Pure & Appl. Chem., Vol. 69, No. 3, pp. 559–564, 1997.
Printed in Great Britain.

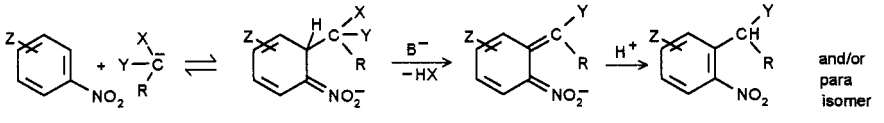
Synthesis of heterocyclic compounds via vicarious nucleophilic substitution of hydrogen

Mieczysław Mąkosza

Institute of Organic Chemistry, Polish Academy of Sciences
ul. Kasprzaka 44, 01-224 Warsaw, Poland

Abstract: Possibilities of synthesis of a variety of nitrogen heterocycles *via* intramolecular VNS reaction in nitroarenes and *via* transformations of products of the VNS reaction are presented.

Vicarious Nucleophilic Substitution of Hydrogen, VNS is presently a well established methodology for direct introduction of functionalized alkyl substituents into electrophilic arenes, mainly nitroarenes (1)

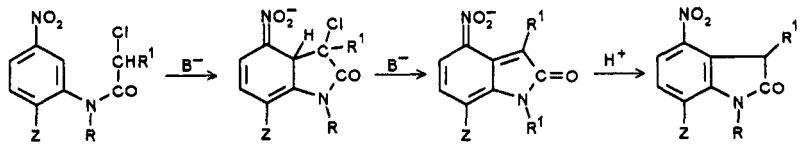


The reaction is a general process applicable also to nitro-derivatives of aromatic heterocycles, heterocycles which are electrophilic due to the electronic configuration (2) and even electrophilic alkenes (3). The VNS can serve also as an efficient method of introduction of hydroxy and amino groups into electrophilic arenes via the reaction with alkylhydroperoxides (4) and aminotriazoles and sulfenamides (5). The VNS reaction can serve therefore as a versatile tool for functionalization and transformation of heterocyclic compounds (2).

This method of direct introduction of functionalized alkyl substituents into nitroaromatic rings, particularly *ortho* to the nitro group, provides broad possibilities in synthesis of heterocyclic rings *via* interaction of the introduced substituents with the nitro group as such or upon its reduction. Potential for controlling the orientation of VNS (6) enhances attractiveness of this approach. In this paper, the rich possibilities of synthesis of a variety of heterocyclic ring systems *via* the VNS reaction will be presented, without discussing introduction of substituents into electrophilic heterocycles.

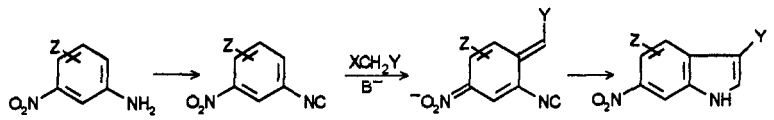
Indoles belong to the most important heterocycles because the indole ring is present in numerous alkaloids and pharmaceuticals. There are many general and specific methods of indole ring synthesis. VNS offers some new possibilities and can provide readily available key starting materials for known methods.

The intramolecular VNS reaction of *m*-nitrochloroacetanilides yields directly substituted nitrooxindoles (7).



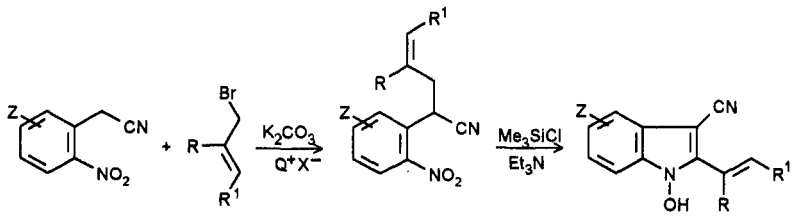
It should be stressed that such nitrooxindoles are not readily available by other methods because nitration of oxindoles gives different isomers whereas the intramolecular Friedel-Crafts approach is not applicable.

Direct synthesis of substituted nitroindoles *via* the VNS reaction in *m*-isocyanonitro benzenes prepared from readily available *m*-nitroanilines represents great practical value (8).

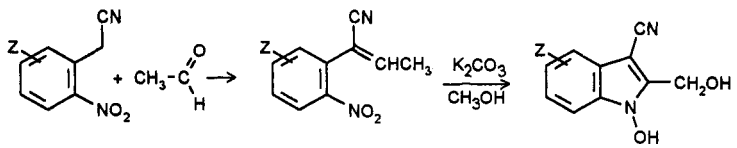


The products of VNS are formed as nitrobenzylic carbanions, which cyclize rapidly *via* intramolecular nucleophilic addition to the isocyano group. Thus, the conversion of the isocyanonitrobenzenes to nitroindoles is practically a one pot reaction.

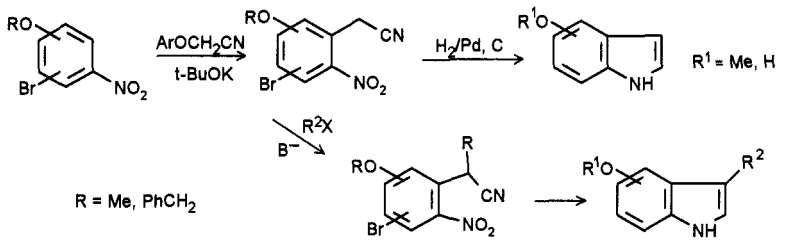
Products of the VNS reaction: *o*-nitrobenzyl aryl sulfones, *o*-nitroarylacetonitriles etc. can be converted into indoles in a variety of ways. Alkylation of the methylene groups in the nitriles with allylic halides produces the corresponding allyl derivatives, which, when treated with triethylamine and trimethylchlorosilane, cyclize to give substituted 1-hydroxy-2-vinyl indoles (9).



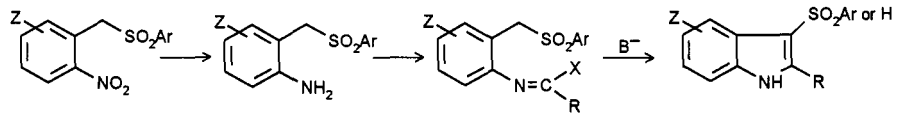
2-(*o*-Nitroaryl)crotonitriles, available *via* the Knoevenagel condensation of *o*-nitroarylacetonitriles with aliphatic aldehydes, cyclize to give indoles and quinolines under various basic conditions. In the presence of potassium carbonate in methanol 1-hydroxy-2-hydroxymethyl indoles can be obtained as the main products (10).



It is well known that catalytic hydrogenation (H_2, Pd/C) of *o*-nitroarylacetonitriles leads to indoles (11). This method was, until recently, of minor practical value because the starting nitriles were difficult to prepare. When, however, direct o-cyanomethylation of nitroarenes via the VNS reaction was introduced to the repertoire of organic synthesis, the hydrogenation method become an attractive and versatile tool for indole synthesis. Its value was shown by synthesis of all isomeric 4-, 5-, 6- and 7-hydroxy and methoxy indoles from nitrophenols. In some cases bromonitrophenols were used in order to assure the desired orientation and to increase activity of nitroarenes(12).



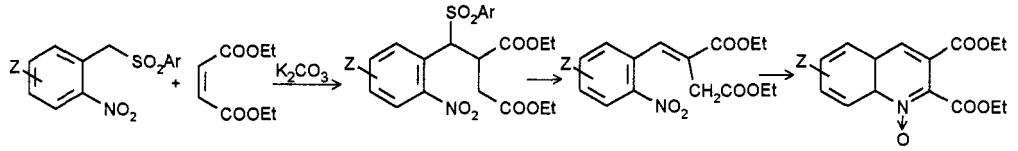
o-Nitrobenzyl aryl sulfones are readily reduced to the corresponding *o*-aminobenzyl sulfones, which in turn can be converted into imines, imidates, isonitriles etc. All these compounds, when treated with a base, cyclize to substituted indoles (13,14).



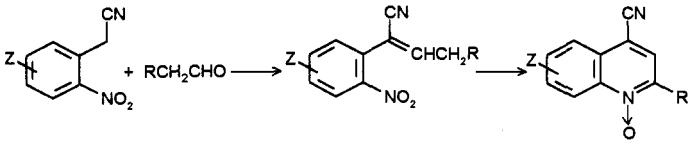
The methods of indole derivatives synthesis presented above are multistep processes but can be competitive for synthesis of products containing a variety of substituents in well defined positions of indole ring.

Quinolines. The availability of nitroarenes containing functionalized substituents *ortho* to the nitro group provides large possibilities for synthesis of quinolines.

Treatment of substituted *o*-nitrobenzyl aryl sulfones with diethyl fumarate or maleate and a base resulted in direct formation of substituted quinoline - N-oxides in an "one pot" operation. This multistep synthesis proceeds apparently as a Michael addition followed by a ß-elimination of the aryl sulfinic acid from the Michael adduct to form the unsaturated diester, which is deprotonated in the next step. The produced allylic carbanion reacts subsequently with the nitro group to form the quinoline ring (15).



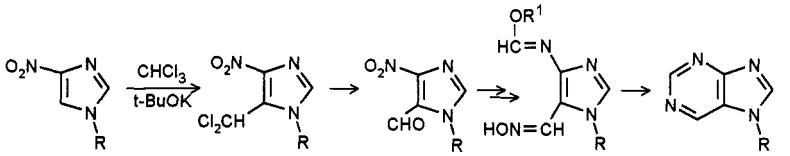
Somewhat similar is synthesis of 4-cyanoquinolines via a base - induced intramolecular condensation of 2-(o-nitroaryl)crotononitriles (10,16).



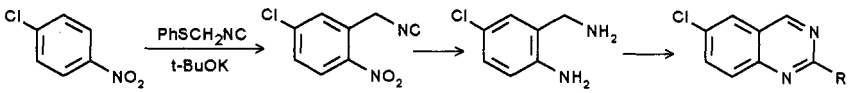
Alkylation of substituted *o*-nitrobenzyl aryl sulfones with esters of α-bromo acids is followed with elimination of arylsulfinic acid to form *o*-nitrocinnamic acid derivatives (17), versatile starting materials for synthesis of quinoline ring system.

Purines form a very important class of heterocyclic systems and there is a continuous interest in methods of synthesis of these compounds. The VNS reaction provides an efficient access to properly substituted nitroimidazoles (18) from which various ways to purines can be envisaged.

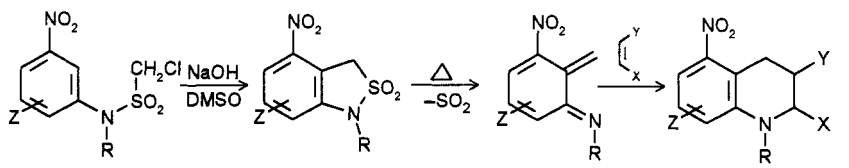
Thus, 1-alkyl-4-nitroimidazoles are efficiently dichloromethylated *via* the VNS reaction with chloroform (19) and the resulting 5-dichloromethyl derivatives can be converted into purines (20). Other pyrimidines fused with aromatic rings can be prepared in a similar way.



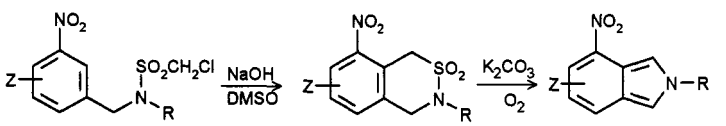
The VNS reaction of nitroarenes with phenylthioisocyanomethane produces the corresponding isocyanomethyl derivatives which can be easily converted into purines or benzopyrimidines (21).



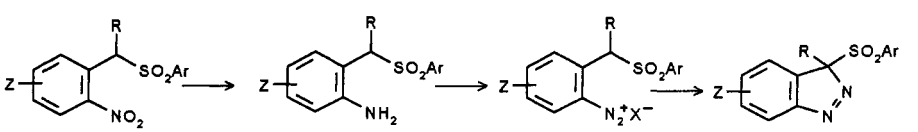
Miscellaneous heterocycles. A rich possibility of synthesis of heterocyclic rings is connected with the intramolecular VNS reaction of N-(3-nitrophenyl) and N-(3-nitrobenzyl) chloromethanesulfonamides, which furnishes 5- and 6-membered sultam derivatives (22). These sultams are valuable starting materials in synthesis of heterocycles. For example, thermal extrusion of SO_2 from the 5-membered sultams, generates the nitro aza-*o*-xylylenes which enter the typical [4+2] cycloaddition process to give 6-membered heterocycles (23).



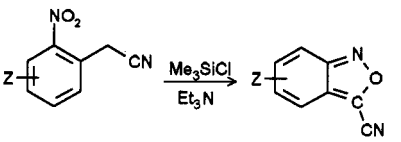
The 6-membered sultams can be efficiently converted into nitro-isoindoles *via* aerial oxidation in a solid-liquid PTC system (24)



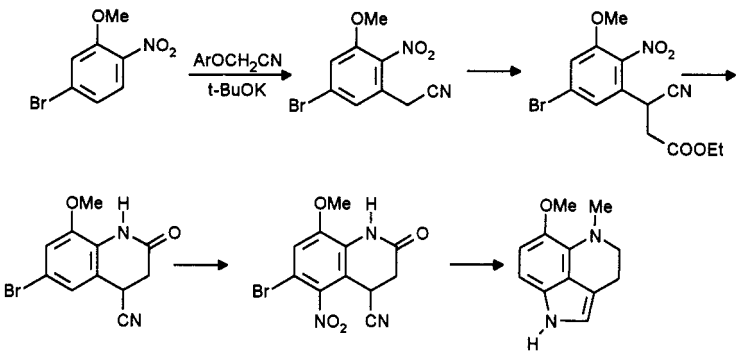
Substituted *o*-aminobenzyl aryl sulfones, readily available *via* the reduction of the corresponding nitrosulfones, form indazoles when subjected to diazotization (25)



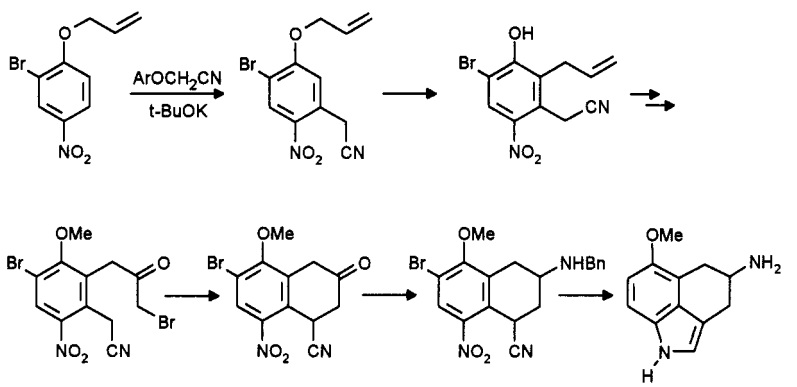
Products of the VNS reaction, *o*-nitrobenzyl aryl sulfones, *o*-nitroarylactonitriles *etc.* can be readily converted into benzisoxazoles (anthraniles) via treatment with Me_3SiCl/triethylamine (26) or, in the case of bicyclic system, *via* a reaction with some nucleophilic agents (27).



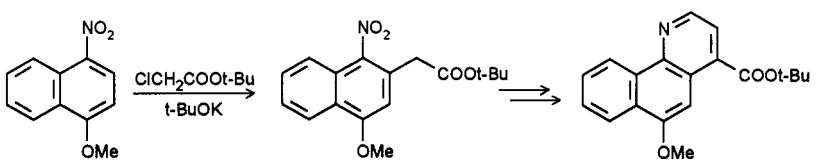
Since the VNS reaction is a versatile tool in the synthesis of a variety of heterocyclic systems it provides an efficient access to natural and biologically active products.
O-Methylnordehydrobufotenine can be efficiently synthesized from 2-nitro-5-bromoanisole *via* the VNS cyanomethylation followed by standard transformations (28).



Similarly, the VNS cyanomethylation of 4-allyloxy-3-bromonitrobenzene provides the key starting material for a simple synthesis of 1,3,4,5-tetrahydrobenz[cd]indoles, which show interesting biological activity particularly as serotonine antagonists (29).



The VNS reaction in 1-nitro-4-methoxynaphthalene allowed us to execute a simple and short synthesis of the benzoquinoline derivative - the key intermediate for a synthesis of eupolauramine.(30)



The rich possibilities of heterocyclic ring synthesis presented in this paper are far from being exhausted. There are practically unlimited variety of substituents which can be introduced into nitroarene rings and there is also a large repertoire of further transformations. One can expect that the VNS approach will be widely used for practical synthesis of many heterocyclic target compounds.

References

1. M. Mąkosza, J. Winiarski. *Acc.Chem.Res.* **20**, 282 (1987).
2. M. Mąkosza. *Synthesis* 103 (1991).
3. M. Mąkosza, A. Kwast. *Tetrahedron* **46**, 5001 (1991).
4. M. Mąkosza, K. Sienkiewicz. *J.Org.Chem.* **55**, 4979 (1990).
5. A.R. Katritzky, K.S.Lorenzo. *J.Org.Chem.* **53**, 3978 (1988); M. Mąkosza, M. Białecki. *J.Org.Chem.* **57**, 4784 (1992).
6. M. Mąkosza, T. Glinka, A. Kinowski. *Tetrahedron* **40,** 1863 (1984).
7. M. Mąkosza, H. Hoser. *Heterocycles* **37**, 1701 (1994).
8. K. Wojciechowski, M. Mąkosza. *Tetrahedron Lett.* **25**, 4793 (1984).
9. Z. Wróbel, M. Mąkosza. *Synlett* 597 (1993).
10. Z. Wróbel, M. Mąkosza. *Tetrahedron* **49**, 5315 (1993).
11. G.N. Walker. *J.Am.Chem.Soc.* **77**, 3844 (1955).
12. M. Mąkosza, W. Danikiewicz, K. Wojciechowski. *Liebigs Ann.Chem.* 203 (1988).
13. K. Wojciechowski, M. Mąkosza. *Synthesis* 651 (1986).
14. K. Wojciechowski, M. Mąkosza. *Bull.Soc.Chim.Belg.* **95**, 671 (1986).
15. M. Mąkosza, A. Tyrała. *Acta Chem.Scand.* **46**, 689 (1992).
16. Z. Wróbel, A. Kwast, M. Mąkosza. *Synthesis* 31 (1993).
17. M. Mąkosza, A. Tyrała. *Synthesis* 1142 (1987).
18. M. Mąkosza, E. Kwast. *Bull.Pol.Acad.Sci.Chem.* **35**, 287 (1987). S. Ostrowski. *Polish J.Chem.* **68**, 2237 (1994).
19. M. Mąkosza, Z. Owczarczyk. *J.Org.Chem.* **54**, 5094 (1989).
20. S. Ostrowski. *Synlett* 253 (1995).
21. S. Ostrowski, *Heterocycles,* **43**, 389 (1996).
22. K. Wojciechowski, M. Mąkosza, *Synthesis,* 571 (1992).
23. K. Wojciechowski, *Tetrahedron,* **49**, 7277 (1993).
24. K. Wojciechowski, *Liebigs Ann.Chem.,* 831 (1991).
25. M. Mąkosza, A. Tomashevskii (in preparation).
26. Z. Wróbel (in preparation).
27. Z. Wróbel, M. Mąkosza, *Heterocycles*, **40**, 187 (1995).
28. M. Mąkosza, J. Stalewski, *Tetrahedron*, **51**, 7263 (1995).
29. M. Mąkosza, J. Stalewski, W. Danikiewicz, K. Wojciechowski, *Tetrahedron* (in print).
30. M. Mąkosza, Z. Wróbel, *Heterocycles*, **33**, 585 (1992).