DOI 10.1007/s10593-015-1687-4

Chemistry of Heterocyclic Compounds **2015**, *51*(3), 210-222

REVIEW

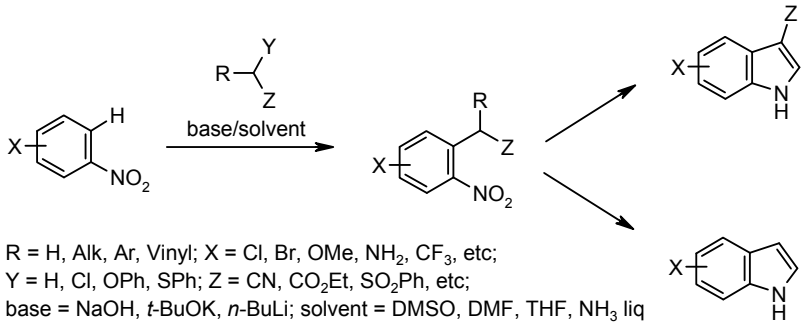
Application of nucleophilic substitution of hydrogen in nitroarenes to the chemistry of indoles

Mieczysław Mąkosza[1], Krzysztof Wojciechowski[1]

[1] *Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, Warsaw 01-224, Poland; e-mail: icho-s@icho.edu.pl*

Published in Khimiya Geterotsiklicheskikh Soedinenii, 2015, *51*(3), 210-222

Submitted February 16, 2015
Accepted March 3, 2015



Application of nucleophilic substitution of hydrogen in nitroarenes to the synthesis and transformation of indoles is discussed.

Keywords: indole, nitroarenes, nucleophiles, alkylation, nucleophilic aromatic substitution, oxidation, reduction.

Indoles are unquestionably the most important heterocyclic systems present in numerous natural products, pharmaceuticals, plant protection agents, etc. Synthesis and transformations of the indole ring systems are therefore of continuous interest and subject of many original publications and reviews. In these papers new approaches to construction of the indole ring systems are presented, as well as new variants and modifications of the classical indole synthesis and numerous ways of introduction of substituents into indoles. Most of the modern methods of indole synthesis use transition metal-catalyzed reactions.[1–4] Although these methods are efficient and versatile they suffer substantial disadvantage – the products contain residual quantities of transition metals. These quantities are really minute, but cannot be accepted in pharmaceutical products and in compounds for biological investigation, thus laborious purification procedures are necessary.[5]

Several years ago we have introduced a few methods of construction of indole ring system based on nucleophilic substitution of hydrogen in nitroarenes (S_NArH).[6–10] These simple, efficient, and versatile methods open a wide avenue for the synthesis of indoles bearing a variety of substituents in both aromatic and heteroaromatic rings, as well as for obtaining of azaindoles and indoles condensed with other ring systems. Moreover, the products do not contain residual transition metals, and thus do not need meticulous purification.

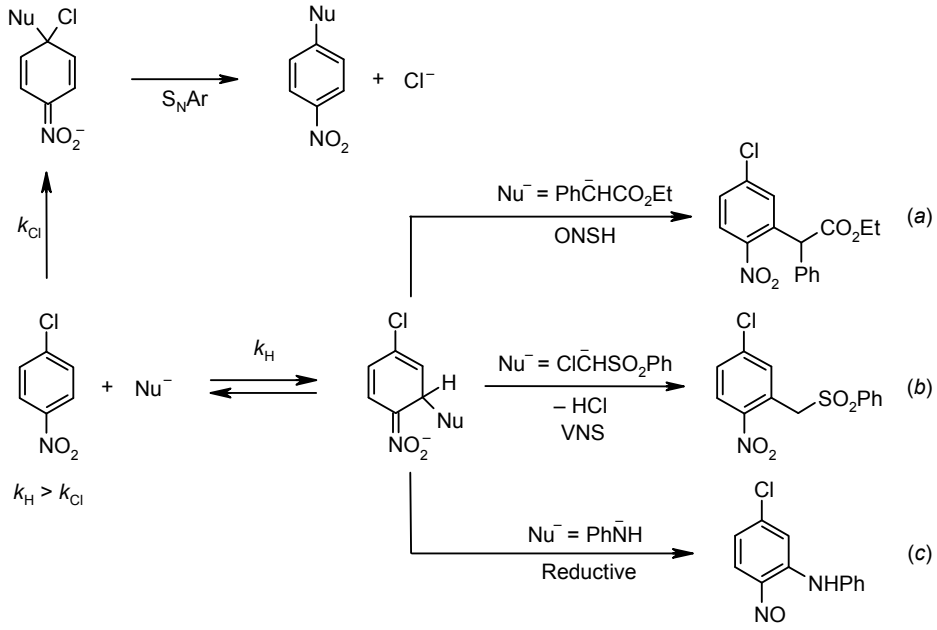
Although great value and versatility of these methods were presented in many our original papers and reviews[11–14] they do not have found wide application they deserve. In this updated review we wish to present basic concepts and examples of the indole synthesis on the basis of S_NArH reactions.

Nucleophilic substitution of hydrogen in nitroarenes (a short outline)

Nucleophiles can react with nitroarenes in a variety of ways, the most important of them being addition to the electron-deficient rings at positions occupied by halogens or hydrogen to form σ^X- and σ^H-adducts, respectively.[15] Fast, spontaneous departure of halogen from the σ^X-adducts results in formation of products of S_NAr reactions. However, the addition at positions occupied by hydrogen proceeds much faster, hence the σ^H-adducts are the initially formed intermediates. Since hydride anions are unable to depart spontaneously from the σ^H-adducts they dissociate to the educts; thus this addition mode is a reversible process, and, therefore, the slower formation of the σ^X-adducts and the S_NAr reaction can proceed. Nevertheless under proper conditions the σ^H-adducts can be converted further in a few ways into products of nucleophilic aromatic substitution of hydrogen. These reactions can proceed provided the conversion of σ^H-adducts is a fast process. As a consequence, S_NArH proceeds faster than conventional S_NAr.

Here and further the corresponding author is marked with *.

Scheme 1



Three most important ways of conversion of σ^H-adducts into products of S_NArH are (Scheme 1): oxidation (oxidative nucleophilic substitution of hydrogen, ONSH) (*a*),[16] elimination of HL (for example HCl) when nucleophiles contain a nucleofugal group L (for example Cl) at the nucleophilic center, the process known as vicarious nucleophilic substitution (VNS) (*b*),[17a] and conversion to nitrosoarenes upon protonation or action of Lewis acids according to intramolecular redox stoichiometry (*c*).[18] Detailed discussion of general character, many variants and mechanisms of these reactions is presented in recent reviews[15,19,20] and monograph.[21]

Construction of indoles *via* nucleophilic substitution of hydrogen in nitroarenes

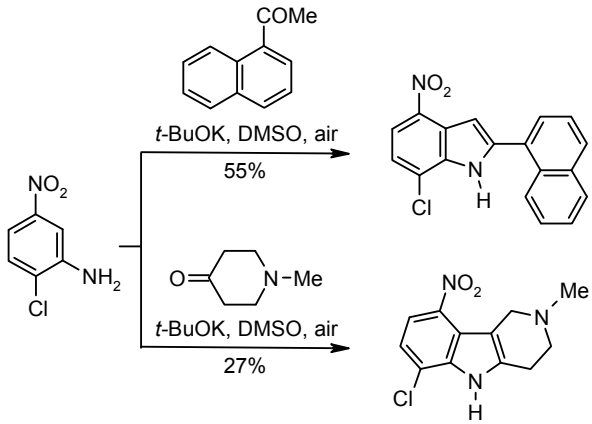
Construction of the indole ring *via* S_NArH reactions consists in introduction of the functionalized carbon substituents into nitroaromatic ring followed by intramolecular reactions to form heterocyclic rings. When in nitroarene there is an amino or a masked amino group as in *meta*-nitroaniline or its analogs, the nitrogen of the amino group takes part in the formation of the indole ring. In other cases the nitrogen of the nitro group becomes the indole nitrogen.

Indoles from *meta*-nitroanilines

The synthesis of 4- and 6-nitroindoles *via* the direct reaction of *meta*-nitroanilines with ketone enolates is undoubtedly the simplest and the most efficient in terms of simplicity and atom economy. This method of the indole moiety construction, exemplified in Scheme 2, is of general character, considering ketones and *meta*-nitroanilines, which can bear a variety of substituents.[7,22] A great variety of substituted indoles, including cycloalkeno[*b*]indoles, tetrahydrocarbazoles, and tetrahydrocarbolines, can be synthesized by this very simple reaction (Scheme 2).[22]

The reaction proceeds *via* addition of the enolate anion to the nitroaromatic ring in vicinity of the amino group and

Scheme 2



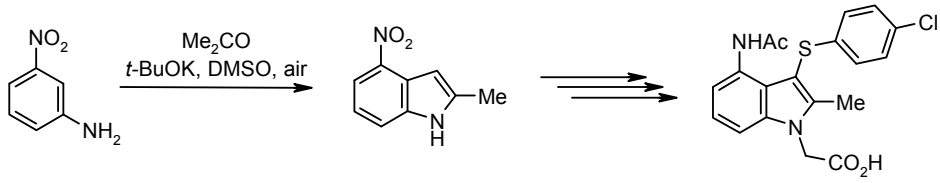
oxidation of the σ^H-adducts by atmospheric oxygen. Further Baeyer type condensation of the produced amino-ketones gives indoles.

In spite of simplicity and versatility of the direct indole synthesis from *m*-nitroanilines and alkyl ketones, there have been only few reports on application of this reaction to the synthesis of compounds of biological interest.[23–25] For example, the starting 2-methyl-4-nitroindole was obtained from *meta*-nitroaniline and acetone (Scheme 3) in one of the variants of synthesis of AZD1981, a potential therapeutic agent in respiratory diseases.[23]

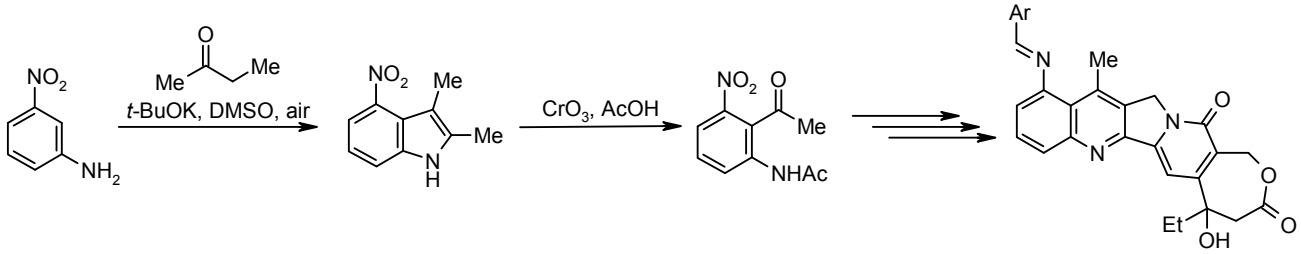
Another example is the synthesis of 2-acetamino-6-nitro-acetophenone, a starting material in the synthesis of homo-camptothecin derivatives, potential inhibitors of DNA topoisomerase I,[25] *via* oxidation of 2,3-dimethyl-4-nitro-indole, obtained from *meta*-nitroaniline and 2-butanone (Scheme 4).[22]

Similarly carbanions generated from alkyl nitriles react with *meta*-nitroanilines to produce 2-amino-4- or 2-amino-6-nitroindoles. For example, the reaction of *meta*-nitroaniline with acetonitrile leads to 2-amino-4-nitro-

Scheme 3

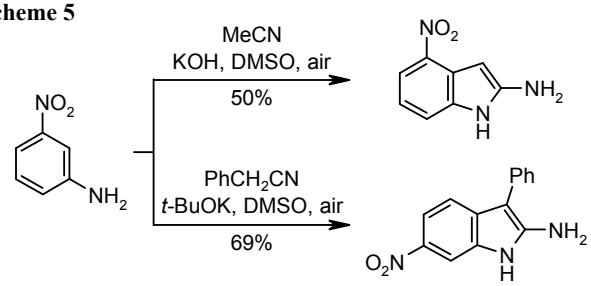


Scheme 4



indole. Analogous reaction of phenylacetonitrile provides 6-nitroindole derivative (Scheme 5).[26] In both reactions the intermediate σ^H-adducts are oxidized by atmospheric oxygen to form the corresponding 2-aminonitrophenylacetonitriles which undergo intramolecular cyclization.

Scheme 5



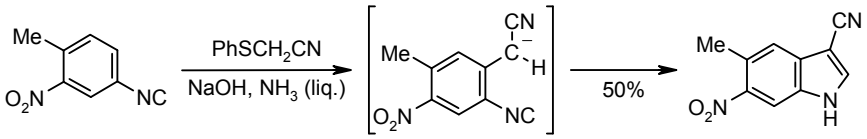
meta-Nitroanilines can be readily transformed into *meta*-nitrobenzoisonitriles. Upon treatment with carbanions of sulfones and nitriles bearing good leaving groups these isonitriles enter VNS reaction to give *ortho*-isocyanobenzyl sulfones and cyanides in the form of carbanions. Under the reaction conditions, the carbanions add to the isocyano group to form substituted indoles (Scheme 6).[8]

Intramolecular ONSH of carbanions of alkanoic acid *meta*-nitroanilides leads to 1,3-dialkyl-4-nitrooxindoles.[27] These oxindoles can be also obtained from nitroanilides of α-chloroalkanoic acids *via* intramolecular VNS reaction (Scheme 7).[28]

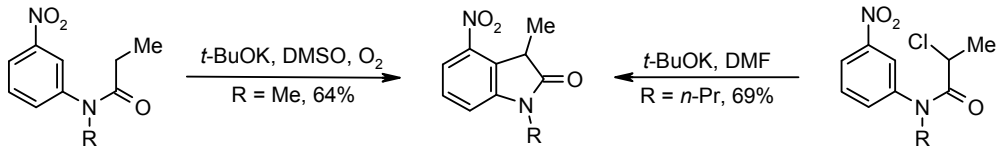
Direct synthesis of indoles from nitroarenes and carbanions

Bicyclic nitroarenes – nitronaphthalenes[29,30] and nitroquinolines[30] – react with some allylic carbanions to form condensed *N*-hydroxyindoles. For instance, phosphonium ylide, generated from allyl triphenylphosphonium chloride in the presence of 1,8-diazabicyclo[5.4.0]undec-8-ene (DBU) and titanium tetraisopropoxide, adds to 1-nitronaphthalene or 5-nitro-8-methoxyquinoline to form *N*-hydroxyindole derivative (Scheme 8).[30]

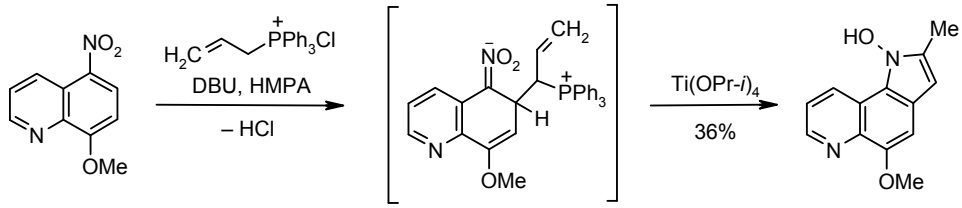
Scheme 6



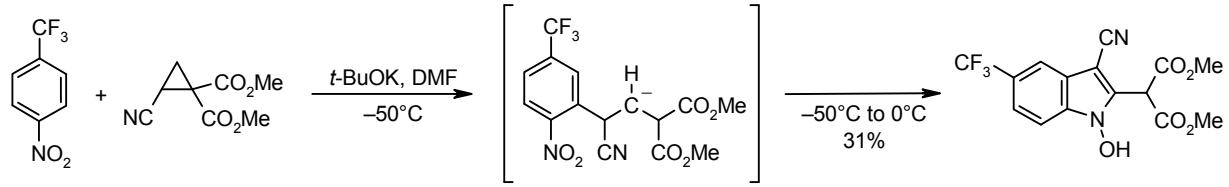
Scheme 7



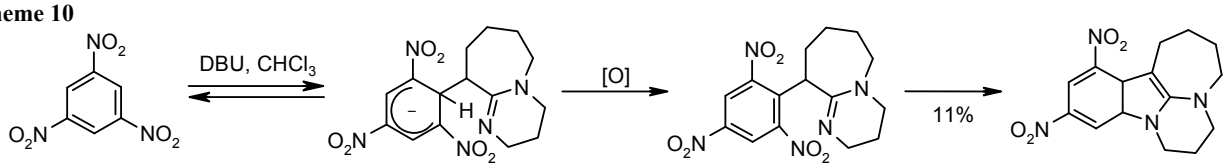
Scheme 8



Scheme 9



Scheme 10



A peculiar example of synthesis of *N*-hydroxyindole in the VNS of hydrogen, proceeding *via* a cyclopropane ring opening, is the reaction of carbanion of dimethyl 2-cyanocyclopropane-1,1-dicarboxylate with 1-nitro-4-(trifluoromethyl)benzene. Quenching of the reaction mixture at low temperature provides 4-aryl-4-cyanobutyric acid derivative. But when the reaction mixture is allowed to warm up to 0°C further cyclization to 1-hydroxyindole takes place *via* an intramolecular addition of the carbanion to the nitro group (Scheme 9).[31]

DBU reacts as a C-nucleophile with 1,3,5-trinitrobenzene to form an σ^H-adduct that is oxidized to 2,4,6-trinitrophenylamidine. Further step is the replacement of the nitro group leading to a condensed tetracyclic indole derivative (Scheme 10).[32] In a similar manner DBU reacts with ethyl 3,5-dinitrobenzoate.

Indoles *via* introduction of functionalized substituents in the *ortho* position to the nitro group

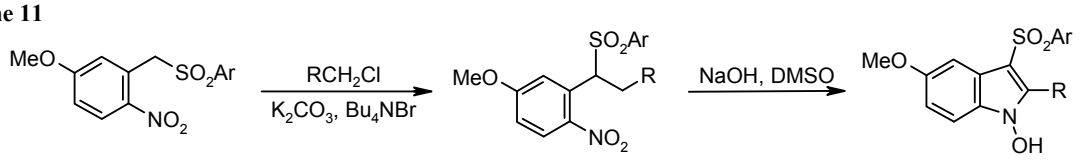
ONSH and, particularly, VNS are efficient tools for introduction of cyanomethyl,[33–35] arenesulfonylmethyl,[17,36,37] and alkoxycarbonylmethyl[38–40] substituents in the *ortho* position to the nitro group of nitroarenes. Introduction of such functionalized carbon substituents provides wide possibilities for the synthesis of indoles. These *ortho*-substituted nitroarenes can be converted into indoles *via* cyclization that directly involves the nitro group or its initial reduction followed by an intramolecular condensation that engages the produced amino group.

Non-reductive transformations of the *ortho*-substituted nitroarenes into indoles

The methylene group in the *ortho*-nitroarylacetonitriles and *ortho*-nitrobenzyl(aryl)sulfones are readily alkylated with allyl and benzyl halides under mild liquid-solid phase-transfer catalysis conditions. The products are converted into substituted *N*-hydroxyindoles upon treatment with basic agents under various conditions. Examples of these reactions and the hypothetical mechanisms are presented in Schemes 11, 12. By this approach 5-methoxy-2-nitrobenzyl aryl sulfones are transformed into 2-substituted 1-hydroxy-3-(arenesulfonyl)-indoles in good yields (Scheme 11).[41] Similar reactions of 2-nitroarylacetonitriles lead to the corresponding 2-phenyl- or 2-vinyl-substituted 3-cyano-1-hydroxyindoles (Scheme 12).[41]

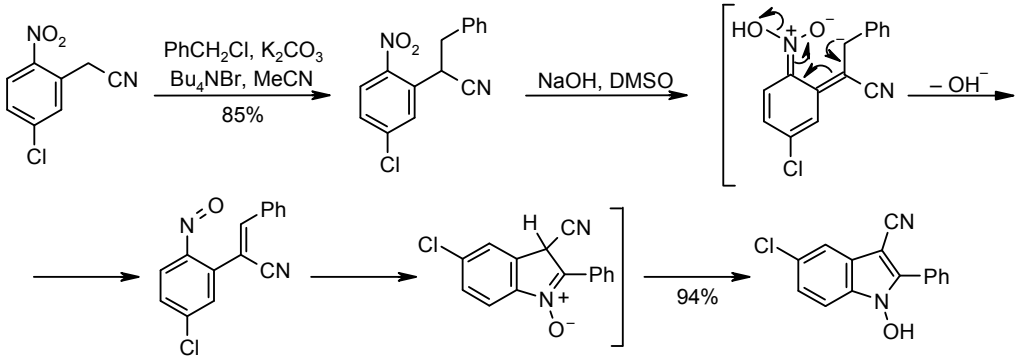
Alkylation of *ortho*-nitroarylacetonitriles with allyl or benzyl halides followed by treatment of the obtained compounds with a base and silylating agents in aprotic medium or with a base in protic solvent results in 3-cyano-1-hydroxy-2-vinylindoles. For example, alkylation of *ortho*-

Scheme 11

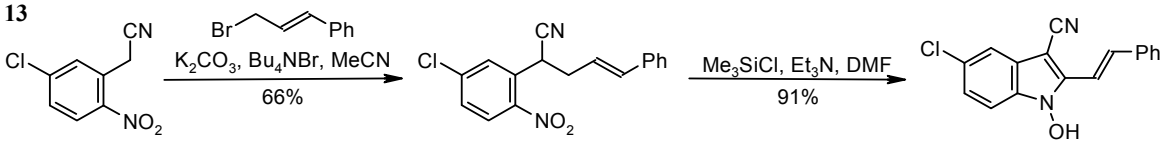


Ar = 4-MeC_6H_4; R = CH=CH_2 (69%);
Ar = Ph; R = Ph (94%)

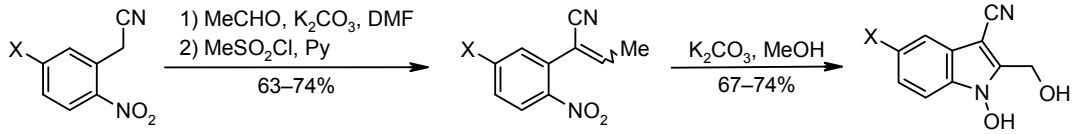
Scheme 12



Scheme 13

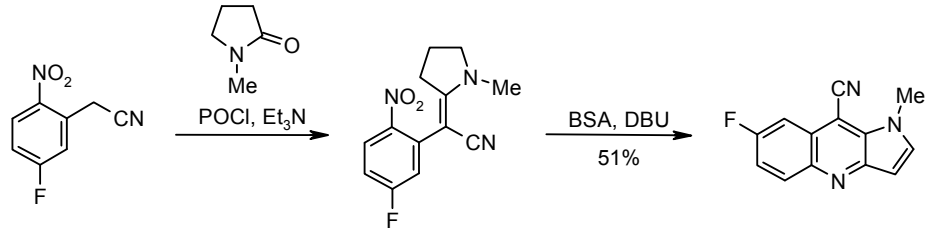


Scheme 14



X = F, Cl, Br

Scheme 15



nitroarylacetonitrile with 3-phenylallyl bromide gives an adduct that in the presence of chlorotrimethylsilane and triethylamine undergo cyclization into 3-cyano-1-hydroxy-2-vinylindole as exemplified in Scheme 13.[42]

Similar transformations as a way to indoles were later reported for 2-nitrophenyl cyanoacetates and malonates. They are, however, less convenient because the starting materials were obtained by S_NAr of fluorine in *ortho*-fluoronitroarenes.[43] Alkyl *ortho*-nitroarylacetates, *ortho*-nitroarylacetonitriles, and *ortho*-nitrobenzyl sulfones enter condensation with aliphatic aldehydes to give the corresponding alkylidene derivatives.[44–47] Treatment of these alkylidene nitriles with a base results in cyclization to indoles (Scheme 14).[48]

Vilsmeier reagent prepared from *N*-methylpyrrolidinone was employed as a precursor of pyrrole ring in pyrrolo[3,2-*b*]-quinoline system. The reaction of *ortho*-nitroarylaceto-nitriles with this reagent led to alkylidene derivative that cyclized in the presence of diazabicycloundecene and bis(tri-methylsilyl)acetamide (BSA) (Scheme 15).[49]

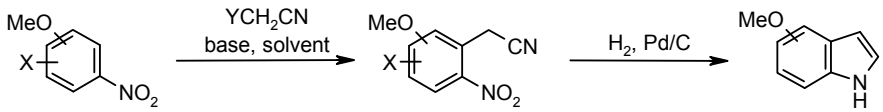
Synthesis of indoles *via* reduction of the nitro group in *ortho*-substituted nitroarenes

Indoles from 2-nitroarylacetonitriles

Synthesis of indoles *via* catalytic hydrogenation of 2-nitro-arylacetonitriles has been well known for many years.[50] It was, however, of a limited value, because *ortho*-nitro-arylacetonitriles were not easily available. Facile synthesis of *ortho*-nitroarylacetonitriles *via* the VNS methodology has opened a wide avenue to synthesis of substituted indoles. There is practically no limitation of this reaction in terms of substituents present in the nitroarene moiety. Moreover, chlorine or bromine substituents in the nitroaromatic ring not only increase electrophilicity of nitroarenes,[51] thus improving effectiveness of the VNS reactions, but also prevent introduction of cyanomethyl substituent into undesired positions.[6,52] These auxilary substituents can be subsequently removed during hydrogenation. To show versatility of this approach to indoles we performed the synthesis of all isomeric 4-, 5-, 6-, and 7-methoxy-substituted indoles *via* the VNS cyano-methylation of isomeric nitroanisoles and their halogenated derivatives (Scheme 16).[6]

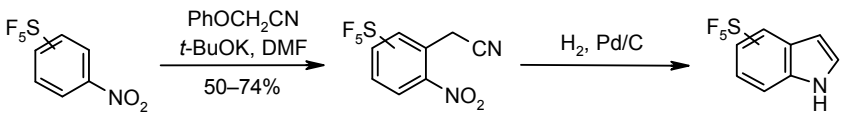
Similarly, VNS cyanomethylation of benzyl nitro-phenyl ethers, eventually containing halogens in the nitro-phenyl ring followed by hydrogenation and simultaneous removal of the benzyl group and halogens provided hydroxyindoles.[6,52] Recently the VNS cyanomethylation followed by hydrogenation has been used for synthesis of indoles containing pentafluorosulfanyl substituents (Scheme 17).[53]

Scheme 16



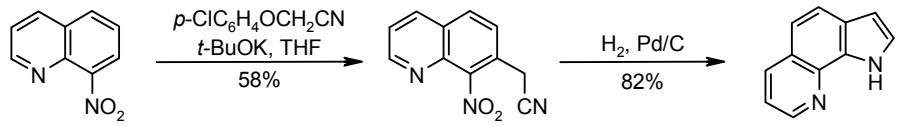
X = H, Cl, Br; Y = *p*-ClC_6H_4O, R_2NCS_2; base: NaOH, *t*-BuOK; solvent: DMSO, DMF

Scheme 17

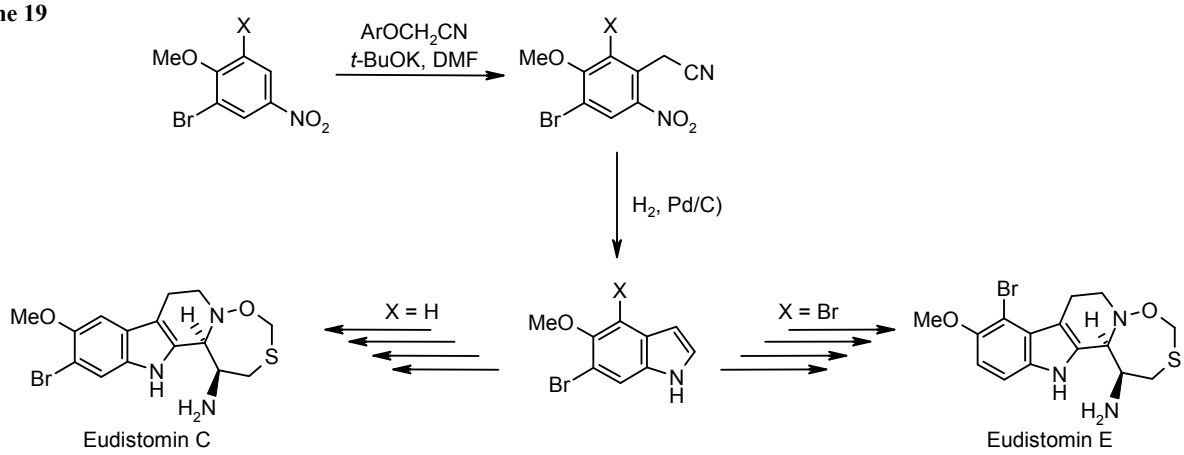


5-SF_5 (69%)
6-SF_5 (50%)

Scheme 18



Scheme 19



Cyanomethylation of nitronaphthalenes[34,54] and nitroquinolines[55–57] offers an access to cyanomethyl derivatives that upon reduction provide benzoindoles[41,58] and pyrroloquinolines,[57] respectively, as exemplified in Scheme 18.

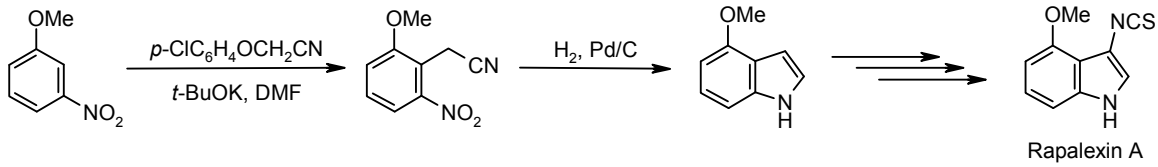
Eudistomins C and E, antiviral alkaloids of marine origin, contain 5-methoxyindole fragment. Most conveniently these indole units were prepared from appropriate bromonitroanisols *via* vicarious nucleophilic substitution with aryloxyacetonitriles followed by catalytic reduction (Scheme 19).[59]

The VNS reaction of 3-nitroanisole and 1-benzyloxy-3-nitrobenzene with 4-chlorophenoxyacetonitrile proceeds in the most hindered position 2.[6,60] 6-Methoxy-2-nitrophenylacetonitrile thus obtained was then reduced and converted into 4-methoxyindole, which was then transformed in three steps into rapalexin A, an unusual isothiocyanate alkaloid derived from *Brassica rapa* (Scheme 20).[61]

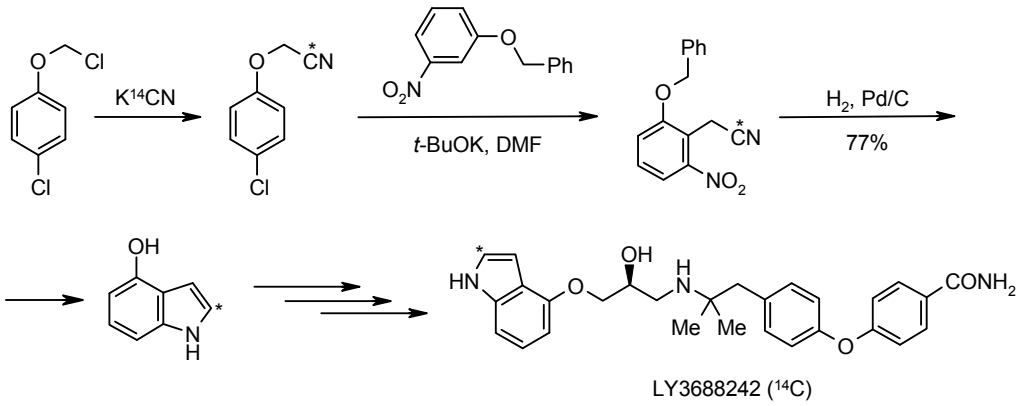
On the other hand, 2-benzyloxy-6-nitrophenylacetonitrile upon catalytic hydrogenation gives 4-hydroxyindole.[6] When the cyano group in 4-chlorophenoxyacetonitrile was labeled with ^{14}C 4-hydroxyindole labeled at position 2 was obtained and used as intermediate for the synthesis of a labeled pindolol analog LY3688242 (Scheme 21).[62]

1-Methoxybrassanin is one of natural defence compounds produced by plants of the family *Cruciferae*. In studies of metabolic pathways of these alkaloids the required 4,5,6,7-tetradeutero-1-methoxybrassanin was synthesized from 4,5,6,7-tetradeuteroindole. This labelled indole was obtained *via* VNS in perdeuteronitrobenzene

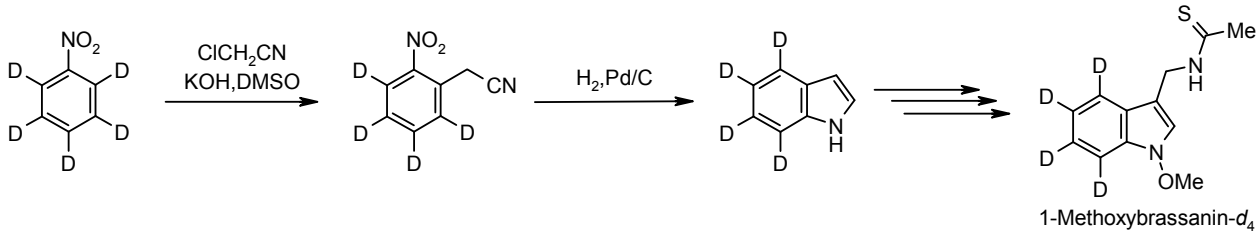
Scheme 20



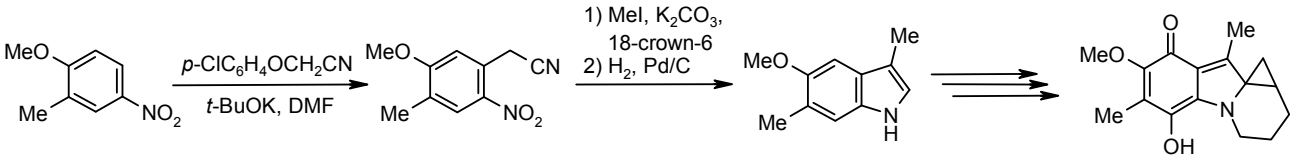
Scheme 21



Scheme 22



Scheme 23



with chloroacetonitrile followed by catalytic reduction of the deuterated 2-nitrophenylacetonitrile (Scheme 22).[63]

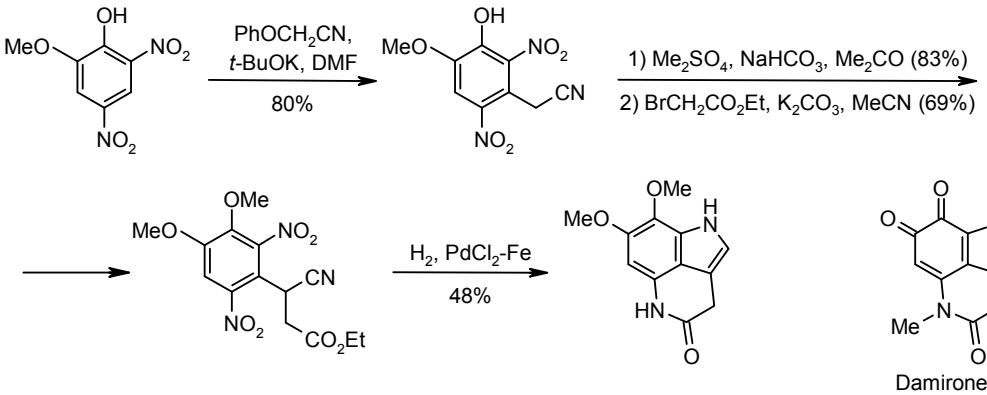
Ortho-nitroaryl-substituted acetonitriles are relatively strong CH acids, and their *C*-alkylation followed by hydrogenation leads to 3-substituted indoles.[6] 3,6-Dimethyl-5-methoxyindole prepared *via* the VNS cyanomethylation of 4-methoxy-3-methylnitrobenzene has been used as starting material for the synthesis of cyclopropano-annulated quinone methide (Scheme 23).[64]

It has been shown earlier, that VNS in 2,4-dinitrophenol proceeds regioselectively at the most hindered position 3 due to electronic configuration of the dinitrophenolate anion.[65] This orientation pattern has been employed for the synthesis of the precursor of damirone B from dinitroguaiacol, in which cyanomethylation proceeds exclusively at position 5 to form upon *O*-methylation 3,4-dimethoxy-2,6-dinitrophenylacetonitrile. Further alkylation of the nitrile carbanion with ethyl bromoacetate and hydrogenation provides the skeleton of damirone tricyclic system (Scheme 24).[66,67]

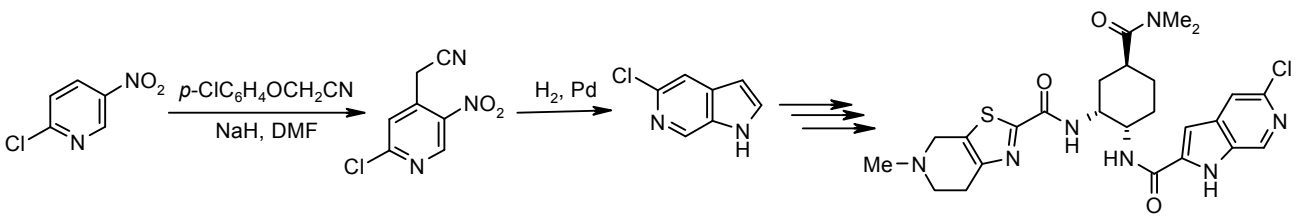
The VNS cyanomethylation of 3-nitropyridines and subsequent hydrogenation of the so formed *ortho*-nitropyridylacetonitriles is a convenient way of the synthesis of 4- and 6-azaindoles, which have found numerous applications in the synthesis of potentially biologically active compounds.[68–75] The VNS of hydrogen in 2-chloro-5-nitropyridine using chlorophenoxyacetonitrile provides a nitropyridylacetonitrile which upon catalytic reduction cyclized to 5-chloro-6-azaindole (Scheme 25), a key starting material for the synthesis of a potential Xa factor inhibitor.[76]

Methoxynitropyridylacetonitrile, the key intermediate in the synthesis of 5-azamelatonin, was obtained by the VNS

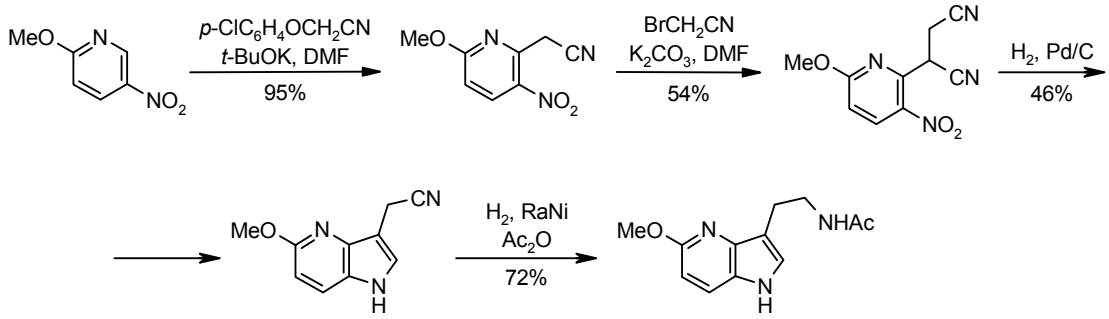
Scheme 24



Scheme 25



Scheme 26



of hydrogen in 2-methoxy-5-nitropyridine with the carbanion of aryloxyacetonitrile. Further steps included alkylation of the obtained pyridylacetonitrile with bromoacetonitrile followed by a two-step reduction and acylation (Scheme 26).[77]

Indoles from 2-nitrobenzyl sulfones

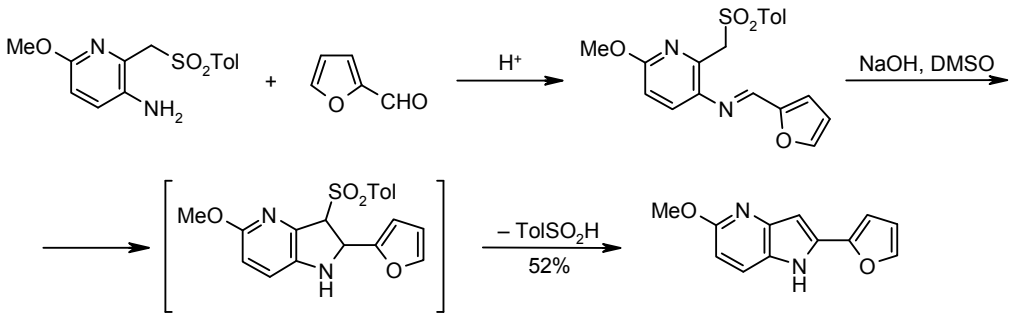
VNS reactions of nitroarenes with the carbanions of chloromethyl aryl sulfones lead to *ortho*-nitrobenzyl aryl sulfones.[17b,36,56,78] This procedure is particularly useful due to the possibility to direct the VNS reaction selectively in *ortho* position to the nitro group when the reaction is carried out in *t*-BuOK/THF (Scheme 29).[17b] Contrary to what is the case with *ortho*-nitroarylacetonitriles, the reduction of the nitro group in *ortho*-nitrobenzyl aryl sulfones proceeds without cyclization, and the *ortho*-aminobenzyl sulfones can be isolated and converted into indoles in separate operations. These sulfones upon conversion of the amino group into imine,[10] imidate,[9,79,80] or isonitrile[81] functionality undergo cyclization into substituted indoles.

ortho-Aminobenzyl sulfones react with aromatic aldehydes furnishing Schiff bases. These imines upon treatment with a base cyclize to 3-arenesulfonylindolines that eliminate toluenesulfinate to form 2-areneindoles. This approach gives access to arene- and heteroarene indoles difficult to obtain by other methods as exemplified in Scheme 27.[10]

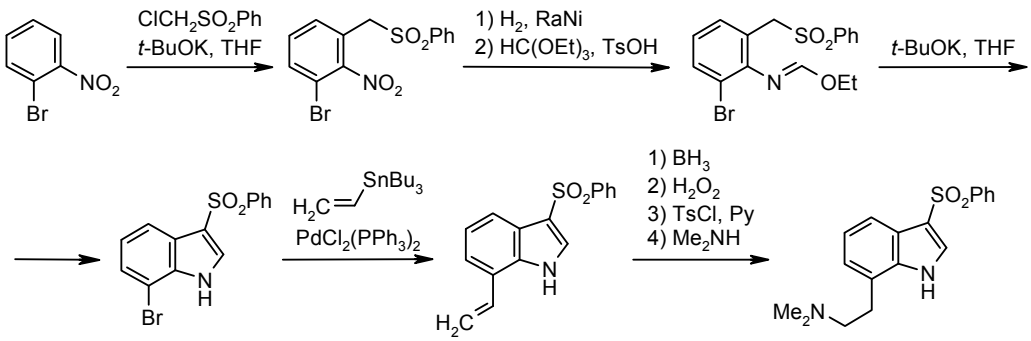
Conversion of such aminobenzyl sulfones into imidates in an acid-catalyzed reaction with orthoesters followed by base-induced intramolecular addition-elimination produces 3-arenesulfonylindoles.[9] This approach was used for the synthesis of 5- and 7-bromo-3-sulfonylindoles that were subsequently used in the synthesis of compounds for biological testing (Scheme 28).[79]

Alternatively, *N*-substituted 3-phenylsulfonylindoles have been synthesized *via* a reductive *N*-alkylation of *ortho*-aminobenzyl sulfones with ketones followed by conden-

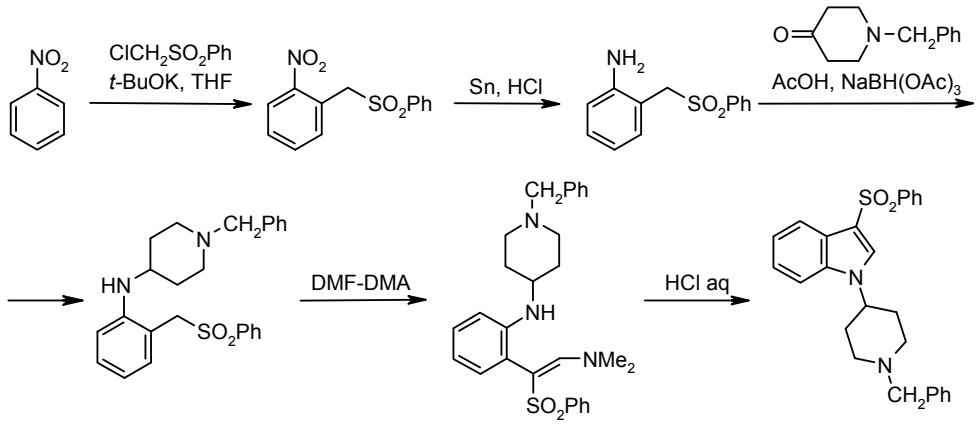
Scheme 27



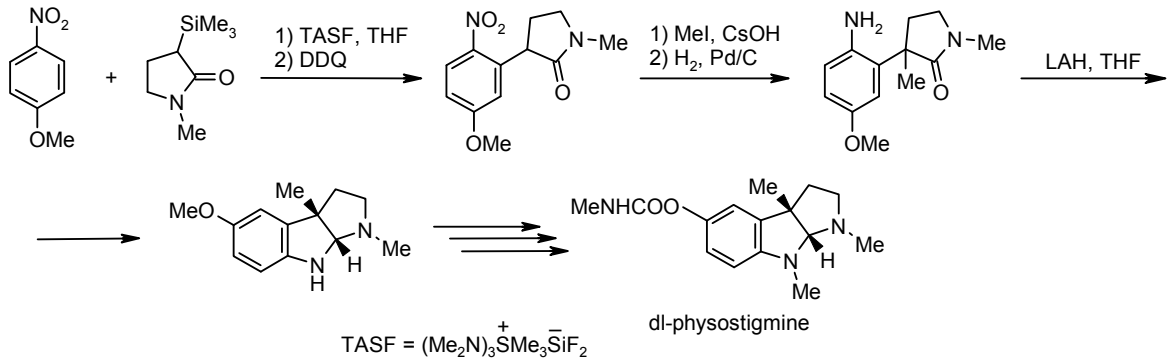
Scheme 28



Scheme 29



Scheme 30



sation with dimethyl formamide dimethylacetal (DMF-DMA) and cyclization (Scheme 29).[80]

Indoles can be also obtained *via* simple transformation of an amino group into an isocyano group followed by a base-induced addition of a carbanion, stabilized by a sulfonyl group, to the isocyano group[81] in a way analogous to the reaction shown in Scheme 6.

Other reductive cyclizations leading to indoles

In the synthesis of physostigmine, the required pyrroloindole skeleton was obtained in a few steps starting from oxidative substitution of hydrogen in *para*-nitroanisole by *N*-methylpyrrolidinone carbanion (Scheme 30).[82]

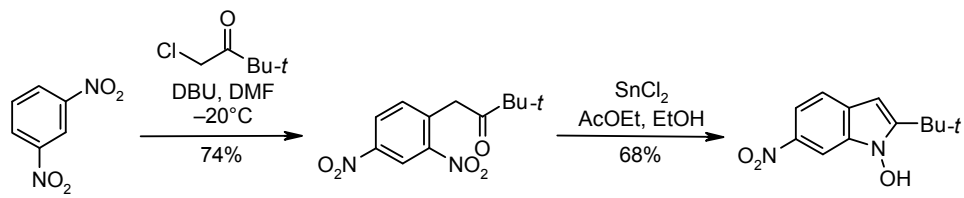
meta-Dinitrobenzene reacts with carbanions of α-halo ketones following the VNS mechanism to form 2,4-dinitrobenzyl ketones, which can be reduced with tin(II) chloride to give 1-hydroxy-6-nitroindoles (Scheme 31).[83]

Oxindoles and azaoxindoles

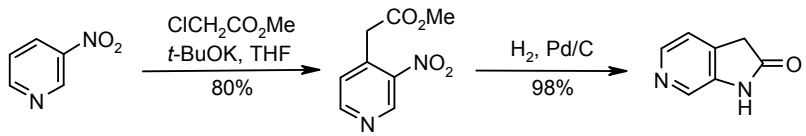
2-Nitroarylacetates are convenient precursors to the synthesis of oxindoles *via* simple reduction of the nitro group and intramolecular formation of amide. VNS with alkyl α-chloroalkanoates solves the problem of availability of these starting materials.[38] The VNS reaction of 3-nitropyridine with methyl chloroacetate under basic conditions furnishes ethyl nitropyridyl acetates which upon catalytic hydrogenation cyclize to azaoxindoles (Scheme 32).[84–86]

The VNS reaction of nitrobenzene with ethyl α-chloropropionate proceeds in the *para* position of the benzene ring.[87] The formed carbanion of 4-nitrophenylpropionate

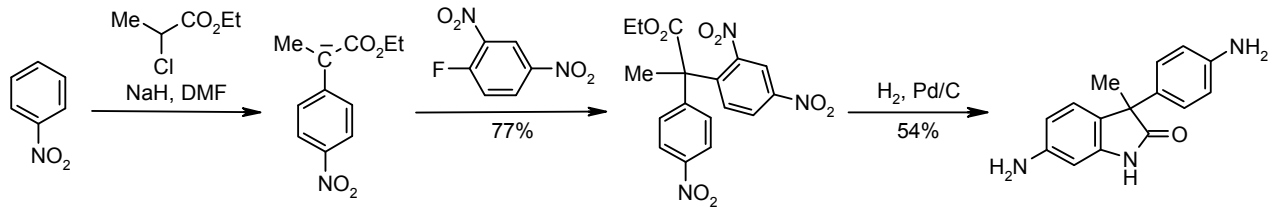
Scheme 31



Scheme 32



Scheme 33



can *in situ* substitute fluorine atom in subsequently added 1-fluoro-2,4-dinitrobenzene to form 2,4,4'-trinitrodiarylpropionate, which upon hydrogenation is transformed into an 3-aryloxindole derivative (Scheme 33).[88,89]

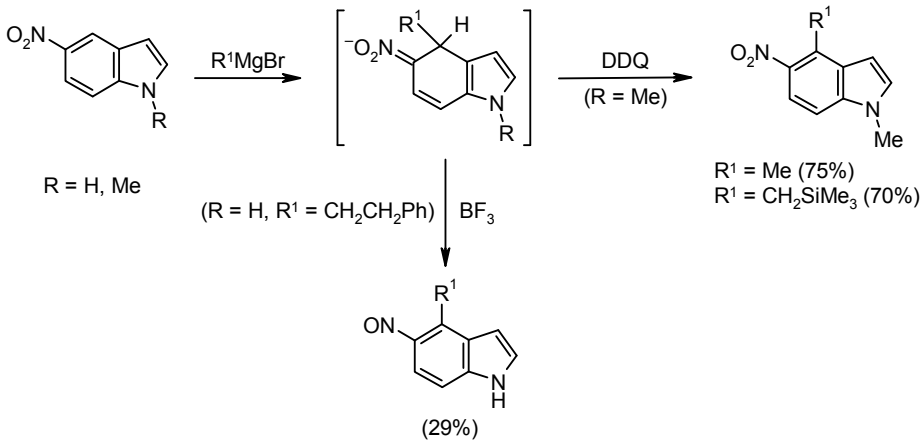
Modification of indoles *via* S_NArH reactions

Introduction of carbon substituent

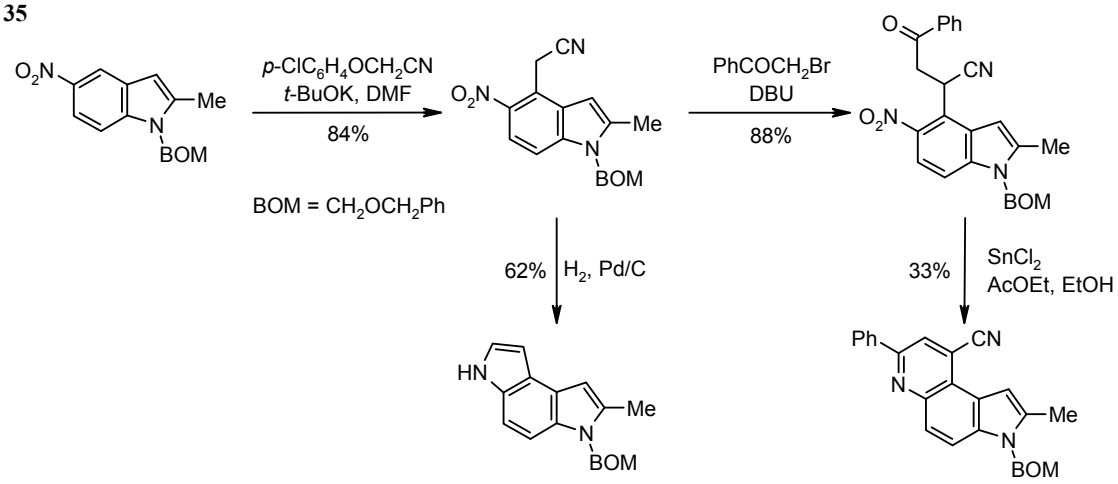
Alkyl substituents can be introduced into 5-nitroindoles by direct action of alkylmagnesium halides. The resulting σ^H-adducts when quenched with BF_3 transformed into 4-alkyl-5-nitrosoindoles,[90] but when the σ^H-adducts were subjected to oxidation with DDQ the corresponding nitro compounds were obtained (Scheme 34).[91,92]

1-Alkyl-5- and 1-alkyl-6-nitroindoles undergo the VNS substitution of hydrogen at positions 4 and 7, respectively, by action of chloromethyl sulfones and (4-chlorophenoxy)-acetonitrile to give the corresponding VNS products in high yields.[93] Catalytic reduction of the obtained cyanomethylnitroindoles provides condensed pyrroloindoles as exemplified by the synthesis of pyrrolo[3,2-*e*]indole shown in the Scheme 35.[94] A versatile synthesis of pyrrolo-annulated quinolines has been reported *via* alkylation of the VNS products, *ortho*-nitroindolylacetonitriles, with α-bromo ketones. The obtained ketonitriles can be reduced under mild conditions with tin(II) chloride in ethyl acetate–ethanol mixture to quinoline-4-carbonitriles.[95] The same reaction sequence has been applied to (nitroindol-4-yl)- and (nitroindol-5-yl)acetonitriles to obtain tricyclic 4-cyano-2-phenyl derivatives of pyrrolo[3,2-*f*]- and pyrrolo[2,3-*h*]-quinolines (Scheme 35).[95]

Scheme 34

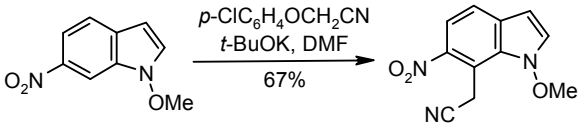


Scheme 35



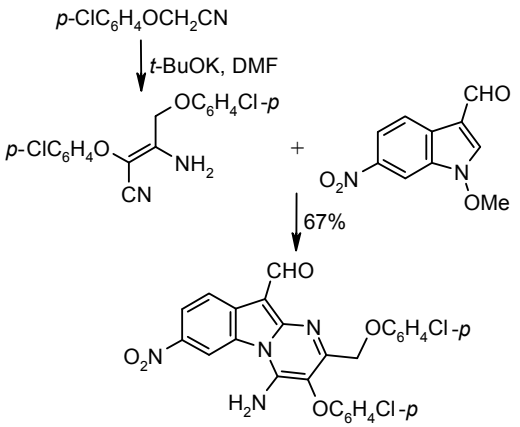
1-Methoxy-6-nitroindole react with aryloxyacetonitrile similarly to 1-alkyl derivatives giving the expected 7-indolylacetonitrile (Scheme 36).[96–98]

Scheme 36



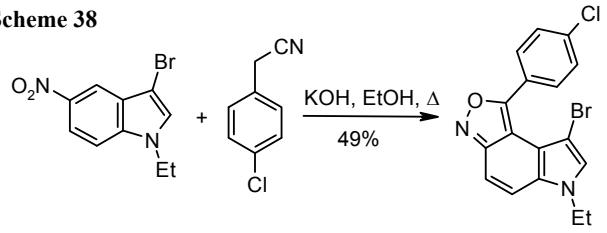
Unusual reaction course was observed when 1-methoxy-6-nitroindole-3-carbaldehyde was treated with this 4-chlorophenoxyacetonitrile-derived carbanion. Instead of the expected substitution of hydrogen at position 7 (as in Scheme 36), a multistep process resulting in formation of pyrimido[1,2-*a*]indole derivative occurred (Scheme 37).[97,98] The process started from the Thorpe condensation of the aryloxyacetonitrile, followed by a *cine* substitution of the *N*-methoxy group and cyclization.

Scheme 37



1-Alkyl-3-bromo-5-nitroindoles react with phenylacetonitriles in the presence of KOH in ethanol to form isoxazolo[4,3-*e*]indoles as exemplified in Scheme 38.[99]

Scheme 38



Reactions of indole and indolyl anions

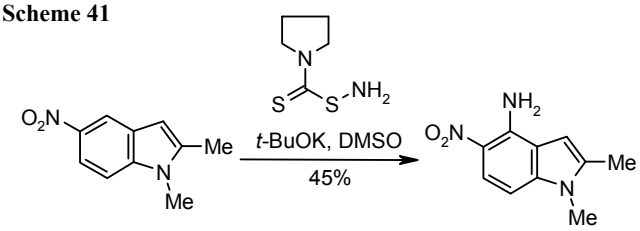
Indolyl-3-acetonitrile carbanions react with nitro derivatives of bicyclic heterocycles, imidazo[1,2-*a*]pyridine[100] and 5-nitrobenzimidazole,[101] to form highly fluorescent pentacyclic heterocycles (Scheme 39).

Indole anions react with nitroarenes to form 3-(nitroaryl)-indoles following oxidative nucleophilic substitution of hydrogen (Scheme 40).[102]

Amination of indoles

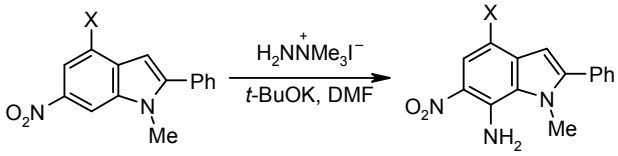
1,2-Dimethyl-5-nitroindole was aminated with *N*-tetramethylenethiocarbamoylsulfenamide to form the corresponding 4-amino derivative in moderate yield (Scheme 41).[103]

Scheme 41



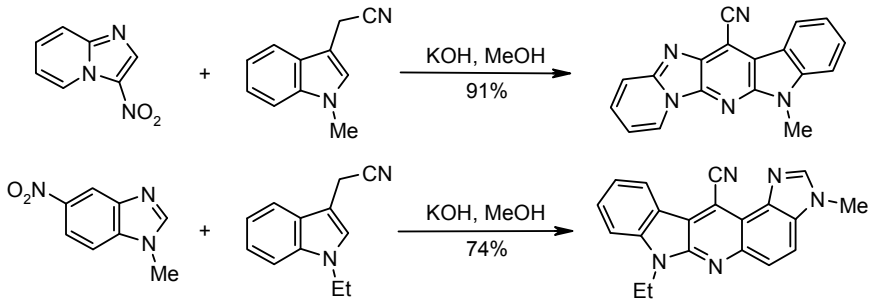
4,6-Dinitroindole derivatives were aminated with trimethylhydrazinium iodide in the presence of *t*-BuOK to form 7-amino-4,6-dinitroindole derivatives (Scheme 42).[104–106]

Scheme 42

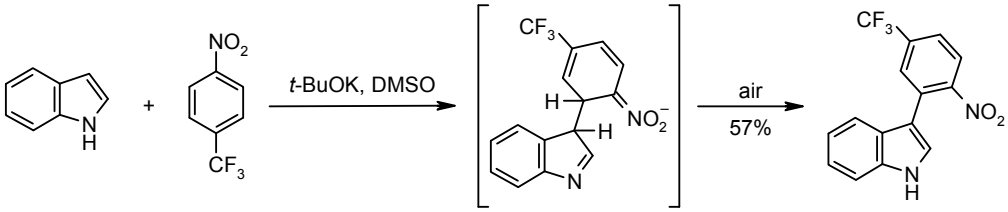


X = NO_2 (88%)
X = *t*-$BuSO_2$ (90%)

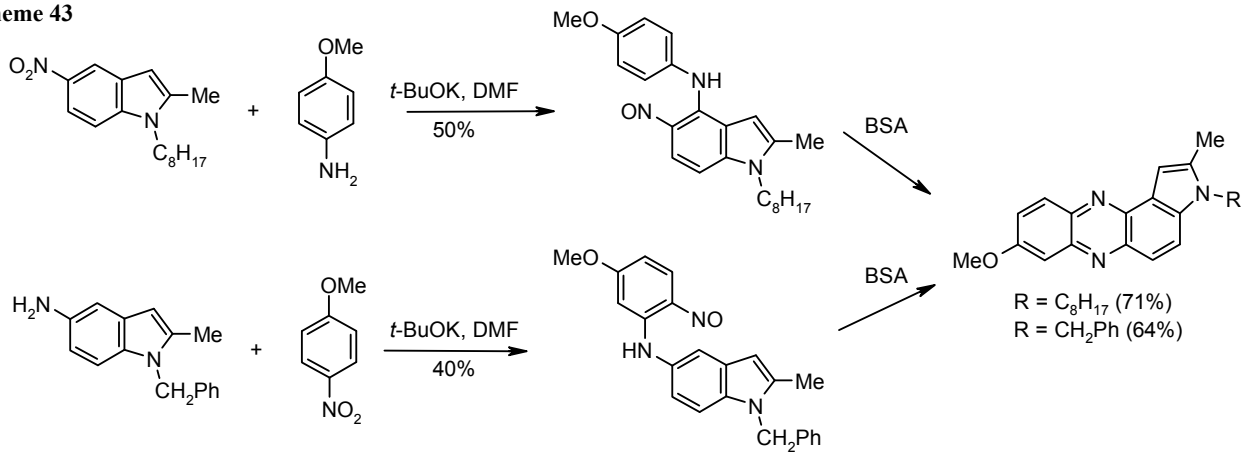
Scheme 39



Scheme 40



Scheme 43



It has recently been found in our laboratory that anilines react with nitroarenes in the presence of a strong base to form 2-nitrosodiphenylamines.[107] The reaction proceeds *via* the addition of the *N*-anion of anilines to nitroarenes in the position *ortho* to the nitro group, followed by conversion of the resulting σ^H-adduct according to the intramolecular redox stoichiometry. The reaction is of general character; thus, a variety of 2-nitrosodiphenylamines become readily available.[18] These compounds upon treatment with acetic acid cyclize to phenazines in high yields. This two-step process is analogous to, but much more efficient than the classic Wohl–Aue synthesis of phenazines.[108]

The availability of nitroarenes and anilines opens almost unlimited simple and efficient access to phenazines, as well as to their derivatives condensed with an additional ring. The versatility of this methodology is demonstrated by the synthesis of pyrrolo[3,2-*a*]phenazines from two properly chosen pairs of nitroarene and arylamine: 5-nitroindole derivative and *p*-anisidine or 5-aminoindole and *p*-nitroanisole, respectively. In these instances, the cyclization was performed with bis-(trimethylsilyl)acetamide (BSA) (Scheme 43).[109]

Conclusions

In this review we have presented numerous ways to construct indole derivatives *via* nucleophilic substitution of hydrogen. It has been shown that this approach is one of the simplest, most versatile, and efficient ways to such ring systems, which can easily be adopted for large-scale operations. Another advantage of this methodology, in contrast to the majority of modern methods, is that no transition metals are used, so the troublesome removal of their impurities from the final products is not necessary.[5]

References

1. Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Org. React. (Hoboken, NJ, U. S.)* **2012**, *76*, 281.
2. Yoshikai, N.; Wei, Y. *Asian J. Org. Chem.* **2013**, *2*, 466.
3. Li, J. J.; Gribble, G. W. *Top. Heterocycl. Chem.* **2010**, *26*, 193.
4. Guo, T.; Huang, F.; Yu, L.; Yu, Z. *Tetrahedron Lett.* **2015**, *56*, 296.
5. Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889.
6. Mąkosza, M.; Danikiewicz, W.; Wojciechowski, K. *Liebigs Ann. Chem.* **1988**, 203.
7. Moskalev, N.; Mąkosza, M. *Tetrahedron Lett.* **1999**, *40*, 5395.
8. Wojciechowski, K.; Mąkosza, M. *Tetrahedron Lett.* **1984**, *25*, 4793.
9. Wojciechowski, K.; Mąkosza, M. *Synthesis* **1986**, 651.
10. Wojciechowski, K.; Mąkosza, M. *Bull. Soc. Chim. Belg.* **1986**, *95*, 671.
11. Mąkosza, M.; Wojciechowski, K. *Chem. Rev.* **2004**, *104*, 2631.
12. Mąkosza, M.; Wojciechowski, K. In *Selected Methods for Synthesis and Modification of Heterocycles – The Chemistry of Synthetic Indole Systems*, Kartsev, V. G., Ed.; IBS Press: Moscow, 2004, vol. 3, p. 103.
13. Mąkosza, M.; Wojciechowski, K. *Heterocycles* **2014**, *88*, 75.
14. Mąkosza, M.; Wojciechowski, K. *Top. Heterocycl. Chem.* **2014**, *37*, 51.
15. Mąkosza, M. *Chem.–Eur. J.* **2014**, *20*, 5536.
16. Mąkosza, M.; Kamieńska-Trela, K.; Paszewski, M.; Bechcicka, M. *Tetrahedron* **2005**, *61*, 11952.
17. (a) Mąkosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282. (b) Mąkosza, M.; Glinka, T.; Kinowski, J. *Tetrahedron* **1984**, *40*, 1863.
18. Wróbel, Z.; Kwast, A. *Synthesis* **2010**, 3865.
19. Mąkosza, M. *Chem. Soc. Rev.* **2010**, *39*, 2855.
20. Mąkosza, M. *Synthesis* **2011**, 2341.
21. Terrier, F. *Modern Nucleophilic Aromatic Substitution*; Wiley-VCH Verlag: Weinheim, 2013.
22. Moskalev, N.; Barbasiewicz, M.; Mąkosza, M. *Tetrahedron* **2004**, *60*, 347.
23. Sulur, M.; Sharma, P.; Ramakrishnan, R.; Naidu, R.; Merifield, E.; Gill, D. M.; Clarke, A. M.; Thomson, C.; Butters, M.; Bachu, S.; Benison, C. H.; Dokka, N.; Fong, E. R.; Hose, D. R. J.; Howell, G. P.; Mobberley, S. E.; Morton, S. C.; Mullen, A. K.; Rapai, J.; Tejas, B. *Org. Proc. Res. Dev.* **2012**, *16*, 1746.
24. Timofeev, E. N.; Kolganova, N. A.; Smirnov, I. P.; Kochetkova, S. V.; Florentiev, V. L. *Russ. J. Bioorg. Chem.* **2008**, *34*, 201. [*Bioorg. Khim.* **2008**, *34*, 220.]
25. Guo, W.; Miao, Z.; Sheng, C.; Yao, J.; Feng, H.; Zhang, W.; Zhu, L.; Liu, W.; Cheng, P.; Zhang, J.; Che, X.; Wang, W.; Luo, C.; Xu, Y. *Eur. J. Med. Chem.* **2010**, *45*, 2223.
26. Moskalev, N.; Mąkosza, M. *Heterocycles* **2000**, *52*, 533.
27. Mąkosza, M.; Paszewski, M. *Synthesis* **2002**, 2203.
28. Mąkosza, M.; Hoser, H. *Heterocycles* **1994**, *37*, 1701.
29. Wróbel, Z. *Eur. J. Org. Chem.* **2000**, 521.
30. Korda, A.; Wróbel, Z. *Synlett* **2003**, 1465.
31. Stalewski, J. *Tetrahedron Lett.* **1998**, *39*, 9523.
32. Sutherland, J. K. *Chem. Commun.* **1997**, 325.
33. Mąkosza, M.; Winiarski, J. *J. Org. Chem.* **1980**, *45*, 1534.
34. Mąkosza, M.; Winiarski, J. *J. Org. Chem.* **1984**, *49*, 1494.
35. Mąkosza, M.; Wenäll, M.; Goliński, M.; Kinowski, A. *Bull. Pol. Acad. Sci., Chem.* **1985**, *33*, 427.

36. Mąkosza, M.; Goliński, J.; Baran, J. *J. Org. Chem.* **1984**, *49*, 1488.
37. Mudryk, B.; Mąkosza, M. *Tetrahedron* **1988**, *44*, 209.
38. Mudryk, B.; Mąkosza, M. *Synthesis* **1988**, 1007.
39. Mąkosza, M.; Sienkiewicz, K.; Wojciechowski, K. *Synthesis* **1990**, 850.
40. Stahly, G. P.; Stahly, B. C.; Maloney, J. R. *J. Org. Chem.* **1988**, *53*, 690.
41. Wróbel, Z.; Mąkosza, M. *Tetrahedron* **1997**, *53*, 5501.
42. Wróbel, Z.; Mąkosza, M. *Synlett* **1993**, 597.
43. Selvakumar, N.; Khera, M. K.; Reddy, B. Y.; Srinivas, D.; Azhagan, A. M.; Iqbal, J. *Tetrahedron Lett.* **2003**, *44*, 7071.
44. Wróbel, Z.; Kwast, A.; Mąkosza, M. *Synthesis* **1993**, 31.
45. Mąkosza, M.; Tyrała, A. *Synth. Commun.* **1986**, *16*, 419.
46. Söderberg, B. C. G.; Banini, S. R.; Turner, M. R.; Minter, A. R.; Arrington, A. K. *Synthesis* **2008**, 903.
47. Banini, S. R.; Turner, M. R.; Cummings, M. M.; Söderberg, B. C. G. *Tetrahedron* **2011**, *67*, 3603.
48. Wróbel, Z.; Mąkosza, M. *Tetrahedron* **1993**, *49*, 5315.
49. Wróbel, Z.; Wojciechowski, K.; Kwast, A.; Gajda, N. *Synlett* **2010**, 2435.
50. Walker, G. N. *J. Am. Chem. Soc.* **1955**, *77*, 3844.
51. Błażej, S.; Mąkosza, M. *Chem.–Eur. J.* **2008**, *14*, 11113.
52. Lerman, L.; Weinstock-Rosin, M.; Nudelman, A. *Synthesis* **2004**, 3043.
53. Iakobson, G.; Pošta, M.; Beier, P. *Synlett* **2013**, *24*, 855.
54. Jończyk, A.; Kowalkowska, A. *Synthesis* **2002**, 674.
55. Maruoka, H.; Tomioka, Y. *J. Heterocycl. Chem.* **2003**, *40*, 1051.
56. Mąkosza, M.; Kinowski, A.; Danikiewicz, W.; Mudryk, B. *Liebigs Ann. Chem.* **1986**, 69.
57. Vlachou, M.; Tsotinis, A.; Kelland, L. R.; Thurston, D. E. *Heterocycles* **2002**, *57*, 129.
58. Wróbel, Z.; Wojciechowski, K. *Synlett* **2011**, 2567.
59. Yamagishi, H.; Matsumoto, K.; Iwasaki, K.; Miyazaki, T.; Yokoshima, S.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2008**, *10*, 2369.
60. Groszek, G.; Bednarski, M.; Dybala, M.; Filipek, B. *Eur. J. Med. Chem.* **2009**, *44*, 809.
61. Pedras, M. S. C.; Zheng, Q.-A.; Gadagi, R. S. *Chem. Commun.* **2007**, 368.
62. Czeskis, B. A.; Clodfelter, D. K.; Wheeler, W. J. *J. Labelled Compd. Radiopharm.* **2002**, *45*, 1143.
63. Pedras, M. S. C.; Okinyo, D. P. O. *J. Labelled Compd. Radiopharm.* **2006**, *49*, 33.
64. Khdour, O.; Ouyang, A.; Skibo, E. B. *J. Org. Chem.* **2006**, *71*, 5855.
65. Mąkosza, M.; Ludwiczak, S. *J. Org. Chem.* **1984**, *49*, 4562.
66. Mąkosza, M.; Stalewski, J.; Maslennikova, O. *Synthesis* **1997**, 1131.
67. Chackal, S.; Dudouit, F.; Houssin, R.; Hénichart, J.-P. *Heterocycles* **2003**, *60*, 615.
68. Macor, J. E.; Burkhart, C. A.; Heym, J. H.; Ives, J. L.; Lebel, L. A.; Newman, M. E.; Nielsen, J. A.; Ryan, K.; Schulz, D. W. *J. Med. Chem.* **1990**, *33*, 2087.
69. Macor, J. E.; Wehner, J. M. *Heterocycles* **1993**, *35*, 349.
70. Larraya, C.; Guillard, J.; Renard, P.; Audinot, V.; Boutin, J. A.; Delagrange, P.; Bennejean, C.; Viaud-Massuard, M.-C. *Eur. J. Med. Chem.* **2004**, *39*, 515.
71. Poël, H. Van de; Guillaumet, G.; Viaud-Massuard, M.-C. *Tetrahedron Lett.* **2002**, *43*, 1205.
72. Papageorgiou, C.; Camenisch, G.; Borer, X. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1549.
73. Saab, F.; Bénéteau, V.; Schoentgen, F.; Mérour, J.-Y.; Routier, S. *Tetrahedron* **2010**, *66*, 102.
74. Carbone, A.; Pennati, M.; Barraja, P.; Montalbano, A.; Parrino, B.; Spano, V.; Lopergolo, A.; Sbarra, S.; Doldi, V.; Zaffaroni, N.; Cirrincione, G.; Diana, P. *Curr. Med. Chem.* **2014**, *21*, 1654.
75. Liedtke, A. J.; Kim, K.; Stec, D. F.; Sulikowski, G. A.; Marnett, L. J. *Tetrahedron* **2012**, *68*, 10049.
76. Yoshikawa, K.; Yokomizo, A.; Naito, H.; Haginoya, N.; Kobayashi, S.; Yoshino, T.; Nagata, T.; Mochizuki, A.; Osanai, K.; Watanabe, K.; Kanno, H.; Ohta, T. *Bioorg. Med. Chem.* **2009**, *17*, 8206.
77. Jeanty, M.; Suzenet, F.; Guillaumet, G. *J. Org. Chem.* **2008**, *73*, 7390.
78. Mąkosza, M.; Danikiewicz, W.; Wojciechowski, K. *Liebigs Ann. Chem.* **1987**, 711.
79. Heffernan, G. D.; Coghlan, R. D.; Manas, E. S.; McDevitt, R. E.; Li, Y.; Mahaney, P. E.; Robichaud, A. J.; Huselton, C.; Alfinito, P.; Bray, J. A.; Cosmi, S. A.; Johnston, G. H.; Kenney, T.; Koury, E.; Winneker, R. C.; Deecher, D. C.; Trybulski, E. J. *Bioorg. Med. Chem.* **2009**, *17*, 7802.
80. Bernotas, R. C.; Antane, S.; Shenoy, R.; Le, V.-D.; Chen, P.; Harrison, B. L.; Robichaud, A. J.; Zhang, G. M.; Smith, D.; Schechter, L. E. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1657.
81. Mąkosza, M.; Stalewski, J.; Wojciechowski, K.; Danikiewicz, W. *Tetrahedron* **1997**, *53*, 193.
82. Rege, P. D.; Johnson, F. *J. Org. Chem.* **2003**, *68*, 6133.
83. Bujok, R.; Wróbel, Z.; Wojciechowski, K. *Synlett* **2012**, *23*, 1315.
84. Andreassen, E. J.; Bakke, J. M. *J. Heterocycl. Chem.* **2006**, *43*, 49.
85. Bakke, J. M. *J. Heterocycl. Chem.* **2005**, *42*, 463.
86. Andreassen, E. J.; Bakke, J. M.; Sletvold, I.; Svensen, H. *Org. Biomol. Chem.* **2004**, *2*, 2671.
87. Stahly, G. P.; Stahly, B. C.; Lilje, K. C. *J. Org. Chem.* **1984**, *49*, 578.
88. Lawrence, N. J.; Davies, C. A.; Gray, M. *Org. Lett.* **2004**, *6*, 4957.
89. Cao, S.; Wu, J. J.; Li, L.; Zhu, L. J.; Zhang, J.; Yu, J. L.; Qian, X. H. *Org. Biomol. Chem.* **2008**, *6*, 1293.
90. Bartoli, G.; Leardini, R.; Medici, A.; Rosini, G. *J. Chem. Soc., Perkin Trans. 1* **1978**, 692.
91. Bartoli, G.; Bosco, M.; Dalpozzo, R.; Todesco, P. E. *J. Org. Chem.* **1986**, *51*, 3694.
92. Forbes, I. T.; Ham, P.; Booth, D. H.; Martin, R. T.; Thompson, M.; Baxter, G. S.; Blackburn, T. P.; Glen, A.; Kennett, G. A.; Wood, M. D. *J. Med. Chem.* **1995**, *38*, 2524.
93. Wojciechowski, K.; Mąkosza, M. *Synthesis* **1989**, 106.
94. Macor, J. E.; Forman, J. T.; Post, R. J.; Ryan, K. *Tetrahedron Lett.* **1997**, *38*, 1673.
95. Bujok, R.; Trawczyński, A.; Wróbel, Z.; Wojciechowski, K. *Synlett* **2012**, 2682.
96. Yamada, K.; Kawasaki, T.; Fujita, T.; Somei, M. *Heterocycles* **2001**, *55*, 1151.
97. Yamada, K.; Yamada, F.; Shiraishi, T.; Tomioka, S.; Somei, M. *Heterocycles* **2009**, *77*, 971.
98. Yamada, F.; Shinmyo, D.; Nakajou, M.; Somei, M. *Heterocycles* **2012**, *86*, 435.
99. Pordel, M.; Abdollahi, A.; Razavi, B. *Russ. J. Bioorg. Chem.* **2013**, *39*, 211.
100. Rahimizadeh, M.; Pordel, M.; Ranaei, M.; Bakavoli, M. *J. Heterocycl. Chem.* **2012**, *49*, 208.
101. Sokhanvar, M.; Pordel, M. *ARKIVOC* **2014**, (iv), 328.
102. Kumar, S.; Rathore, V.; Verma, A.; Prasad, C. D.; Kumar, A.; Yadav, A.; Jana, S.; Sattar, M.; Meenakshi; Kumar, S. *Org. Lett.* **2015**, *17*, 82.
103. Mąkosza, M.; Białecki, M. *J. Org. Chem.* **1998**, *63*, 4878.
104. Bastrakov, M. A.; Starosotnikov, A. M.; Leontieva, M. A.; Shakhnes, A. K.; Shevelev, S. A. *Mendeleev Commun.* **2009**, *19*, 47.
105. Bastrakov, M. A.; Starosotnikov, A. M.; Shakhnes, A. K.; Shevelev, S. A. *Russ. Chem. Bull.* **2008**, *57*, 1539. [*Izv. Akad. Nauk* **2008**, 1508.]
106. Rozhkov, V. V.; Kuvshinov, A. M.; Shevelev, S. A. *Synth. Commun.* **2002**, *32*, 1465.
107. Wróbel, Z.; Kwast, A. *Synlett* **2007**, 1525.
108. Wohl, A.; Aue, W. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2442.