opens with sodium methoxide to an amido ester (**151**). This compound undergoes intramolecular oxidative nucleophilic substitution of hydrogen in the presence of potassium *tert*-butoxide and cerium ammonium nitrate to give lactam **152**. Further standard transformations shown in Scheme 39 lead to the makaluvamine C (**157**).

Scheme 39



5. CONCLUSIONS

The reactions of nucleophilic substitution of hydrogen open new and wide perspectives in the chemistry of aromatic compounds. The variety of functionalized substituents which can be introduced into nitroarenes, carbo- and heterocyclic, is practically unlimited. Thus, this process provides versatile and easy access to many compounds which can serve as starting materials for further transformations and are particularly useful for the synthesis of heterocyclic systems of indole and quinoline.

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