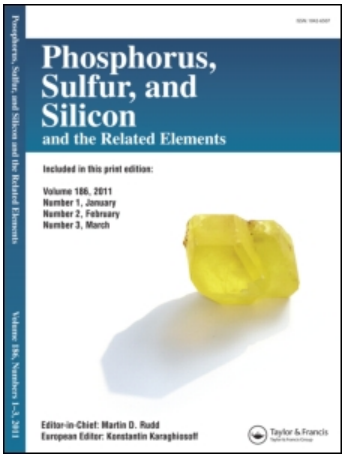

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VICARIOUS NUCLEOPHILIC SUBSTITUTION WITH SULFUR CONTAINING CARBANIONS

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Review

VICARIOUS NUCLEOPHILIC SUBSTITUTION WITH SULFUR CONTAINING CARBANIONS

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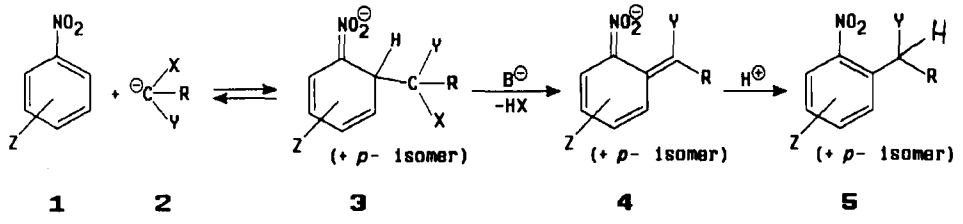
1. INTRODUCTION

Carbanions stabilized with sulfur containing substituents are versatile intermediates in organic synthesis. The great value and importance of such carbanions is connected with specific properties of the sulfur atom which is capable to exist in a variety of valent states and to form many functional groups. These various sulfur-containing groups exert different carbanion stabilizing effects and can also serve as leaving groups in nucleophilic substitution or elimination reactions. Taking into account numerous types of sulfur containing functional groups and a variety of reactions they can promote, it is well understandable that reactions of sulfur-containing carbanions have been thoroughly studied and widely exploited in organic synthesis. The reactions of such carbanions with aliphatic electrophilic partners: alkylating agents, carbonyl compounds and Michael acceptors consist a major section of this field and were subject of numerous studies as well as many monographs.[1] Contrary to that, not very much was known about reactions of such carbanions with electrophilic aromatic compounds. Actually, there are only few reports on nitroarylation of sulfur-containing carbanions *via* replacement of halogen *ortho-* or *para-* to the nitro group in halonitrocompounds.[2] There are also some reports on the alkylation of nitroarenes and heterocyclic compounds in the reaction with sulfonium[3] and sulfoxonium[4] ylides, dimethylsulfoxide carbanion,[5] and dialkyl or alkyl aryl sulfones carbanions.[6]

In 1978 we formulated the concept of a new reaction between carbanions and nitroarenes which we called "Vicarious Nucleophilic Substitutions of Hydrogen" (VNS).[7,8] The VNS consists in a reaction between nitroarenes (**1**) (or other electrophilic arenes—*vide infra*) and carbanions (**2**) containing a leaving group X at the carbanionic center. It proceeds *via* formation of the σ-adducts **3** in the hydrogen-containing *ortho-* and/or *para*-positions of the nitroarene, followed by base-induced β-elimination of HX, leading to the nitrobenzylic carbanions **4** of the products.[9,10] Protonation during a work-up procedure give the final products **5** of the substitution of hydrogen by the carbanion moiety (Scheme 1).

† Author to whom all correspondence should be addressed.



X = leaving group, Y = carbanion-stabilizing group, R = substituent

SCHEME 1

Since the VNS products exist in the reaction mixture in form of the corresponding nitrobenzylic carbanions **4** which are unreactive toward nucleophilic addition, the reaction is highly selective in sense of monosubstitution. Another very important feature of this process is that it proceeds usually much faster than conventional nucleophilic substitution of halogen located in similarly activated positions. The orientation pattern (*ortho*- versus *para*-substitution) depends mostly on the steric requirements of the carbanion. Secondary carbanions (**2**, R = H) can replace hydrogen *ortho*- or *para*- to the nitro group, the *o*-/*p*-ratios depending on the kind of X and Y and the reaction conditions, whereas tertiary carbanions (**2**, R = alkyl, aryl, halogen etc.) react, in the majority of cases, preferentially at the *para* position, however it is possible to force their reactions at the *ortho* position too.[10]

The orientation of the VNS can be to some extend manipulated by the reaction conditions. When the reaction is carried out in the presence of *t*-BuOK in THF, substitution with the secondary carbanions derived from α-halomethylsulfones takes place predominantly in the *ortho*-position. The explanation of this phenomenon has been given.[11]

The VNS is a general process concerning electrophilic arenes and carbanions. Nitroarenes and other electrophilic aromatic systems can contain almost unlimited variety of substituents, such as halogens, alkyl, alkoxy, aryloxy, alkylthio, dialkylamino, cyano, carboxy, alkoxycarbonyl, nitro, sulfonyl and many other groups, which do not disturb the reaction course. Only substituents which under strongly basic conditions are deprotonated giving anions in which the negative charge is conjugated with the aromatic ring and the nitro group, as in the case of nitrophenols, inhibit the reaction, however dinitrophenols enter this reaction satisfactorily.[12] On the other hand when the benzene ring contains two or three nitro groups di- and even trisubstitution is possible.[12]

Nitroderivatives of such heterocyclic compounds as pyridine,[13,14] quinoline,[15] indole,[16] furan,[17] thiophene,[17] pyrrole,[17,18] imidazole[19] or pyrazole[20] enter readily the VNS reaction. Some highly electrophilic heterocycles which do not contain a nitro group, for example: 1,2,4-triazine,[21,22] benzoxazole,[21] benzothiazole,[21] quinoline-*N*-oxide,[23] quinoxaline-*N*-oxide,[24] azaquinoxalines,[25] acridine,[21] pteridine[26] and their derivatives are also good substrates for this reaction. VNS reaction was successfully performed even for tropylium tetrafluoroborate.[27]

The VNS is also a general process in respect to the carbanions. Actually, when

$[X—CR—Y]^{\ominus}$ represents general structure of the carbanion, any combination of such leaving groups X as Cl, Br, —OPh, —SPh, $—SC(S)NMe_2$, carbanion stabilizing groups Y as $—SO_2R$, $—SO_2NR_2$, —SOAr, —CN, —COOR, $—P(O)(OEt)_2$, and substituents R as H, alkyl, aryl, Cl, —OPh, —SPh, etc. produces carbanions which are able to replace *ortho*- and/or *para*-hydrogen atoms in the nitroarenes according to the VNS scheme.

The purpose of this paper is to present a comprehensive review on the Vicarious Nucleophilic Substitution of hydrogen in nitroarenes and related reactions with sulfur containing carbanions of general structure of $[X—CR—Y]^{\ominus}$ in which at least one of the substituents X, Y or R is a sulfur functional group. The main stress will be put on the scope, limitations and practical value of these reactions.

Because many of the sulfur-containing substituents act as a carbanion activating group and also as a leaving group, the order of the presentation will be according to the decrease of oxidation level of sulfur in these groups, i.e. sulfonic acid esters and amides, sulfones, sulfoxides and sulfides.

The material in each section will be organized as follows:

1. The reactions of carbanions in which Y is a sulfur functional group which remains in the product.
2. The reactions of carbanions with a sulfur-containing leaving group X, in which the products formed do not contain sulfur.

2. ALKANESULFONIC ACIDS DERIVATIVES

Alkoxysulfonyl groups are efficient carbanion stabilizing substituents. However application of such carbanions in the synthesis encounter some difficulties since alkyl sulfonates are also active alkylating agents. For this reason attempts to afford the VNS with methyl chloromethanesulfonate failed.

On the other hand neopentyl and phenyl sulfonates do not have alkylating properties, consequently the corresponding esters of α-chloroalkanesulfonic acids react with nitrobenzene derivatives according to the VNS scheme to form neopentyl and phenyl *ortho*- and *para*-nitrobenzylsulfonates in good yields[28] (Table I).

Similarly proceed reactions of *N,N*-dialkyl α-chloroalkanesulfonamides with nitroarenes and some highly electrophilic heterocyclic compounds (Table II).

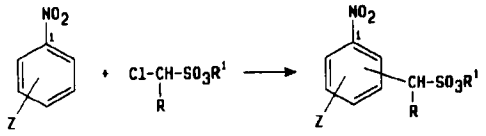
Chloromethanesulfonamides substituted at nitrogen with a *meta*-nitrophenyl or *meta*-nitrobenzyl group undergo intramolecular VNS reaction leading to γ- or δ-sultams[31] (Scheme 2).

Some interesting observations have been made in the reactions of fluoroderivatives **6** and **7**. In these cases the VNS competes with the conventional substitution of fluorine. When the precursor of a five membered ring **6** was treated with a base, substitution of fluorine predominated. However, in the case of **7** which leads to the six-membered ring the VNS was the only observed process (Scheme 3).[31]

These results are in good agreement with the proposed mechanism of the VNS, since the elimination step requires an antiperiplanar conformation of the Cl and

TABLE I

Reactions of α-chloroalkanesulfonic esters with nitrobenzene derivatives[28]

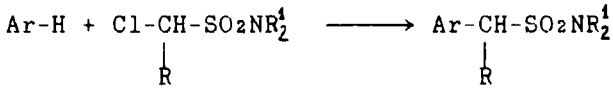


No.	Nitrocompound Z	R	Sulfonate R^1	Position of $-CHR-SO_3R^1$	Yield %
1	H	H	*neo*-C_5H_{11}	2	53
				4	30
2	H	H	Ph	2	24
				4	30
3	2-Cl	H	*neo*-C_5H_{11}	4	40
				6	40
4	2-Cl	H	Ph	4	16
				6	64
5	4-F	H	*neo*-C_5H_{11}	2	31
				4 (R = Cl)[a]	31
6	4-F	H	Ph	2	24
				4 (R = Cl)[a]	48
7	3-NO_2	H	*neo*-C_5H_{11}	4	47
8	H	Ph	*neo*-C_5H_{11}	4	68
9	H	Et	*neo*-C_5H_{11}	4	59

[a] Product of the S_NAr substitution of the halogen.

TABLE II

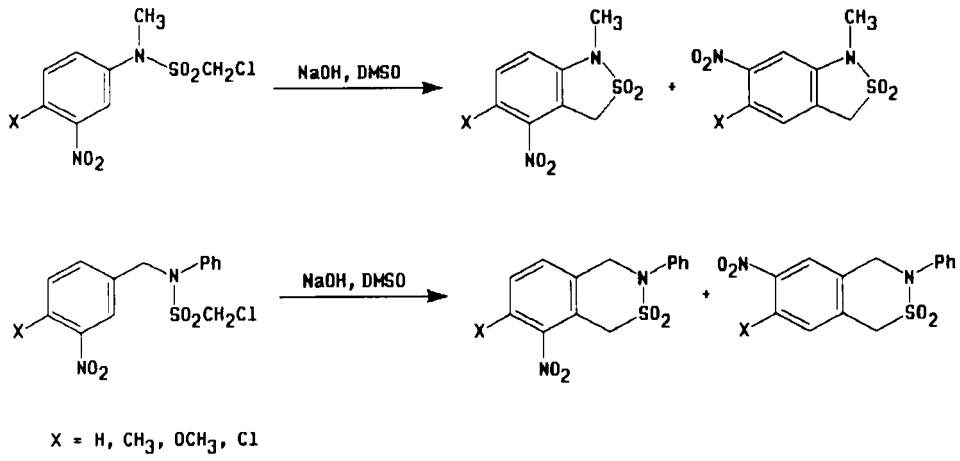
Reactions of α-chloroalkanesulfonamides with electrophilic arenes



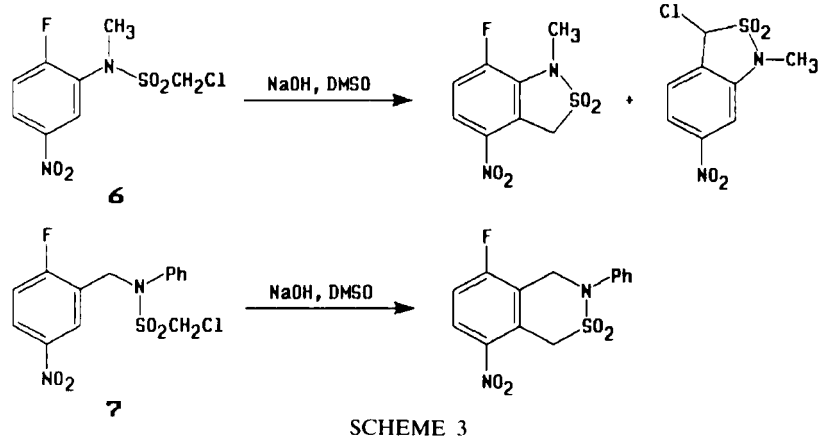
No.	Arene	Sulfonamide R	Sulfonamide R^1	Method	Position of $-CHR-SO_2NR^1_2$	Yield [%]	Ref.
1	1-chloro-4-nitrobenzene	H	Morph.[a]	A	3	67	7
2	nitrobenzene	*n*-C_4H_9	Morph.	B	4	52	29
3	nitrobenzene	Ph	Morph.	B	4	62	29
4	1-chloro-2-nitrobenzene	*n*-C_3H_7	Morph.	B	5	46	29
5	4-nitrobenzoic acid	H	Morph.	A	3	60	30
6	2-nitrothiophene	H	CH_3	C	3	81	17
7	5-nitroquinoline	H	CH_3	A	6	92	15
8	5-nitroquinoline	H	CH_3	D	6	88	15
9	6-nitroquinoline	H	CH_3	A	5	78	15
10	6-nitroquinoline	H	CH_3	D	5	92	15
11	8-nitroquinoline	H	CH_3	A	7	92	15
12	benzoxazole	H	Morph.	B	2	14	21
13	benzothiazole	H	Morph.	B	2	67	21

[a] Morph. = $(-CH_2CH_2)_2O$ 

Method: A—NaOH/DMSO, B—KOH/DMSO, C—$KOH/NH_{3\,liq}$, D—*t*-BuOK/THF



SCHEME 2



SCHEME 3

H atoms and this is fulfilled satisfactorily in the case of an intermediate leading to the six-membered ring.

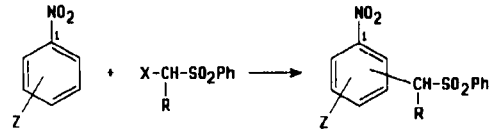
3. SULFONES

Sulfonyl stabilized carbanions are often used as intermediates in organic synthesis,[32] particularly as synthons for single and double carbon–carbon bond formation.[33] The sulfonyl group can be easily removed from the organic moiety via base induced elimination[34,35] or reduction[36]—this approach is widely used in the synthesis of the natural products.

Anions derived from α-chloromethyl sulfones are relatively stable provided they do not contain hydrogen atoms in the α' position, otherwise the Ramberg–Bäcklund reaction takes place.[37] Thus, carbanions of halomethyl aryl sulfones have no tendency to self-condensation and can react with alkyl halides[38,39] and carbonyl compounds.[38]

TABLE III

Reactions of α-haloalkyl phenyl sulfones with nitrobenzene derivatives



No.	Arene Z	Sulfone X	Sulfone R	Method	Position of —CHRSO$_2$Ph	Yield [%]	Ref.
1	H	F	H	A	2/4 = 74:26	63	29
2	H	Cl	H	A	2/4 = 53:47	75	29
3	H	Br	H	A	2/4 = 35:65	40	29
4	H	Cl	Et	A	2/4 = 0:100	68	29
5	H	Cl	Ph	A	2/4 = 0:100	93	29
6	2-Cl	Cl	H	A	4/6 = 65:35	85	29
7	2-OCH$_3$	Cl	H	A	4/6 = 80:20	71	29
8	2-CF$_3$	Cl	H	A	4/6 = 50:50	67	29
9	3-CO$_2$H	Cl	H	B	4/6 = 39:61	57	30
10	3-OCH$_3$	Cl	H	C	2/4/6 = 85:0:15	42	11
11	3-OCH$_3$	Cl	H	A	2/4/6 = 25:61:14	75	11
12	3-NMe$_2$	Cl	H	C	2	10	11
13	3-NMe$_2$	Cl	H	A	4/6 = 84:16	44	11
14	3-Cl	Cl	H	C	2/4/6 = 60:5:35	77	11
15	3-Cl	Cl	H	A	2/4/6 = 6:73:21	93	11
16	3-F	Cl	H	C	2/6 = 93:7	90	11
17	3-F	Cl	H	A	2/4/6 = 32:57:8	86	11
18	4-CF$_3$	Cl	H	A	2	85	29
19	4-CN	Cl	H	D	2	53	29
20	4-*t*-Bu	Cl	H	A	2	71	29
21	4-SO$_3$H	Cl	H	E	2	72	40

Method: A—KOH/DMSO, B—NaOH/DMSO, C—*t*-BuOK/THF, D—KOH/NH$_{3\,liq}$, E—*t*-BuOK/DMF.

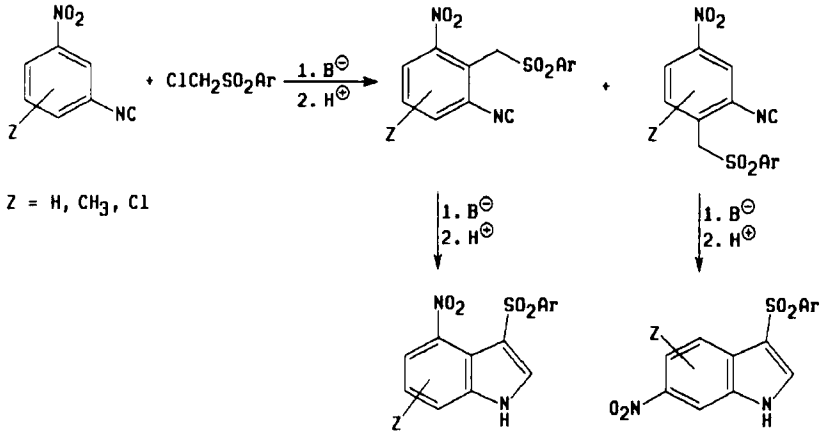
Therefore α-chloroalkyl aryl sulfones were chosen as model compounds for the investigation of the VNS, particularly of its scope, mechanism and specific features. We have found that α-chloromethyl aryl sulfones enter the VNS reaction with nitrobenzene derivatives containing a practically unlimited variety of substituents (Table III). The yields of products are generally high and often close to quantitative. The reaction does not occur only in the cases of mononitrophenols however dinitrophenols give products of the VNS in high yields.[12]

VNS in *meta*-nitrophenyl isonitriles gives *ortho*-isocyanobenzyl sulfones in high yields which can be isolated or, under the reaction conditions, can undergo cyclisation to 3-sulfonyl substituted 4- and 6-nitroindoles[41] (Scheme 4).

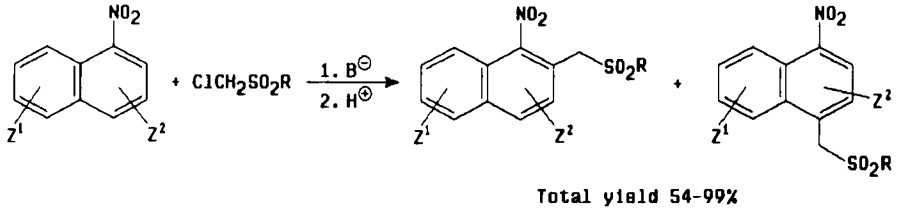
1- and 2-nitronaphthalene derivatives react with chloromethyl aryl or *t*-butyl sulfones to give appropriate VNS reaction products in high yields[42] (Scheme 5).

A similar result was obtained for 2-nitro-1,6-methano[10]annulene[43] (Scheme 6).

Nitroderivatives of a variety of heterocycles such as furan,[17] pyrrole,[17,18] thiophene,[17] imidazole,[19] indole,[16] pyridine,[13,14] quinoline[15] etc. also give arylsulfonylmethyl derivatives in high yields (Table IV).



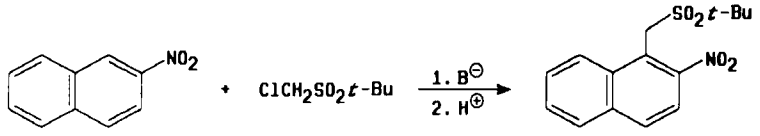
SCHEME 4



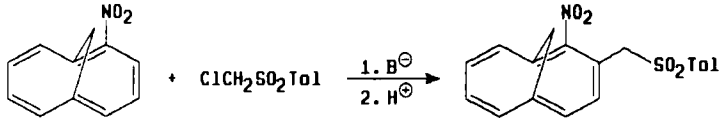
Z^1 = H, Br, NH_2, OCH_3, CN, 1,2-dioxolan-2-yl, NO_2

Z^2 = H, CH_3, OCH_3, NO_2

R = Tol, *t*-Bu



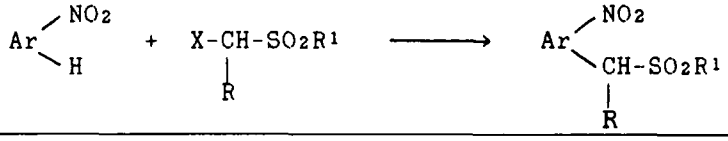
SCHEME 5



SCHEME 6

TABLE IV

Reactions of α-chloroalkyl aryl sulfones with heterocyclic nitrocompounds



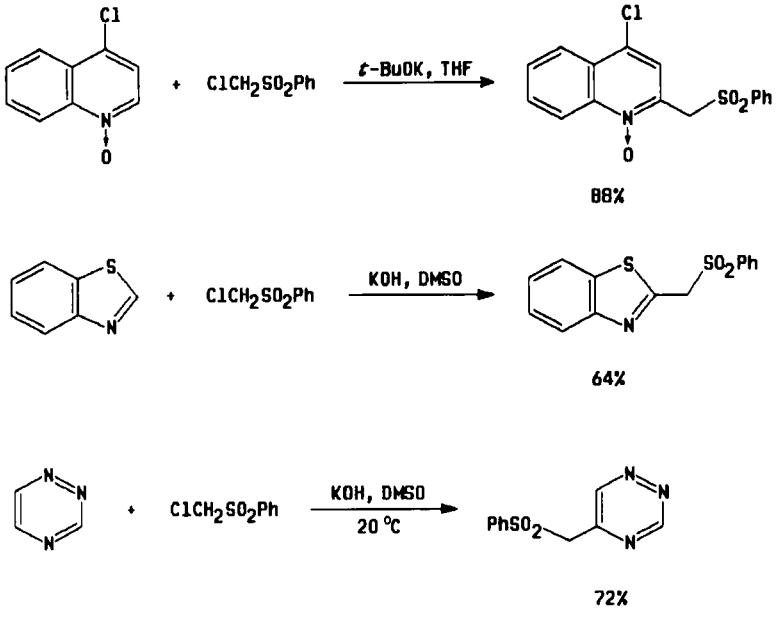
No.	Nitrocompound $ArNO_2$	Sulfone R	Sulfone R^1	Method	Position of $CHRSO_2R^1$	Yield [%]	Ref.
1	2-nitrofuran	H	Ph	A	3	8	17
2	2-nitrothiophene	H	Ph	A	3	74	17
3	2-nitrothiophene	Me	Ph	A	3	64	17
					5	16	
4	3-nitrothiophene	H	Ph	A	2	90	17
5	3-nitrothiophene	Me	Ph	A	2	94	17
6	1-methyl-2-nitropyrrole	H	Ph	A	5	90	18
7	1-tosyl-2-nitropyrrole	H	Ph	A	3	72	18
8	1-methyl-3-nitropyrrole	H	Ph	A	2	86	17
9	1-methyl-4-nitroimidazole	H	Ph	B	5	83	19
10	1-methyl-5-nitroimidazole	H	Ph	B	4	63	19
11	1-methyl-4-nitropyrazole	H	Tol	B	5	87	20
12	3-nitropyridine	H	Ph	B	4	66	13
					6	22	
13	4-nitropyridine	H	Ph	B	3	72	13
14	2-chloro-3-nitropyridine	H	Ph	B	4	48	13
					6	7	
15	4-methyl-2-nitropyridine	H	Ph	B	3	20	13
					5	60	
16	5-nitroquinoline	H	Ph	C	6	83	15
17	6-nitroquinoline	H	Ph	C	5	83	15
18	6-nitroquinoline	Et	Ph	C	2	16	15
19	8-nitroquinoline	H	Ph	C	5	12	15
					7	84	
20	6-nitroquinoxaline	H	Tol	B	2	73	24
21	1-methoxymethyl-5-nitroindole	H	Tol	C	4	79	16
22	1-methyl-6-nitroindole	H	Tol	C	7	88	16

Method: A—$KOH/NH_{3\,liq}$, B—KOH/DMSO, C—NaOH/DMSO.

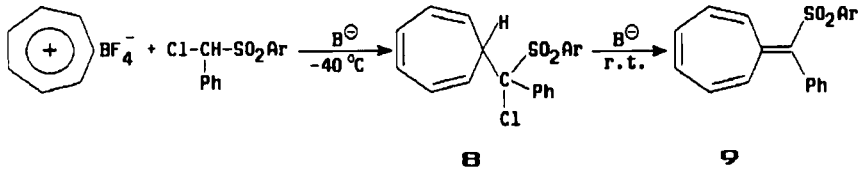
Chloromethyl phenyl sulfone reacts according to the VNS pathway also with some highly electrophilic heterocycles which do not contain a nitro group, for example: quinoline-*N*-oxide,[23] quinoxaline-*N*-oxide,[24] benzoxazole,[21] benzothiazole,[21] acridine,[21] 1,2,4-triazine,[21,22] pteridine,[26] azaquinoxaline.[25] Representative examples are shown on Scheme 7.

Also such a highly electrophilic aromatic system as tropylium tetrafluoroborate reacts with α-chlorobenzyl aryl sulfones according to the VNS scheme[27] (Scheme 8). In this case addition product **8** can be isolated and further transformed into elimination product **9**.

When some other functional groups are present in the nitroarene moiety, the reactions of these groups can compete with the VNS. One can expect that



SCHEME 7

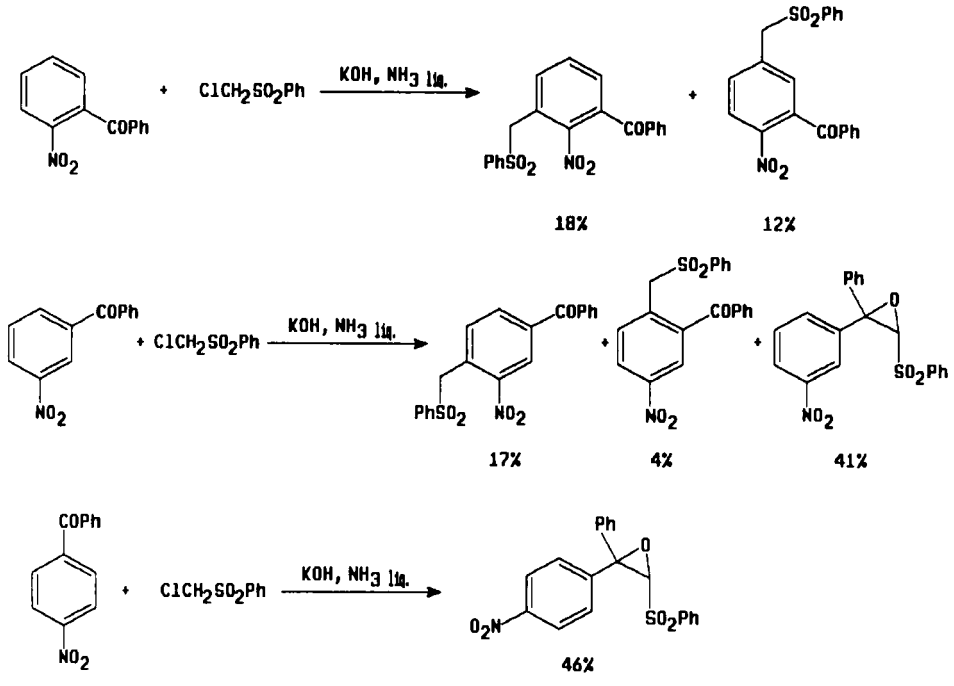


SCHEME 8

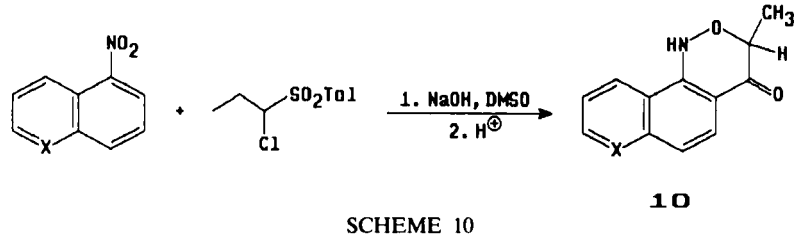
substitution of the fluorine atom in position *ortho-* or *para-* to the nitro group should compete with the VNS of hydrogen. This was, however, observed only in some instances,[9,10,31] particularly in the reactions with tertiary carbanions.[9,10] In these cases steric factors governed the observed reaction course.

The reactions of carbanions of chloromethyl phenyl sulfone with 2-, 3- and 4-nitrobenzophenones[44,45] can proceed along two pathways: addition of the carbanion to the carbonyl group resulting in the Darzens condensation and to the aromatic ring which leads to the VNS. Actually, in majority of cases the reaction of the 2-nitro isomer resulted in the VNS, the 3-nitro isomer reacted along both pathways, the extent of these two reactions can be controlled by the conditions, whereas the 4-nitro isomer entered the Darzens condensation. As an example the ratios of the products obtained in $KOH/NH_{3\,liq}$ system are given on Scheme 9.

In the reactions of the tertiary α-chloropropyl tolyl sulfone anion with some nitronaphthalenes[42] and nitroquinolines[15] peculiar heterocyclic products of type **10** were formed (Scheme 10). The reaction pathway leading to these products has been proposed.[15]



SCHEME 9



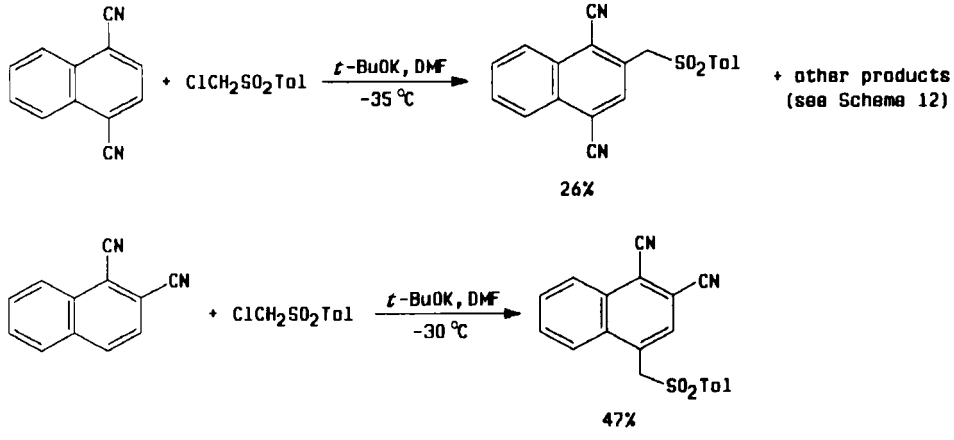
10

SCHEME 10

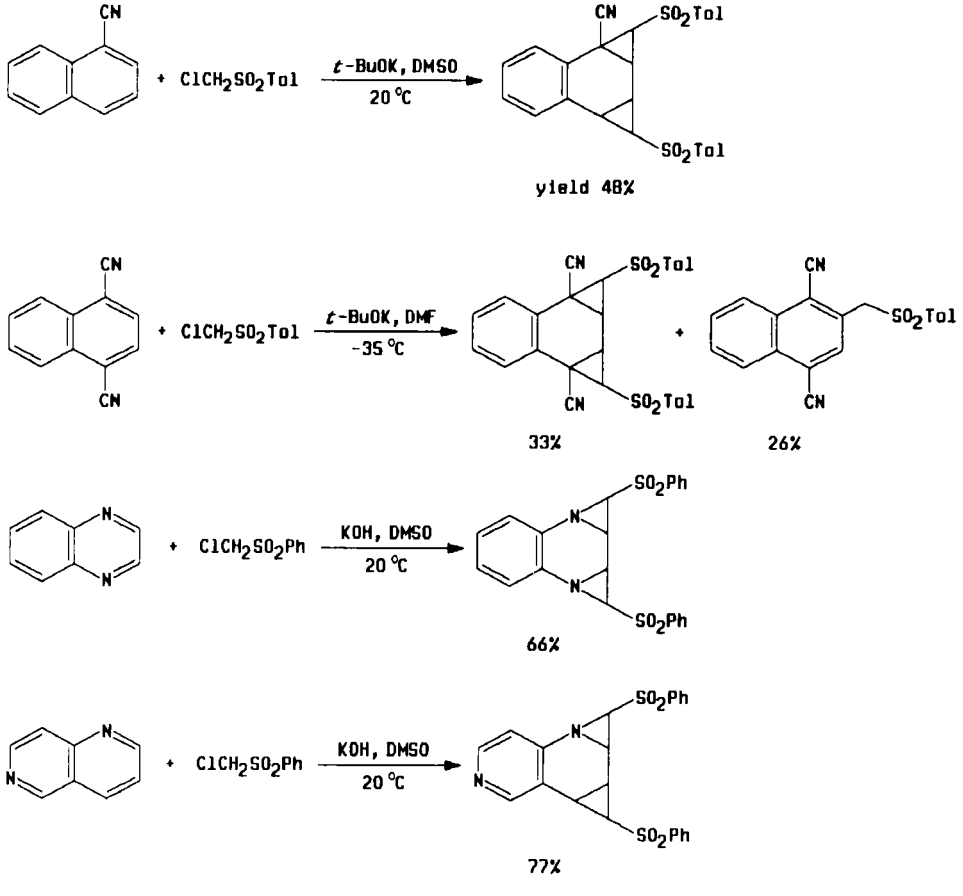
Benzene derivatives bearing electron-withdrawing substituents other than the nitro group (e.g. $—SO_2CF_3$ or —CN groups) are also able to form σ-adducts.[46] However their reactions according to the VNS scheme have not been observed, except of some dicyanonaphthalenes[24] (Scheme 11).

Another process competing with the VNS is the bis-annulation leading to tri- or tetracyclic products (Scheme 12). These products are formed particularly when naphthalene derivatives bearing electron-withdrawing substituents other than the nitro group (e.g. 1-cyanonaphthalene and 1,4-dicyanonaphthalene[24]) or some heterocyclic compounds (e.g. quinoxalines,[24,47] naphthyridines,[47] 6-azaquinoxaline[25]) are introduced in the reactions with chloromethyl aryl sulfone anions.

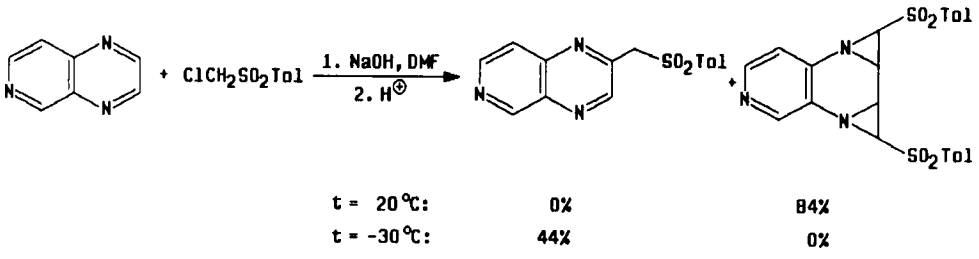
This different mode of the transformation of the initially formed σ-adduct is apparently connected with substantial negative charge density on particular carbon or nitrogen atoms in the ring, so they behave as strong nucleophiles, whereas β-elimination is suppressed. The ratio of the bis-annulation to the VNS



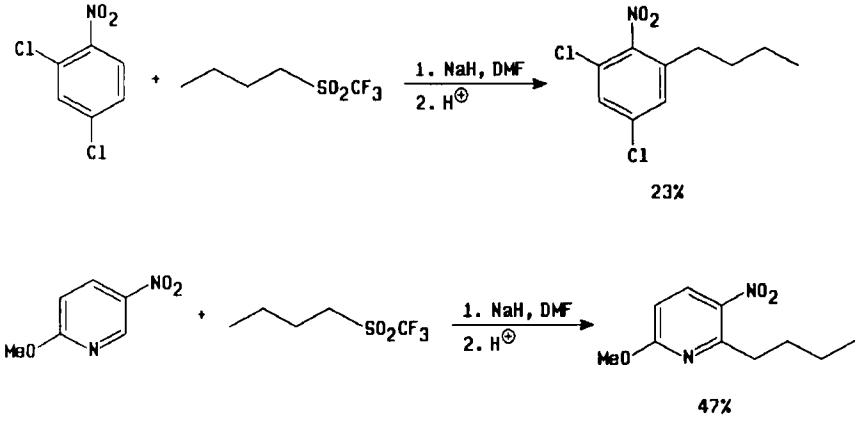
SCHEME 11



SCHEME 12



SCHEME 13



SCHEME 14

reaction products can be often manipulated by the reaction conditions (base, solvent, temperature). This has been shown in the model reaction of 6-azaquinoxaline with chloromethyl tolyl sulfone[25] (Scheme 13).

In all the reactions described previously the sulfonyl group acted as a carbanion stabilizing group and was present in the VNS reaction product. It was found however that the trifluoromethylsulfonyl group attached to the alkyl chain can act both as a carbanion stabilizing and a leaving group as well.[48] The reaction of trifluoromethyl alkyl sulfones with nitroarenes which proceeds according to the VNS scheme offers a method for the introduction of alkyl groups into the nitroaromatic moiety (Scheme 14). This reaction may be competitive in some instances to the methodology developed by Bartoli.[49]

Some other examples of the alkylation of electrophilic aromatic compounds using dialkyl or aryl alkyl sulfones, in which an $—SO_2R$ group acted both as a carbanion stabilizing and leaving group have been described.[6] These reactions can be considered to proceed along the VNS scheme.

3. SULFOXIDES

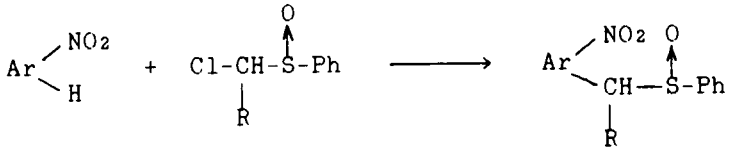
a-Chlorosubstituted sulfoxides exhibit lower acidity than the corresponding sulfones, nevertheless they have been efficiently deprotonated and serve as suitable nucleophiles for the VNS in nitroarenes. Taking into account the ability

of —$SOCH_3$ group for elimination and that a chlorine atom is also a good leaving group in the VNS, one could expect two ways of the elimination from the σ-adduct formed from chloromethyl aryl sulfoxide anion and nitroarene, namely elimination of hydrogen chloride or arenesulfenic acid. In the investigated reactions, elimination of Cl^- takes place and the only observed products in these reactions were *ortho*- and *para*-nitrobenzyl sulfoxides. Due to lower acidity of the sulfoxides and to their moderate stability in basic media it was necessary to select carefully a base/solvent system to carry out this reaction. To compare the influence of different factors on the reaction course, several reactions in various base-solvent systems (NaOH/DMSO; $NaOH/NH_{3\,liq}$; tetrabutylammonium hydroxide/*o*-dichlorobenzene; 50% NaOH/tetrabutylammonium hydrogen sulfate/benzene) were performed.[50] Usually these reactions gave moderate yields of the expected nitrobenzyl sulfoxides (Table V).

When sulfoxide stabilized carbanions do not contain other leaving groups, the elimination of sulfenate anion can result in nucleophilic methylation. This process was reported for some nitroarenes and heterocycles.[5] Similarly, methylation of nitroarenes using dimethylsulfoxonium methylide has been performed.[4] These reactions can be recognized as the early examples of the VNS.

TABLE V

Reactions of α-chloromethane sulfoxide derivatives with nitroarenes[50]



No.	Aromatic nitrocompound	R	Method	Position of —CHRS(O)Ph	Yield [%]
1	Nitrobenzene	Ph	A	4	53
			B	4	50
			C	4	66
2	2-Chloronitrobenzene	Ph	A	4	57
3	Nitrobenzene	Cl	B	2	14
				4	43
			C	2	17
				4	51
4	3-Chloronitrobenzene	Cl	B	4	68
			C	4	64
5	Nitrobenzene	H	C	2	15
				4	30
			D	2	18
				4	36
6	1-Nitronaphthalene	H	C	2	29
				4	29
7	4-Nitrobiphenyl	H	C	2	52
			D	2	59

Method: A—NaOH/DMSO, B—$NaOH/NH_{3\,liq}$, C—tetrabutylammonium hydroxide/*o*-dichlorobenzene, D—50% NaOH/tetrabutylammonium hydrogen sulfate.

5. SULFIDES AND OTHER BIVALENT SULFUR DERIVATIVES

Carbanions substituted at the α-position with alkylthio-, arylthio- and dialkyldithiocarbamoyl groups were found to be suitable starting materials for the VNS. These substituents were found to be good leaving groups in this reaction, they provide also substantial carbanion stabilizing effect.

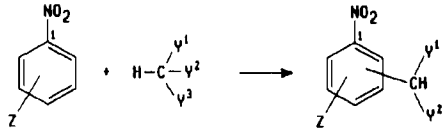
The carbanions derived from dithioacetals are widely used in organic synthesis as acyl anion equivalents (Umpolung).[51] They can also react with nitroarenes according to the VNS scheme, producing the corresponding *ortho*- and *para*-nitrobenzyl sulfides[52] (Table VI). In some instances, particularly when σ-adducts are formed at the position *ortho*- to the nitro group direct oxidation of the σ-adduct leading to aldehyde dithioacetals competes with the VNS.

The anion obtained from triphenylthioorthoformate replaces hydrogen exclusively in the position *para*- to the nitro group (Table VI) giving the thioacetals which can be easily hydrolyzed to corresponding nitroaryl aldehydes. Thus, this is a new method of nucleophilic formylation of nitroarenes.[53]

High nucleophilic activity of thiolate anions which are eliminated from σ-adducts sometimes lead to the formation of sulfur-containing products. This side reaction is observed when in the nitroarene moiety at the position *ortho*- or *para*- to the nitro group the substituents susceptible to the nucleophilic replacement (e.g. chlorine or fluorine atoms or the nitro group) are present. Addition of *n*-butyl bromide, which acts as a thiolate anion scavenger, to the reaction mixture helps to overcome this side process.[53] To avoid this competing

TABLE VI

Reactions of aldehyde dithioacetals and triphenylthioorthoformate with nitrobenzene derivatives

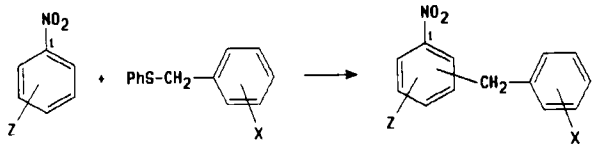


	Z	C–H acid Y^1	Y^2	Y^3	Method	Position of CHY^1Y^2	Yield[a] [%]	Ref.
1	H	H	SPh	SPh	A	2	27(4)	52
						4	14	
2	4-Ph	H	SPh	SPh	A	2	27(14)	52
3	H	Ph	SPh	SPh	A	4	52	52
4	H	H	$[SC(S)NEt_2]_2$		B	2	23	52
						4	27	
5	4-Cl	H	$[SC(S)NEt_2]_2$		B	2	55	52
6	H	SPh	SPh	SPh	C	4	57	53
7	2-F	SPh	SPh	SPh	C	4	46[b]	53
8	2-F	SPh	SPh	SPh	C[c]	4	23	53
9	3-Cl	SPh	SPh	SPh	C	4	15	53

[a] Yield of the oxidation product in parentheses.
[b] Z = SPh (substitution of fluorine occured).
[c] Reaction was carried out in the presence of *n*-butyl bromide.
Method: A—*t*-BuOK/DMSO, B—*t*-BuOK/DMF, C—NaOH/DMSO.

TABLE VII

Reactions of nitroarenes with benzyl phenyl sulfides[54]



No.	Nitrocompound Z	Sulfide X	Method	Position of —CH_2Ar	Yield [%]
1	H	2-CN	A	2	4
				4	38
2	H	4-CN	A	2	4
				4	36
3	H	4-SO_2Ph	B	4	47
4	3-Cl	2-CN	A	4	59
5	4-Ph	2-CN	A	2	32
6	(1-NN)[a]	4-NO_2	B	2	10
				4	10

[a] 1-NN = 1-nitronaphthalene.
Method: A—NaH/DMF, B—NaOH/DMSO.

S_NAr reaction, dialkyldithiocarbamoyl derivatives can also be recommended as starting materials.

Benzyl aryl sulfides react with nitroarenes giving *ortho*- and *para*-nitroaryl arylmethanes[54] (Table VII). In general, these reactions gave good results when additional electron-withdrawing substituents, like —CN or —SO_2Ph groups, are present at *ortho*- or *para*-positions of the aromatic ring of the benzyl group, but this is not essential for the reaction.

Of a great practical value in organic synthesis are reactions of carbanions derived from α-substituted carboxylic acid esters and nitriles.

Anions obtained from alkanenitriles substituted at the α-position with arylthio- or dialkyldithiocarbamoyl groups react according to the VNS scheme yielding expected nitroaryl derivatives.[14,15,30,55,56,57,58,59] Depending on the structure of starting materials these reactions gave moderate to good yields of nitroaryl alkanenitriles (Table VIII). Although in such VNS process corresponding α-halocarbanions can be applied,[15,17,19,55,56,57] they are of limited use due to their tendency for self-condensation.

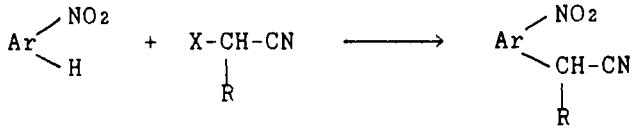
An interesting example of an application of the intramolecular VNS employing α-phenylthiosubstituted nitrile is the synthesis of the aklavinone precursor presented by Cava and Murphy[60] (Scheme 15).

Methylthio(phenoxy)acetonitrile—a molecule containing two potential leaving groups—reacts with nitrobenzene and its derivatives giving both expected products[59] (Scheme 16). This reaction can also be considered as an introduction of the masked formyl group.

Esters of (phenylthio)acetic and α-(phenylthio)propionic acids react with nitroarenes in the presence of sodium hydride or sodium hydroxide in DMSO leading to esters of nitrophenylacetic or propionic acids[56] (Table IX). In these reactions the product of direct substitution of hydride anion is sometimes formed,

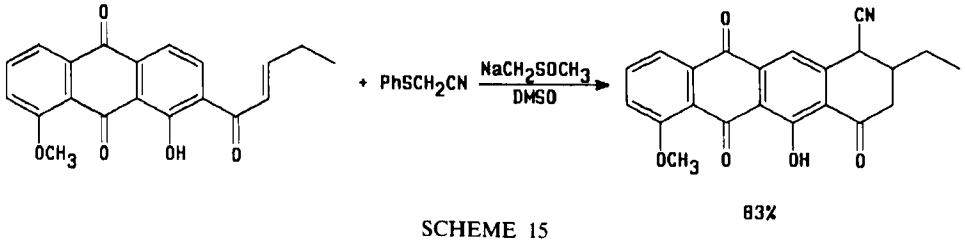
TABLE VIII

Cyanoalkylation of nitroarenes



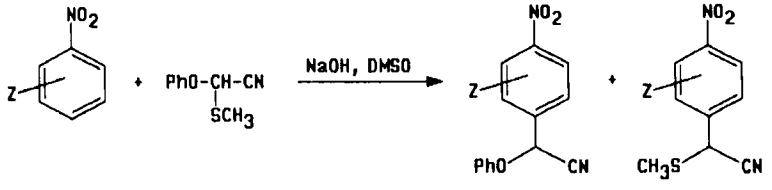
No.	Nitrocompound	Nitrile X	Nitrile R	Method	Position of —CHR—CN	Yield [%]	Ref.
1	Nitrobenzene	PhS	H	A	4	50	56
					2	18	
2	3-Chloronitro-benzene	PhS	H	A	2	8	56
					4	67	
					6	17	
3	3-Methoxynitro-benzene	Me_2NCS_2	H	B	2	16	57
					6	4	
4	3-Fluoronitro-benzene	Me_2NCS_2	H	B	2	41	57
					6	6	
5	3-Cyanonitro-benzene	Me_2NCS_2	H	B	2	11	57
					6	51	
6	1,3-dinitrobenzene	Me_2NCS_2	H	B	4	50	57
7	4-(Phenylthio)-nitrobenzene	PhS	H	A	2	74	56
8	Nitrobenzene	PhS	Me	A	4	79	56
9	3-Chloronitro-benzene	PhS	*i*-Pr	A	4	63	56
10	1-Nitronaphthalene	PhS	H	A	2	86	56
					4	8	
11	5-Nitroquinoline	PhS	H	B	6	62	15
12	6-Nitroquinoline	PhS	H	A	5	30	15
13	8-Nitroquinoline	PhS	H	B	7	45	15

Method: A—NaOH/DMSO, B—*t*-BuOK/THF.



83%

SCHEME 15

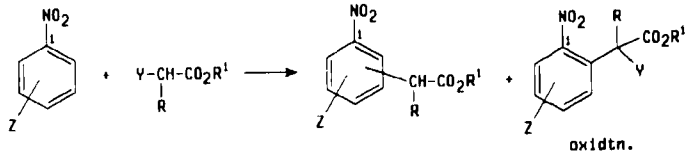


Z = H	25%	50%
Z = 2-Cl	18%	53%
Z = 3-SPh	15%	25%

SCHEME 16

TABLE IX

Reactions of α-thiosubstituted esters[56]



No.	Nitroarene Z	C—H acid Y	R	R^1	Method	Position of —CHRCOOR^1	Yield [%]
1	H	SPh	H	Me	A	4	41
2	H	$SC(S)NMe_2$	H	Me	A	4	27
3	4-Cl	$SC(S)NMe_2$	H	Me	A	2	52
4	4-PhCO	SPh	H	*t*-Bu	B	oxidtn.	30
5	H	SPh	Me	*t*-Bu	B	4	44
6	3-Cl	SPh	Me	*t*-Bu	B	4	42

Method: A—NaH/DMSO, B—NaOH/DMSO

probably as a result of an oxidation of the intermediate σ-adduct by DMSO or another molecule of nitroarene. This reaction course was observed particularly in the case of σ-adducts formed *via* an attack of the carbanion on the position *ortho*- of the nitroarene moiety. Due to the steric factors, elimination, which requires an antiperiplanar configuration of hydrogen and the leaving group, in this case is slower than the competing oxidation.

Introduction of α-cyanoalkyl or α-alkoxycarbonylalkyl substitutents into the nitroarene moiety, particularly in the *ortho* position to the nitro group gives an access to esters and nitriles of α-(*o*-nitroaryl)alkanoic acids—starting materials for the synthesis of indole[14,61] and oxindole[62] derivatives and their hetero-analogues.

6. CONCLUSIONS

In this review we have tried to show that Vicarious Nucleophilic Substitution of Hydrogen (VNS) using sulfur-stabilized carbanions containing leaving groups is a valuable method for the introduction of a variety of substituted alkyl groups into molecules of electron deficient aromatic compounds. This methodology can be considered as a supplement to the well-known Friedel-Crafts reaction providing a possibility for the direct functionalization of the aromatic compounds, particularly nitroarenes which do not enter electrophilic substitution reactions.

REFERENCES

1. For a comprehensive review see: (a) J. F. Bielmann and J.-B. Ducep, *Org. Reactions*, **27**, 1 (1982). (b) "Methoden der Organischen Chemie" (Houben-Weyl), (E. Klamann, Ed.), Stuttgart 1985, Vol. E11.

2. S. Bradamante and G. Pagani, *J. Chem. Soc., Perkin Trans. 1*, **1973,** 163.
3. B. M. Trost, *Tetrahedron Lett.*, **1966,** 5761.
4. H. Metzger, H. Koenig, and K. Seelert, *Tetrahedron Lett.*, **1964,** 867, H. Koenig, H. Metzger, and K. Seelert, *Chem. Ber.*, **98,** 3712 (1965), V. J. Traynelis and J. V. McSweeney, *J. Org. Chem.*, **31,** 243 (1966).
5. G. A. Russel and S. A. Weiner, *J. Org. Chem.*, **31,** 248 (1966), Y. Hamada and I. Takeuchi, *J. Org. Chem.*, **42,** 4209 (1977).
6. Y. Yamamoto, T. Nisimura, and H. Nozaki, *Bull. Chem. Soc. Japan*, **44,** 541 (1971), H. Nozaki, T. Nisimura, and Y. Yamamoto, *Bull. Chem. Soc. Japan*, **45,** 301 (1972).
7. J. Goliński and M. Mąkosza, *Tetrahedron Lett.*, **1978,** 3495.
8. For a general review of the VNS see: M. Mąkosza and J. Winiarski, *Acc. Chem. Res.*, **20,** 282 (1987). M. Mąkosza, *Uspiekhi Khim.*, **58,** 1289 (1989).
9. M. Mąkosza and T. Glinka, *J. Org. Chem.*, **48,** 3860 (1983).
10. M. Mąkosza and B. Mudryk, *Tetrahedron*, **44,** 209 (1988).
11. M. Mąkosza, T. Glinka, and A. Kinowski, *Tetrahedron*, **40,** 1863 (1984).
12. M. Mąkosza and S. Ludwiczak, *J. Org. Chem.*, **49,** 4562 (1984).
13. M. Mąkosza, B. Chylińska, and B. Mudryk, *Liebigs Ann. Chem.*, **1984,** 8.
14. M. Mąkosza, W. Danikiewicz, and K. Wojciechowski, *Liebigs Ann. Chem.*, **1988,** 203.
15. M. Mąkosza, A. Kinowski, W. Danikiewicz, and B. Mudryk, *Liebigs Ann. Chem.*, **1986,** 69.
16. K. Wojciechowski and M. Mąkosza, *Synthesis*, **1989,** 106.
17. M. Mąkosza and E. Slomka, *Bull. Pol. Acad. Sci., Chemistry*, **32,** 69 (1984).
18. E. Kwast and M. Mąkosza, *Tetrahedron Lett.*, **1990,** 121.
19. M. Mąkosza and E. Kwast, *Bull. Pol. Acad. Sci., Chemistry*, **35,** 287 (1987).
20. M. K. Bernard, M. Mąkosza, B. Szafran, and U. Wrzeciono, *Liebigs Ann. Chem.*, **1989,** 545.
21. M. Mąkosza, J. Goliński, and A. Rykowski, *Tetrahedron Lett.*, **24,** 3277 (1983).
22. M. Mąkosza and A. Rykowski, *Liebigs Ann. Chem.*, **1988,** 627.
23. M. Hamana, Y. Fujimura, and T. Haradahira, *Heterocycles*, **25,** 229 (1987).
24. M. Mąkosza, T. Glinka, S. Ostrowski, and A. Rykowski, *Chemistry Lett.*, **1984,** 61.
25. S. Ostrowski and M. Mąkosza, *Tetrahedron*, **44,** 1721 (1988).
26. M. Mąkosza and S. Ostrowski, *J. Prakt. Chem.*, **330,** 789 (1988).
27. S. Ostrowski and M. Mąkosza, *Liebigs Ann. Chem.*, **1989,** 95.
28. M. Mąkosza and J. Goliński, *Synthesis*, **1983,** 1023.
29. M. Mąkosza, J. Goliński, and J. Baran, *J. Org. Chem.*, **49,** 1488 (1984).
30. M. Mąkosza and S. Ludwiczak, *Synthesis*, **1986,** 50.
31. M. Mąkosza and K. Wojciechowski, *Tetrahedron Lett.*, **25,** 4791 (1984).
32. See ref. 1 b), p. 1239.
33. P. Kocienski, *Phosphorus and Sulfur*, **24,** 97 (1985).
34. M. Mąkosza and A. Tyrała, *Synthesis*, **1987,** 1142.
35. C. J. M. Stirling, *Int. J. Sulfur Chem., Part C*, **6,** 41 (1971).
36. See ref. 1 b), p. 1262.
37. L. Paquette, *Org. Reactions*, **25,** 1 (1977).
38. A. Jończyk, K. Bańko, and M. Mąkosza, *J. Org. Chem.*, **40,** 266 (1975).
39. J. Goliński and M. Mąkosza, *Synthesis*, **1978,** 823.
40. M. Mąkosza and A. Kinowski, *Bull. Pol. Acad. Sci., Chemistry*, **37,** 127 (1989).
41. K. Wojciechowski and M. Mąkosza, *Tetrahedron Lett.*, **25,** 4793 (1984).
42. M. Mąkosza, W. Danikiewicz, and K. Wojciechowski, *Liebigs Ann. Chem.*, **1987,** 711.
43. R. Neidlein and G. Lautenschlaeger, *Chem. Ber.*, **122,** 493 (1989).
44. M. Mąkosza, J. Goliński, J. Baran, and D. Dziewońska-Baran, *Chemistry Lett.*, **1984,** 1619.
45. M. Mąkosza, J. Baran, D. Dziewońska-Baran, and J. Goliński, *Liebigs Ann. Chem.*, **1989,** 825.
46. E. Buncel, M. R. Crampton, M. J. Strauss, and F. Terrier, "Electron Deficient Aromatic- and Heteroaromatic-Base Interactions," (Elsevier, Amsterdam, 1984), Chap. 4.
47. J. Goliński, M. Mąkosza, and A. Rykowski, *Tetrahedron Lett.*, **24,** 3279 (1983).
48. M. Mąkosza and Z. Wróbel, *Org. Prep. Proc. Int.*, (submitted).
49. G. Bartoli, *Acc. Chem. Res.*, **17,** 109 (1984).
50. M. Mąkosza, J. Goliński, and J. Pankowski, *Synthesis*, **1983,** 40.
51. B.-T. Groebel and D. Seebach, *Synthesis*, **1977,** 357.
52. M. Mąkosza and J. Winiarski, *J. Org. Chem.*, **49,** 5272 (1984).
53. M. Mąkosza and J. Winiarski, *Chemistry Lett.*, **1984,** 1623.
54. J. Pankowski, PhD. Thesis, (Warsaw Technical University 1986).
55. M. Mąkosza and J. Winiarski, *J. Org. Chem.*, **45,** 1534 (1980).
56. M. Mąkosza and J. Winiarski, *J. Org. Chem.*, **49,** 1494 (1984).
57. M. Mąkosza, M. Wenäll, M. Goliński, and A. Kinowski, *Bull. Pol. Acad. Sci., Chemistry*, **33,** 427 (1985).

58. A. Jończyk, Z. Owczarczyk, M. Mąkosza, and J. Winiarski, *Bull. Soc. Chim. Belg.*, **96,** 303 (1987).
59. A. Jończyk, M. Goliński, and J. Winiarski, *Liebigs Ann. Chem.*, **1989,** 203.
60. R. A. Murphy, Jr. and M. P. Cava, *Tetrahedron Lett.*, **25,** 803 (1984).
61. R. J. Sundberg, "The Chemistry of Indoles," (Academic Press, New York, 1970), Chap. IIIC.
62. See ref. 61, Chap. VIIB.