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Regioselective methods of synthesis of asymmetrically substituted diazene oxides

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Contents

I.	Introduction	143
II.	Oxidation of asymmetrically substituted azo-compounds	143
III.	Reactions of *syn*-diazotates with alkylating agents	147
IV.	Reactions of nitro- and nitroso-compounds with amino-derivatives	148
V.	Interaction of anions containing the N_2O_2 fragment with electrophiles	160
VI.	Other methods of synthesis of asymmetrically substituted diazene *N*-oxides	163
VII.	Conclusion	165

Abstract. Regioselective methods of synthesis of asymmetrically substituted diazene oxides, in which the diazene oxide group is linked to carbon, oxygen, sulphur, nitrogen, and phosphorus atoms, are examined. Data on the reaction conditions, yields, and structures of azoxy-products are presented. The bibliography includes 232 references.

I. Introduction

The first azoxy-compounds were synthesised almost 150 years ago,[1] but almost up to the middle of the present century these were mainly compounds containing identical structural fragments at the nitrogen atoms of the diazene *N*-oxide group. The vigorous development of the chemistry of the diazene *N*-oxides was stimulated by the isolation from natural sources of compounds of this type exhibiting a high biological activity (carcinogenic,[2-9] antibacterial,[10-16] tuberculostatic,[7-8] fungicidal,[10,16-18] and nematocidal[19,20]) and also of the discovery in the series of asymmetrically substituted *N*,*N'*-diaryldiazene *N*-oxides of substances exhibiting the properties of liquid crystals.[21-30]

Although a series of reviews has been devoted to the chemistry of azoxy-compounds,[31-35] the regioselective methods of synthesis of asymmetrically substituted compounds of the given series are dealt with in a fragmentary fashion in these publications. Furthermore, since the appearance of the last of the published reviews[34] more than ten years have elapsed, which makes it timely to survey the large amount of synthetic data which have been published during this period.

This review is devoted to the consideration of modern methods of synthesis of asymmetrically substituted diazene *N*-oxides from compounds which do not contain the diazene *N*-oxide group.

The data are classified in terms of the N→O, C–N, and N=N bonds formed with participation of the nitrogen atoms of the diazene group. The reactions involving the alkylation of anions containing the N_2O_2 structural fragments (salts of *N*-nitrosohydroxylamines, *N*-nitroamines, and hyponitrous acid), accompanied by the formation of a C–O bond separated from the diazene *N*-oxide group and leading to the formation of O-substituted azoxy-compounds which have been actively investigated in recent years (*N'*-alkoxydiazene *N*-oxides, O,N-disubstituted nitroamines) are included in the review as a separate section.

In order to cover more fully the synthetic data and to facilitate the use of the review, a considerable proportion of the information has been arranged systematically in the form of tables containing detailed data on the initial compounds and reagents, the reaction conditions, and the yields and structures of the azoxy-products. Only studies where details of the methods used in carrying out the reactions are given and the structures of the asymmetrically substituted azoxy-compounds have been reliably demonstrated have been included, as a rule, in the sources quoted.

II. Oxidation of asymmetrically substituted azo-compounds

When an azo-compound is treated with oxygen-containing oxidants, a mixture of diazene *N*-oxides with different positions of the oxygen atom in the diazene *N*-oxide group is as a rule formed:[34]

$$R^1-N=N-R^2 \xrightarrow{Ox} \underset{\mathbf{A}}{R^1-\overset{\uparrow}{\underset{O}{N}}=N-R^2} + \underset{\mathbf{B}}{R^1-N=\overset{\uparrow}{\underset{O}{N}}-R^2} \quad (1)$$

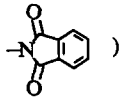
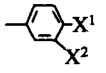
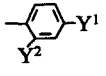
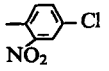
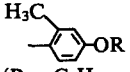
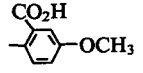
However, in a number of instances, the structural features of the starting substances ensure the preferential or exclusive formation of one of the regioisomeric oxidation products (Table 1).

The influence of the electronic and steric nature of the substituents at the nitrogen atoms of the azo-group on the regiospecificity of the oxidation process is clearly manifested in the series of *N*,*N'*-diaryldiazenes. The oxidation of *p*-nitro-[38] and *p*-alkoxy-diaryldiazenes[38-40] proceeds fairly selectively, in contrast to the oxidation of the majority of other asymmetric aromatic azo-compounds containing substituents in the *meta*- and *para*-positions in the aromatic ring, and makes it possible to synthesise azoxy-products in which the oxidised nitrogen atom is linked to the unsubstituted aromatic ring[38-40] (Table 1). The phenomenon of the identical directing effect of groups having completely different electronic characteristics has not yet received a satisfactory theoretical explanation,[34,38] but it can be used successfully in synthetic practice.

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Table 1. Conditions in the reactions of asymmetric azo-compounds with oxidants and the ratios and yields of the isomeric oxidation products.

R^1	R^2	Oxidant	Solvent	Reaction temperature/ °C	Reaction time/h	A/B ratio	Overall yield of oxidation products (%)	Ref.
$-C_6H_5$	$-C_6H_4-R$-*m*, *p* ($R = NO_2, SO_2CH_3, SO_2C_6H_5, NHC(O)CH_3, NHSO_2C_6H_4CH_3$-*p*, $OC(O)CH_3, OC(O)C_6H_5$, F, Cl, Br, )	36% H_2O_2	CH_3CO_2H	50	20–60	1.07–1.73	–	36, 37
$-C_6H_5$	$-C_6H_4-NO_2$-*p*	t-$C_4H_9OOH/MoO_2(dpm)_2$	C_6H_6	60	24	>100	73	38
		CH_3CO_3H	CH_3CO_2H	60	20	>100	84	38
		m-$ClC_6H_4CO_3H$	$CHCl_3$	60	24	>100	86	38
$-C_6H_5$	$-C_6H_4-OCH_3$-*p*	t-$C_4H_9OOH/MoO_2(dpm)_2$	C_6H_6	60	4	>100	81	38
		t-$C_4H_9OOH/Mo(CO)_6$	C_6H_6	60	24	0.89	88	38
		CH_3CO_3H	CH_3CO_2H	60	20	2.85	75	38
$-C_6H_4-X$-*p* ($X = H, n$-$C_4H_9, OC(O)CH_3$)	$-C_6H_4-Y$-*p* ($Y = CH_3, OCH_3, OC_2H_5$, Cl)	40% CH_3CO_3H	40% CH_3CO_3H	118	12	0.78–1.22	70–85	39
$-C_6H_4-Cl$-*p*	$-C_6H_4-OC_2H_5$-*p*	30% H_2O_2	CH_3CO_2H (glacial)	118	5	>100	50	40
			CH_3CO_2H (80%)	118	5	<0.01	51	40
 ($X^1 = H, CH_3, Cl, OCH_3$; $X^2 = H, Cl$)	 ($Y^1 = H, CH_3, Cl, OCH_3, CO_2CH_3$; $Y^2 = CH_3, Cl, OCH_3, CO_2CH_3, CO_2H$)	90% H_2O_2	CH_3CO_2H	25	12–24	5–24	82–92	41, 42
$-C_6H_4-Cl$-*p*		30% H_2O_2	CH_3CO_2H	70–75	1	>100	79	43
$-C_6H_4-C_4H_9$-*p*	 ($R = C_nH_{2n+1}$, $n = 1-6$)	30% H_2O_2	CH_3CO_2H (glacial) + $(CH_3CO)_2O$	20	24	>100	47–91	44
$-C_6H_5$	 (Y = H, CH_3)	30% H_2O_2	CH_3CO_2H	70–80	–	>100	38–75	45, 46
$-C_6H_4-OCD_3$-*p*		CH_3CO_3H	$CHCl_3$	20	18	2.67	55	47

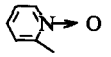
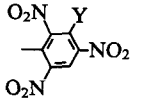
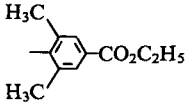
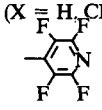
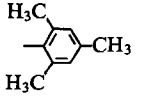
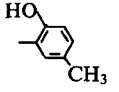
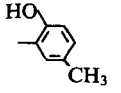
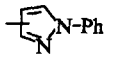
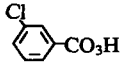
$-C_6H_5$		30% H_2O_2	CH_3CO_2H	–	–	> 100	–	48
$-C_6H_5$	 ($Y^1 = N\rightarrow O$, $Y^2 = CH$; $Y^1 = CH$; $Y^2 = N\rightarrow O$)	30% H_2O_2	CH_3CO_2H	–	–	2 – 3	–	48
$-C_6H_4-NO_2$-*p*	 (Y = H, Cl, $-N=N-C_6H_4-NO_2$-*p*)	CrO_3 + 98% HNO_3	98% HNO_3	70 – 80	2 – 3	> 100	40 – 92	49, 50
$-C_6H_5$		30% H_2O_2	CH_3CO_2H	–	–	> 10	80	51
$-C_6H_4-X$-*p* (X = H, CH_3, OCH_3, Br, Cl)	$-C_6Cl_5$	CF_3CO_3H	$CHCl_3$	61	2	> 100	> 95	52
		CF_3CO_3H	$CHCl_3$	61	2	< 0.01	75	53
$-C_6F_5$	$-C_6H_5$	CF_3CO_3H	CH_2Cl_2	40	5	> 100	87	54
$-C_6H_5$		90% H_2O_2	CH_3CO_2H	25	24	0.38	90	41
$-C_6H_4-X$-*o* (X = OCH_3, CH_3, Br, Cl)		30% H_2O_2	CH_3CO_2H	75 – 80	18	< 0.01	15 – 33	55
$-C_6H_5$	$-CH_3$	$C_6H_5CO_3H$	CH_2Cl_2	0	12	~ 10	–	56
$-C_6H_4-X$-*p* (X = H, Br)	$-CH_2-C_6H_4-Cl$-*p*	$C_6H_5CO_3H$	$(C_2H_5)_2O$	0	16	~ 10	~ 100	57
$-C_6H_4-X$ (X = H, Cl, Br, NO_2, OCH_3, CO_2CH_3)	$-C\equiv N$	85% H_2O_2	CF_3CO_2H	45	0.2 – 7.0	> 100	17 – 84	58-60
$-C_6H_4-X$-*p* (X = CH_3, Cl, NO_2, CO_2CH_3, CO_2H)	$-C(O)NH_2$	30% H_2O_2	HCO_2H or AcOH	40	~ 10	> 100	70 – 80	15, 61, 62

Table 1 (cont.).

R^1	R^2	Oxidant	Solvent	Reaction temperature/ °C	Reaction time/h	A/B ratio	Overall yield of oxidation products (%)	Ref.
	$-C\equiv N$	85% H_2O_2	CF_3CO_2H	45	–	> 100	65–70	63
$-C_6H_4-X$ [a] (X = H, Cl, Br, NO_2, OCH_3, CH_3)	$-CO_2Y$ (Y = CH_3, C_2H_5), $-C(O)C_6H_5$	85% H_2O_2 + maleic anhydride	CH_2Cl_2	40	0.5–1.5	> 100	70–90	58, 64
$-C_6H_4-X$ (X = H, CH_3, OCH_3, Cl, $CO_2C_2H_5$)	$-NH-C_6H_4-Y$ (Y = H, CH_3, OCH_3, Cl, $CO_2C_2H_5$, NO_2)	$C_6H_5CO_3H$	$(C_2H_5)_2O$ or $C_6H_5CH_3$	0	10–112	> 100 [b]	40–100	65
$-CH_3$ [c]		40% CH_3CO_3H	$(C_2H_5)_2O$	20	2	> 100	21	66
$-CX_2-OC(O)CH_3$ (X = CH_3, X_2 = $-(CH_2)_5-$)	$-CH_3$, $-C_6H_5$	40% CH_3CO_3H	CH_2Cl_2 or $(C_2H_5)_2O$	20	2–3	> 100	50–78	67
$-C(CH_3)=CH_2$	$-CH_3$	40% CH_3CO_3H	$(C_2H_5)_2O$	36	several hours	> 100	44	68
	$-CH_3$	40% CH_3CO_3H	$(C_2H_5)_2O$	20	1	> 100	66	68
$-CH=C(CH_3)_2$	$-CH_3$	40% CH_3CO_3H	$(C_2H_5)_2O$	20	1	< 0.01	34	68
$-C(CH_3)=C(CH_3)_2$	$-CH_3$		$(C_2H_5)_2O$	exothermic reaction	1	< 0.01	42	68
$-CH_3$	$-C(O)N(CH_3)_2$	90% H_2O_2 + 	CH_2Cl_2	40	3	> 100	50	69

[a] The initial arylazo-compounds may be generated *in situ* by oxidising the corresponding hydrazo-compounds and can be introduced into the process without isolation and purification.

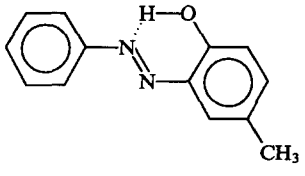
[b] For X ≠ Y, a mixture of the isomers $X-C_6H_4-\overset{\overset{O}{\uparrow}}{N}=N-NH-C_6H_4-Y$ and $X-C_6H_4-NH-N=\overset{\overset{O}{\uparrow}}{N}-C_6H_4-Y$ is formed. The component in which the oxidised nitrogen atom is linked to the aromatic ring containing a substituent with weaker electron-accepting properties predominates.

[c] The initial azo-compounds are generated *in situ* by oxidising the corresponding hydrazones.

In the case of *N,N'*-diaryl(heteroaryl)diazenes[53,54] containing substituents in the *ortho*-position relative to the azo-group, the sterically more accessible nitrogen atom, linked to the unsubstituted aromatic ring, is oxidised preferentially, the regioselectivity of the process reaching 75–100%.[41,47] Alkyl,[41,44] cycloalkyl,[45,46] alkoxy-,[41] ester,[41] carboxy,[42,47] and nitro-groups,[43] as well as halogen atoms[41] can be used as regio-controlling *ortho*-substituents. The *N*-oxide fragment of the heterocycle in the *ortho*-position relative to the azo-group exerts a similar directing effect[48] (Table 1).

The introduction of a second *ortho*-substituent into the aromatic ring as a rule fully inhibits the oxidation of the nitrogen atom of the azo-group linked to this ring.[49–52] The regiospecificity of the oxidation reactions of *N*-tetrafluoro-pyridyl-*N'*-(2,4,6-trimethylphenyl)diazene[53] and *N*-pentafluoro-phenyl-*N'*-phenyldiazene,[54] leading to the formation of azoxy-compounds in which the oxidised nitrogen atom is linked to the aromatic ring containing more bulky substituents in the *ortho*-position, therefore appears anomalous. A possible cause of the unexpected mode of oxidation of the above compounds may be, according to Miller and Furin, the increase in the nucleophilicity of the α-nitrogen atom induced by the decrease in the effectiveness of the interaction between the lone pair of the latter and the π-systems of the perfluoro- and 2,4,6-trimethyl-substituted aromatic rings.[54]

Processes involving the protonation of the reaction centre and the ability of the nitrogen atoms of the azo-group to participate in the formation of intramolecular hydrogen bonds can also exert a significant influence on the mode of oxidation of *N,N'*-diaryldiazenes. Thus, whereas the majority of *ortho*-substituents direct the oxidation of the N=N bond to the most remote nitrogen atom, in the case of *N*-(2-hydroxy-5-methylphenyl)-*N'*-aryldiazenes[41,55] (Table 1) a different mode of oxidation takes place preferentially, which is apparently due to the "blocking" of the lone pair of the β-nitrogen atom by the hydrogen atom of the hydroxy-group.[41]



The important role of the protonation of the reaction centre is confirmed by the different regiospecificities of the oxidation of *N*-(*p*-chlorophenyl)-*N'*-(*p*-alkoxyphenyl)-diazene[40] and *N*-phenyl-*N'*-(*p*-alkoxyphenyl)diazene[38] in media of different acidity (Table 1).

The oxidation reactions of asymmetrical azo-compounds in which one of the atoms is linked to an aromatic or heterocyclic system and the other to alkyl,[56,57] nitrile,[58,60,63] amino-carbonyl,[15,61,62] ester,[58,64] keto-,[58] or amino-group[65] are characterised as a rule by a high regioselectivity (Table 1). The reaction products are in this case usually asymmetrically substituted diazene *N*-oxides in which the oxygen atom is fixed in the α-position relative to the aromatic or heteroaromatic ring. The choice of the oxidant is determined by the stability under reaction conditions of the functional groups present in the molecule. Thus the synthesis of *N'*-cyanodiazene *N*-oxides from the corresponding cyanodiazenes[58–60,63] requires the use of 85% H_2O_2, because a more dilute hydrogen peroxide solution induces the hydrolysis of the nitrile group to the amide group.[15,58]

The oxidation of *N*-aryl-*N'*-(arylamino)diazenes (1,3-diaryltriazenes)[65] proceeds with participation of the nitrogen atom of the amino-group. The reaction results in the formation of a mixture of isomeric oxidation products (triazene oxides) in which the oxidised nitrogen atom is linked to one of the aromatic rings forming part of the molecule (preferentially to the ring containing electron-donating substituents).[65]

Data on the regioselective oxidation reactions of asymmetrically substituted aliphatic azo-compounds are limited to information about the oxidation of *N,N'*-dialkyldiazenes containing the acetoxy-group in the α-position relative to the azo-group[66,67] and about reactions with participation of *N*-alkenyl-[68] and *N*-dimethylaminocarbonyl-*N'*-alkyldiazenes[69] (Table 1).

The mode of reaction depends very greatly on the detailed characteristics of the structure of the initial compounds; slight changes in the structure of the substrates being oxidised (for example, in the number and disposition of the substituents at the double bond) entail a change in the site where the oxygen atom is attached in the azoxy-products formed. In our view, one should adopt a critical attitude to the conclusion[68] that the oxidation products have a regiostructure because it was based only on ^{1}H NMR spectroscopic data and is not supported by other reliable results (^{13}C and ^{14}N NMR and X-ray diffraction).

Thus oxidation of asymmetric azo-compounds to diazene *N*-oxides by oxygen-containing oxidants takes place regioselectively only in those cases where the substituents R^1 and R^2, linked to the nitrogen atoms of the azo-group, differ appreciably in their electronic and steric structures. The regiospecificity of the process is frequently unexpected and is not always susceptible to a simple interpretation from the standpoint of the structures of the initial compounds. The complexity of the detailed allowance for all the factors determining the direction of attack by the oxygen atom of the oxidant on a particular atom in the azo-group and the unpredictability of the mode of oxidation associated with this factor greatly reduce the synthetic value of the method and hinder its use for the specific synthesis of asymmetrically substituted diazene *N*-oxides.

III. Reactions of *syn*-diazotates with alkylating agents

In 1969 Moss and coworkers[70,71] proposed a direct method of synthesis of asymmetrically substituted *N,N'*-dialkyldiazene *N*-oxides and *N*-arylalkyl-*N'*-alkyldiazene *N*-oxides from *syn*-alkyldiazotates and alkylating agents (Table 2).

An intramolecular version of the reaction has been described:[79]

$$R^1-N=N-O^-K^+ + R^2X \rightarrow R^1-N=\overset{\overset{O}{\uparrow}}{N}-R^2 . \qquad (2)$$

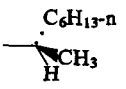
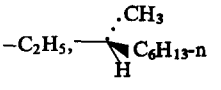
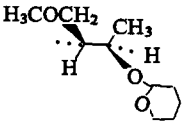
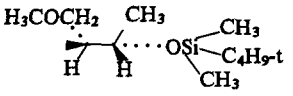
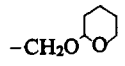
The reaction is regiospecific (the oxidised nitrogen atom in the azoxy-products formed is linked to the substituent R^2, which forms part of the alkylating agent). It involves nucleophilic attack by the N^2 atom of the diazotate anion on the electron-deficient carbon centre of the alkylating agent[80] and leads to complete or partial inversion of the configuration of the latter.[73]

The stereoselectivity of the reaction and the configurational stability of the alkyldiazotates make it possible in a number of instances to construct optically active azoxy-compounds with chiral centres at both nitrogen atoms of the diazene *N*-oxide group[73–75] (Table 2). In particular, the complete synthesis of elaiomycin[75]—a natural diazene *N*-oxide with powerful antibactericidal and carcinogenic properties—was achieved for the first time by the method considered.[7,81]

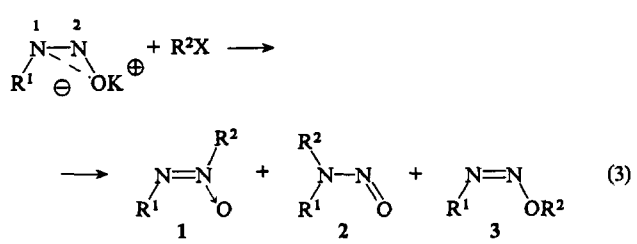
A serious disadvantage of Moss's method is the formation, together with the target azoxy-compounds **1**, of isomeric dialkylnitrosoamines **2** and diazoesters **3**—the products of alkylation at the N^1 and O atoms of the ambident diazotate anion.[80,82]

The diazoesters **3** are extremely unstable compounds and decompose under the reaction conditions, affording a mixture of nitrogen-free substances.

Table 2. Reaction conditions and the yields of products of the reactions of *syn*-alkyldiazotates with alkylating agents.

R^1	R^2	X	Solvent	Reaction temperature/°C	Time/h	Yield of product (%)[a]	Ref.
$-C_4H_9$-i, $-C_8H_{17}$-n, $-CH(CH_3)C_6H_5$, $-C_8H_{17}$-i	$-C_2H_5$	[b]	CH_2Cl_2	–	–	46 – 64	70, 71
$-C_8H_{17}$-n, $-CH(CH_3)C_6H_5$	$-C_2H_5$, $-C_4H_9$-n, $-C_3H_7$-i, $-C_4H_9$-i	I	HMPA	40	7	28 – 47	70, 71
$-C_8H_{17}$-i	$-CH_3$, $-C_3H_7$-n, $-CH_2CH=CH_2$	Br, I	HMPA	0–5	–	17 – 40	72
$-C_2H_5$, 	$-C_2H_5$, 	Cl, I	HMPA, CH_2Cl_2	–	–	20 – 50	73
	$-C_8H_{17}$-n	I	HMPA	20	15	65	74
$-CH(CH_3)C_6H_5$, $-CH(CH_3)C_6H_{11}$-cyclo	$-C_2H_5$	[b]	CH_2Cl_2	–30	2	53	11
	$-CH_3$	I	HMPA	25	12	29	75
$-CH(CH_3)C_6H_5$	$-C_2H_5$	I	THF	35	8	28	76
	$-CH_3$	I	Glyme	20	4	13	77
$-C_2H_5$	$-CH_3$	I	HMPA	25	20	37	78
			EPA	25	20	12	78

[a] The yields of products have been calculated relative to the *N*-nitrosourethanes used to obtain the *syn*-diazotates *in situ*.
[b] $(C_2H_5)_3OBF_4$ was used as the alkylating agent.
Note. HMPA = hexamethylphosphoramide; THF = tetrahydrofuran (Translator).



(3)

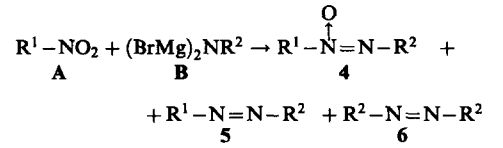
The influence of various factors on the mode of alkylation has been discussed in detail.[35] It is noteworthy that necessary conditions for the preferential formation of azoxy-compounds by Moss's reactions are the use of alkyldiazotates having the *syn*-configuration relative to the N=N bond[82] and the use of highly polar aprotic solvents, such as hexamethylphosphoramide[78] or glyme,[77] as the medium for carrying out the processes. However, even when the above conditions are maintained, it is not always possible to obtain the required azoxy-products.[77] The impossibility of using the more readily available *anti*-alkyldiazotates for the synthesis of diazene *N*-oxides[82] and also the impossibility of obtaining aromatic diazotates,[35] which are alkylated exclusively at the oxygen atom of the diazotate anion, significantly restricts the applications of Moss's reaction.

IV. Reactions of nitro- and nitroso-compounds with amino-derivatives

A more universal approach to the synthesis of asymmetrically substituted diazene *N*-oxides is based on the reactions of nitro- or nitroso-compounds with amino-derivatives. By varying the structures of the initial compounds, this procedure makes it possible to synthesise in one stage a wide range of products with the required combinations of substituents at the nitrogen atoms of the diazene *N*-oxide group.

1. Reactions of nitro-compounds with dimagnesyl derivatives of amines

In 1983 Japanese investigators[83] observed that aromatic nitro-compounds afford diazene *N*-oxides in their reactions with organodimagnesium derivatives of arylamines:

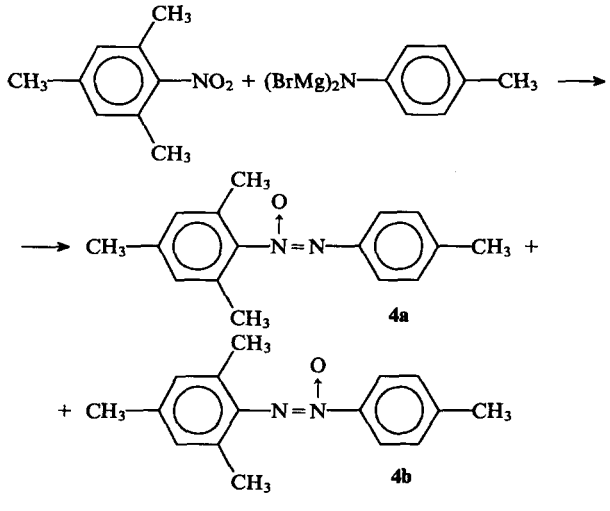


(4)

This reaction served as the basis of a new method of synthesis of asymmetrically substituted *N,N'*-diaryl(heteroaryl)diazene *N*-oxides. Its advantages are the ready availability of the initial compounds and the possibility of obtaining azoxyarenes with a fixed disposition of the oxidised nitrogen atom.

The reaction may be used to synthesise substituted *N,N'*-diaryldiazene *N*-oxides. Nitroarenes and dimagnesyl derivatives of arylamines containing alkyl, alkoxy-, and carbonyl substituents as well as halogen atoms in the aromatic ring enter into this reaction (Table 3). Azoxy-derivatives of naphthalene,[87,88] benzothiazole,[89] pyridine,[90] and ferrocene,[91] as well as polynuclear aromatic polyazoxy-compounds[92,93] have been obtained with its aid (Table 3). The synthesis of asymmetrically substituted azoxy-products from aliphatic nitro-compounds has been described.[94] The yields of diazene *N*-oxides **4** in this reaction reach 20–80% depending on the structure of the initial substances.

Unfortunately, together with the azoxy-compounds **4**, an appreciable amount of side products are formed during the reaction. These include in the first place, the diaryldiazenes **5** and **6**. The formation of the azo-compounds **5** and **6** can be explained[89–91] by the deoxygenation of the azoxyarenes **4** by the excess of the organomagnesium reagent $(BrMg)_2NR^2$ and by the oxidative dimerisation of the latter as a result of electron transfer from the reagent to the substrate. In this instance, the main factors influencing the relative yields of the products are the reactant ratio and the effectiveness of the one-electron transfer estimated from the oxidation-reduction potentials of the initial compounds.[86] Thus the introduction of electron-accepting substituents into the aryliminodimagnesyl reagent leads[83,84] to some increase in the yield of the azoxy-products **4**, while an increase in the ratio [B]/[A] is accompanied as a rule by an increase in the fraction of diaryldiazenes.[90] In a number of instances, the concept of the preliminary association under reaction conditions of the molecules of the initial compounds was used to account for the observed proportions of the products:[86,89]



The interaction of nitro-compounds with dimagnesyl derivatives of arylamines takes place as a rule regiospecifically and leads to the formation of azoxy-products in which the oxidised nitrogen atom is linked to the substituent R^1 forming part of the initial nitro-compound. This factor was used to obtain the isomeric *N,N'*-diaryldiazene *N*-oxides, which cannot be obtained by other methods and which differ in the position of the oxidised nitrogen atom in the diazene *N*-oxide group.[83,85,86,88,92] Substances having the properties of liquid crystals[29] and components of photosensitive compositions[88] have been synthesised in this way.

The only example of the isomerisation of the azoxy-group under the reaction conditions is the formation of isomeric azoxyarenes **4a** and **4b** from the sterically hindered 1-nitro-mesityl and *N,N*-bis(bromomagnesio)toluidine. The fraction of the rearrangement product **4b** increases with increase in the amount of the organometallic reagent, which indicates the involvement in the latter in the isomerisation process.[85]

Thus the interaction of nitro-compounds with dimagnesyl derivatives of arylamines constitutes a promising method of synthesis of asymmetrically substituted *N,N'*-diaryldiazene *N*-oxides of different structure. The wide scale employment of this reaction in synthetic practice has been held back, however, by the appreciable influence of the structure of the starting materials on the mode of this reaction and by the difficulty of isolating the target azoxy-compounds from the multicomponent mixtures of products formed in the course of the process. Furthermore, despite the data of Okubo et al.,[92] it is necessary to assess critically the possibility of synthesising with the aid of this method azoxyarenes carrying, apart from the azoxy-group, other functional group substituents sensitive to the action of bases.

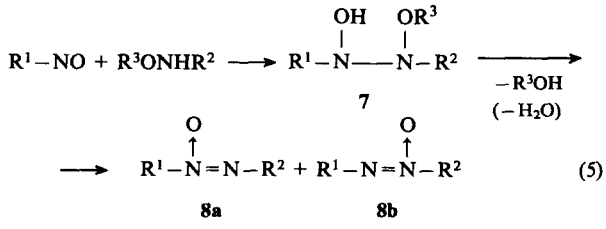
2. Synthesis of asymmetrically substituted diazene *N*-oxides by the reactions of nitroso-compounds with amino-derivatives

In our view, the synthesis of asymmetrically substituted diazene *N*-oxides from organic amino- and nitroso-compounds is the most promising. N-Substituted and O,N-disubstituted hydroxylamines as well as amino-derivatives containing an *N*–halogen bond are used as the amine component. It is noteworthy that reactions of this type were frequently considered in the chemical literature as special methods permitting the synthesis of definite fairly narrowly defined types of azoxy-compounds: triazene *N*-oxides,[95,96] *N'*-alkoxydiazene *N*-oxides,[97,98] *N'*-fluorodiazene *N*-oxides,[99,100,110] etc. In the present review, the processes involving the formation of the diazene *N*-oxide group from nitroso-compounds and amino-derivatives are presented for the first time as a general method of synthesis of carbo- and hetero-substituted azoxy-compounds.

a. Reactions of nitroso-compounds with N-substituted and O,N-disubstituted hydroxyl amines

The traditional method of synthesis of asymmetrically substituted azoxy- compounds involves reactions of aliphatic and aromatic nitroso-compounds with *N*-alkyl- and *N*-aryl-hydroxylamines (Table 4). The reactions are carried out as a rule in organic solvents (C_2H_5OH,[54,56,102] CH_3OH,[103,104] aqueous tetrahydrofuran,[104] and CH_2Cl_2[105]) over a wide temperature range. The use of UV irradiation, promoting the dissociation of dimeric nitrosoalkanes to the monomers, has a favourable effect.[104] Depending on the structure of the compounds involved in the reaction, the yields of the azoxy-products range from 5 to 85%.

A possible reaction mechanism involves the formation of the N=N bond between the nitrogen atoms of the hydroxyamino- and nitroso-groups and the elimination of one of the oxygen-containing substituents from the intermediate **7** with formation of the final reaction products.[104]



(5)

The observed regiospecificity of the process is determined by the structure of the OR^3 fragment and that of the substituents R^1 and R^2. Thus the use of N-substituted *O*-methyl-[104] and *O*-pivaloyl-hydroxylamines,[42] containing the readily removed methoxy- (R^3 = CH_3) and pivaloyl [R^3 = $C(O)C_4H_9$-t] groups, permits the regiospecific synthesis of diazene *N*-oxides in which

Table 3. The ratios of the reactants and the yields of the products of the reactions of nitro-compounds with dimagnesyl derivatives of arylamines (tetrahydrofuran, 55 °C, 1.5–5.0 h).

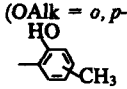
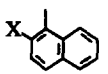
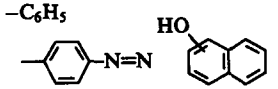
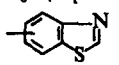
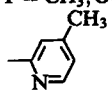
R^1	R^2	A/B molar ratio	Yields of products (%)			Ref.
			4	5	6	
$-C_6H_4-Hal$ (Hal = *o*, *m*, *p*-Cl, *o*, *p*-Br, *o*, *p*-I, *o*, *p*-F)	$-C_6H_4-Y$-*p* (Y = H, OCH_3, CH_3)	2.0–8.0	14–71	9–45	6–22	83–85
$-C_6H_4-X$-*p* (X = H, OCH_3, Cl)	$-C_6H_4-Hal$ (Hal = *m*, *p*-Cl)	2.0–5.0	65–81	10–15	6–12	83, 84
$-C_6H_4-Alk$ (Alk = *o*, *p*-CH_3, *m*-C_2H_5, *p*-C_3H_7)	$-C_6H_4-Y$ (Y = *o*, *m*, *p*-OCH_3, *m*-C_2H_5, *p*-CH_3, *p*-C_5H_{11}, *p*-$OC_6H_{13}-OC_{17}H_{35}$)	1.2–4.2	11–62	12–71	1–24	29, 83–86
$-C_6H_4-OAlk$ (OAlk = *o*, *p*-OCH_3, *p*-$OC_8H_{17}-OC_{22}H_{45}$)	$-C_6H_4-CH_3$-*p*	1.2–6.2	24–44	14–52	4–17	83, 85, 86
	$-C_6H_4-Y$-*p* (Y = CH_3, Cl)	2.0–8.0	14–43	7–33	6–12	87
 (X = H, OH)	$-C_6H_4-Y$-*p* (Y = H, Alk, OAlk)	2.0–3.0	13–40	~13	~4	87, 88
$-C_6H_5$	$-C_{10}H_7$-α	2.0	63	–	–	88
	$-C_6H_4-CH_3$-*p*	3.0	34–36	41–44	7	87
$-C_6H_4-[N=N-C_6H_4-N(CH_3)_2$-*p*$]$-*p*	$-C_6H_4-CH_3$-*p*	3.0	55	18	9	87
	$-C_6H_4-Y$-*p* (Y = CH_3, OCH_3, Cl)	2.0–7.0	17–74	0–34	4–31	89
$-C_6H_4-X$-*p* (X = CH_3, OCH_3, Cl)		1.1–10.0	1–24	7–74	4–14	90
$-C_5H_4FeC_5H_5$	$-C_6H_4-Y$-*p* (Y = H, CH_3, OCH_3, Cl)	5.0	52–73	9–34	4–12	91
$-C_6H_4-(X-C_6H_4-NO_2$-*p*$)$-*p* (X = CH_2, O, S)	$-C_6H_4-CH_3$-*p*	5.0	26–29 (bis-azoxy) 30–32 (azoxy-azo)	8–10	22–29	92, 93
$-C_6H_4-CH_3$-*p*	$-C_6H_4-[O-C_6H_4-N(MgBr)_2$-*p*$]$-*p*	0.63	12 (bis-azoxy) 13 (azoxy-azo)	–	–	92
$-C_6H_4-NO_2$-*m*, *p*	$-C_6H_4-CH_3$-*p*	5.0–6.0	26–43 (bis-azoxy) 11–15 (azoxy-azo)	0	18–25	92
$-C_6H_4-X$-*p* (X = CHO, $C(O)C_6H_4CH_3$-*p*)	$-C_6H_4-CH_3$-*p*	5.0	30–38	25–28	13–18	92
C_4H_9-t	$-C_6H_5$	2.5	35	–	–	94

Table 4. Reaction conditions and the yields of products in the reactions of nitroso-compounds with N-substituted and O,N-disubstituted hydroxylamines ($R^1 \neq R^2$).

R^1	R^2	R^3	Solvent	Reaction temperature/°C	Reaction time/h	Yield of **8a** (%)	Yield of **8b** (%)	Ref.
$-C(CH_3)_2CH_2CH_2CH(CH_3)_2$	$-CH_3$	H	–	110	2.0	57	–	56, 101
$-CF_3$	$-CH_3$, $-C_2H_5$, $-CH(CH_3)_2$, $-C_6H_5$	H	C_2H_5OH	–50	–	not quoted	–	102
$-C_6H_5$	$-CF_3$	H	C_2H_5OH	78	2.0	~5	–	102
$-C_6F_5$	$-C_6H_5$	H	C_2H_5OH	20	1.0	34	–	54
$-C_6H_5$	$-C_6F_5$	H	C_2H_5OH	20	24.0	–	70	54
$-C_6H_5$	$-CH(CH_3)C(NOH)C_6H_5$ (*syn*-isomer)	H	DMF	0	0.25	30	–	103
$-C_6H_5$	 (*syn*-isomer)	H	CH_3OH (CH_3ONa)	–10	0.33	30	–	103
$-C_6H_5$	$-CH_3$, $-CH_2C_6H_5$	H	C_2H_5OH, THF–H_2O	0–78	10.0	68–69	–	56, 104
$-C_4H_9$-t	$-CH_3$	H	THF–H_2O or without solvent	38–100	1.0–2.0	52–63	1	56, 104
$-CH_3$	$-C_4H_9$-t	H	CH_3OH (*hv*)	45	–	7	–	104
$-C_6H_{11}$-cyclo	$-CH_3$	H	CH_3OH	10–65 (*hv*)	–	70–76	7–14	104
		CH_3	THF–H_2O	50	–	55	–	104
$-CH_3$	$-C_6H_{11}$-cyclo	H	CH_3OH	45 (*hv*)	–	6	38	104
		CH_3	THF–H_2O	50		16	–	104
$-CH_2C_6H_5$, $-CH(CH_3)C_6H_5$	$-CH_3$	H	$CH_3OH - H_2O$	0–65 (*hv*)	–	39–64	16–18	104
$-C_6H_4-CH_3$-*o*	$-CH_3$	H	$THF - H_2O$	0	–	60	7	104
$-C_6H_5$, $-C(CH_3)_2NO_2$	$-CH_2CH(OH)CH_2OC_6H_5$	H	CH_2Cl_2	0–10	72	27–50	–	105
$-C_6H_3Cl_2$-*m, p*	$-C_6H_4-Cl$-*p*	$-C(O)C_4H_9$-t	–	–	–	not quoted	–	42
$-C_6H_4-Cl$-*p*	$-C_6H_3Cl_2$-*m, p*	$-C(O)C_4H_9$-t	–	–	–	not quoted	–	42

the nitrogen atom forming part of the initial nitroso-compound is oxidised. The stabilisation of the adducts **7**, formed from N-monosubstituted hydroxylamines and containing two hydroxy-groups (R^3 = H) is usually achieved as a result of the splitting off of the OH group from the nitrogen atom linked to the least sterically hindered hydrocarbon substituent[104] or the substituent having weaker electron-accepting properties.[54]

However, reactions with participation of N-substituted hydroxylamines most often lead to the formation of both possible regioisomers (Table 4).[104] In certain cases, the reaction proceeds via an alternative rather than the expected pathway.[102,104] Such unpredictability of the regiospecificity of the reaction significantly hinders the use of the method for the synthesis of asymmetrically substituted diazene *N*-oxides with the required structure.

$$Ar^1NO + HONHAr^2 \longrightarrow \underset{\mathbf{9a}}{[Ar^1NHO]^{\bullet}} + \underset{\mathbf{9b}}{[Ar^2NHO]^{\bullet}} \xrightarrow[(-H_2O)]{} \longrightarrow \begin{cases} Ar^1-\overset{\uparrow O}{N}=N-Ar^1 \\ Ar^1-\overset{\uparrow O}{N}=N-Ar^2 \\ Ar^2-\overset{\uparrow O}{N}=N-Ar^1 \\ Ar^2-\overset{\uparrow O}{N}=N-Ar^2 \end{cases} \quad (6)$$

Ar^1, Ar^2 = Ph, *p*-C_6H_4Cl, *p*-$C_6H_4CH_3$.

The reaction of nitroso-compounds with N-monosubstituted hydroxylamines (R^3 = H) is unsuitable for the selective synthesis of asymmetrically substituted aromatic diazene *N*-oxides. In this case, one observes the formation of a mixture of azoxy-arenes—the products of the disproportionation of the aminoxyl radicals **9a** and **9b** detected by the EPR method.[106-109]

The reaction of nitroso-compounds with O,N-disubstituted hydroxylamines (Table 4) has not come to be widely used in synthetic practice owing to the low availability of the initial compounds and the low yields of the azoxy-products.[42,104]

b. The reaction of nitroso-compounds with amino-derivatives containing N–halogen bonds

The method of synthesis of asymmetrically substituted azoxy-compounds based on the reaction of nitroso-compounds with amino-derivatives containing reactive N-halogen bonds has developed appreciably in recent years (Table 5).

$$R^1-NO + XYNR^2 \xrightarrow{Cat} R^1-\overset{\uparrow O}{N}=N-R^2 \quad (7)$$

Derivatives of ammonia,[99,112,118,119,124] aliphatic amines,[105,112-115] the amides of carboxylic[112] and sulphonic[114,116,120-122] acids, urethane,[64,111,112,114,149] urea,[112] tetrafluorohydro-azine,[99,100,121,123,125-128] and 4-(dichloroamino)tetrafluoropyridine[53] are used as the amino-derivatives and aliphatic,[99,100,105,112,113,115,123-132,134,149] aromatic,[53,64,99,105,112-116,118-123,133] and heterocyclic[117,122] *C*-nitroso-compounds are used as the nitroso-derivatives (Table 5). The initial nitrosoalkanes can be introduced into the reaction in a pure state or can be generated *in situ* from olefins,[100,125] *gem*-dinitroalkanes,[126] and oximes[123,132,133] under the reaction conditions.

The reactions occur as a rule at room temperature in organic solvents. Processes with participation of tetrafluorohydrazine,[125,127-131,134] which are frequently carried out by heating the components up to 60–80 °C in the absence of a solvent, are an exception.

A wide variety of asymmetrically substituted azoxy-compounds containing various functional group substituents were synthesised in this way: esters,[64,100,111,112,114-116,121,131,149] carboxy-derivatives,[116,122] sulphoxy-derivatives,[120-122] nitriles,[100,113,114] nitro-derivatives,[64,99,105,115,120,124,126,129] carbonyl derivatives,[111,112] hydroxy-derivatives,[105,123] difluroamino-derivatives,[100,123,125,132] halo-derivatives,[99,112,118,119,121,123-125] etc. The method is applicable to the synthesis of azoxy-compounds in which the diazene *N*-oxide group is linked to a carbon, chlorine, bromine, fluorine, or sulphur atom (Table 5). The involvement of bisnitroso-compounds in the reaction ensures a single-stage synthesis of azoxy-products containing two diazene *N*-oxide groups.[112,113,133]

The reaction is regiospecific. In all cases, its products are asymmetrically substituted diazene *N*-oxides, in which the nitrogen atom of the initial nitroso-compound is oxidised. The chemical nature of the substituent R^2 in the amino-derivative does not affect the mode of reaction.

Whereas the regiospecificity of this process is independent of the nature of the amino-derivative, the reactivity of *N*-haloamines in the given reaction is determined by the type of halogen atom forming part of their composition. *N*-Bromo-derivatives of amines and amides containing the exceptionally reactive N–Br bonds exhibit a high reactivity in reactions with nitroso-compounds.[114] The more stable *N*-chloroamines are distinguished by a greater inertness and interact with nitroso-compounds only in the presence of promoting agents (zerovalent silver,[112] pyridine,[116,118,120-122] alkali metal hydroxides,[113] and Ag^+, K^+, Cu^+, Cu^{2+}, Co^+, Co^{2+}, and Fe^{2+} halides or cyanides[53,64,105,111,112,114]). Among the *N*-fluoroamines, only difluoroammonia and tetrafluorohydrazine, containing N–H and N–N bonds weakened by fluorine atoms and tending as a result to dissociate, have been involved in the reactions with nitroso-compounds (Table 5).

The mechanism of the reaction of nitroso-compounds with *N*-haloamines has not been studied in detail owing to the low stability of the latter. However, it has been suggested that in most cases a radical process mechanism operates and includes the following stages: (1) homolytic dissociation of the N–Y bond in the R^2NXY molecule; (2) the addition of the *N*-haloaminyl radicals **10** formed to the nitroso-compound present in the system; (3) stabilisation of the spin-active adducts **11** as a result of the elimination of the halogen atom.

$$R^2-\overset{X}{\underset{Y}{N}} \xrightarrow[-\dot{Y}]{} R^2-\dot{N}-X \xrightarrow{R^1-NO} \underset{\mathbf{10}}{} \longrightarrow \underset{\mathbf{11}}{R^2-\overset{X}{N}-\overset{O^{\bullet}}{N}-R^1} \xrightarrow[-\dot{X}]{} R^2-\overset{\uparrow O}{N}=N-R^1 \quad (8)$$

X = Cl, Br, F; Y = Cl, Br, H, NF_2.

This mechanism has been confirmed by the EPR detection of the $\dot{N}F_2$ and $R^1-N(\dot{O})-NF_2$ radicals formed in the reaction of nitroso-compounds with tetrafluorohydrazine[128] and by the first order of the reaction of *N*,*N*-dibromoalkylamines with nitrosobenzene.[114] The increase in the reactivity of *N*-haloamines with decrease in the strength of the N–halogen bond and the role of promoting agents, involving the substitution of chlorine atoms in the amino-group by the more reactive bromine

Table 5. Reaction conditions and the yields of the products of the reactions of nitroso-compounds with *N*-haloamines, *N*-haloamides, and halohydrazines.

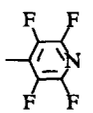
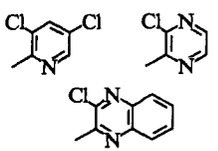
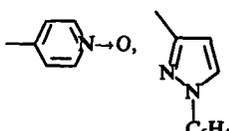
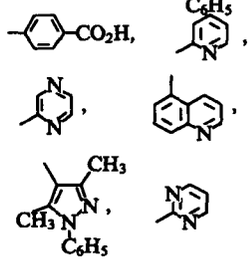
R^1	R^2	X	Y	Catalyst (Cat)	Solvent	Reaction temperature/°C	Reaction time/h	Product yield relative to to R'NO (%)	Ref.
$-C_6H_5$, $-\overline{CCl-(CH_2)_4}CH_2$	$-Alk$, $-CO_2C_2H_5$, $-C(O)C_6H_5$, $-C(O)N(CH_3)_2$	Cl	Cl	CuCl	CH_3CN	20	12	38–83	111, 112, 149
$-C_6H_5$	$-C_4H_9$-t, $-CO_2C_2H_5$	Cl	Cl	Ag^0, CuCN, CuBr, CuI, Cu_2S, $FeCl_2$, $CoBr_2$, KI, AgCN	CH_3CN	20	12	35–90	112
$-C_6H_5$, $-C_4H_9$-t, -Ad-1, $-C(CH_3)_2CN$, $-\overline{CZ-(CH_2)_4}CH_2$, (Z = Cl, CN)	$-C_4H_9$-t, $-C(CH_3)_2CN$, -Ad-1, $-\overline{C(CN)(CH_2)_4}-CH_2$	Cl	Cl	KOH, NaOH	CH_3OH-H_2O	20	1.0–2.0	36–80	113
$-C_6H_5$,	$-$Alk-t, $-CO_2C_2H_5$,	Br	Br	–	CH_2Cl_2 or CH_3CN	0–20	~0.2	70–92	114
$-\overline{CZ-CHZ-(CH_2)_3}-CH_2$	$-SO_2-C_6H_4-CH_3$-*p* (Z = Cl, Br)	Cl	Cl	$CuBr_2$, $CoBr_2$	CH_3CN	0–20	0.75	70–92	114
$-C_6H_5$, $-C(CH_3)_2NO_2$	$-CH_2CO_2$Alk	Br	Br	–	CH_2Cl_2	20	0.5–0.7	75–100	115
$-C_6H_4-Z$ (Z = H, Cl, Br, NO_2, OCH_3, CH_3, CO_2H)	$-CO_2$Alk	Cl	Cl	CuCl	CH_3CN	20	–	~50	64, 116
$-C_6H_5$, $-C_6H_4-CH_3$-*o*, 1,3,5-$(CH_3)_3C_6H_2-$, $-C_6F_5$		Cl	Cl	CuCl	CH_3CN	20	12	20–56	53
$-C_6H_5$, $-C(CH_3)_2NO_2$	$-CH_2CH(OH)CH_3$, $-CH_2CH_2OH$	Cl	Cl	$CuBr_2$	CH_3CN	0–2	0.5	64–98	105
	–Alk	Br	Br	–	–	–	–	–	117
$-C_6H_5$	Cl	Cl	H		CH_2Cl_2	20	0.3	43	118
$-C_6H_5$	Cl	Cl	Cl	KI	CH_2Cl_2	20	12	60	112
$-C_6H_5$, 1,3,5-$Cl_3C_6H_2-$	Br	Br	Br	–	CH_2Cl_2, CH_3CN	0	1.0	85–90	119

Table 5 (cont.).

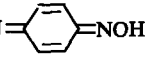
R^1	R^2	X	Y	Catalyst (Cat)	Solvent	Reaction temperature/°C	Reaction time/h	Product yield relative to to R'NO (%)	Ref.
$-C_6H_4-Z$ (Z = H, CH_3, NO_2, NR_2, CO_2H, $CO_2C_2H_5$)	$-SO_2-C_6H_4(Z)$ (Z = H, CH_3)	Cl	Na			80	2–4	50–92	116, 120, 121
	$-SO_2-C_6H_4-(Z)$-*p* (Z = H, CH_3)	Cl	Na			80	2–4		122
	$-SO_2-C_6H_4-(Z)$-*p* (Z = H, CH_3)	Cl	Na	$Cl^-N^+(CH_3)_3CH_2C_6H_5$	$CHCl_3/H_2O$	–	–		122
$-C_6H_4-Z$ (Z = H, *p*-Alk, *p*-Br, *p*-OH, *o*-$CO_2C_2H_5$)	F	F	NF_2	–	C_6H_5Cl, $CHCl_3$	0–70	2–3	30–90	99, 121, 123
$-C_6H_4-R$ (R = C_4H_9-t, $C(CH_3)_2Z$, CF_3)	F	F	H		CH_2Cl_2	20	–	23–50	99
$-\overline{CH(NO_2)-(CH_2)_4-CH_2}$	F	F	H	$BF_3-H_3PO_4$	HNF_2	–23	0.75	53	124
$CHR'(NF_2)-CR''R'''-$ (R', R'' = H, Alk; R''' = H, Alk, CO_2CH_3, CN)	F	F	NF_2	–	$CHCl_3$ –	20 80	19.0 8.0	34–48 [a] ~42 [a]	100 125
$-C(NO_2)_2-C_3H_7$-n	F	F	NF_2	–	CH_3OH	20	20.0	6 [b]	126
$-CF_3$	F	F	NF_2	–	–	120 20	1.0 6.0	45 23	127 128
$-CF_2CF_2NO_2$	F	F	NF_2	–	–	25	74.0	67	129
$-C(CF_3)_2CF_2OC_2H_5$	F	F	NF_2	–	–	80	3.0	35	130

$-CZ'Z''-CO_2C_2H_5$ ($Z', Z'' = F, Cl, CF_3$)	F	F	NF_2	–	–	70–80	4.0	24–45	131
$-CZ'Z''NF_2$ ($Z', Z'' =$ Alk)	F	F	NF_2	–	$CH_3CO_2C_2H_5$	60–80	8.0	~20[c]	132
					Freon-112	80	7.0–8.0	~35[c]	123
$-C_6H_4-NO$-*p* (in initial compound)	F	F	NF_2	–		20	–	61[d]	133
$-C_6H_4-(\overset{\uparrow}{N}(O)=NF)$-*p* (in reaction product)									
$-C(CH_3)_2Cl$	F	F	NF_2	–	–	0	4.0	61	128
$-CF-(CF_2)_n-CF_2$ ($n = 2, 3$)	F	F	NF_2	Pyrex glass	–	55	16.0	–	134

[a] Yield calculated relative to XCH=CYZ.

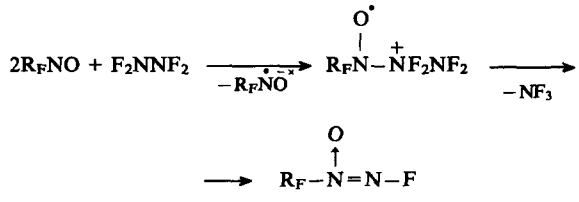
[b] Yield calculated relative to $C_3H_7C(NO_2)_2Na$.

[c] Yield calculated relative to XYC=NOH.

[d] Yield calculated relative to HON==NOH .

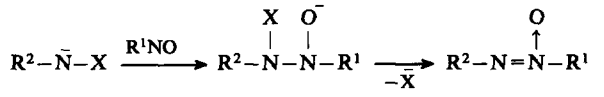
atoms[114] or the initiation of oxidation-reduction reactions of the amine component accompanied by the dissociation of the N–halogen bond therefore become understandable.[112,113]

In the reactions involving perfluoronitrosoalkanes, which exhibit an exceptionally high electron affinity,[110] a radical-anion mechanism is more probable. This has been confirmed by the EPR method, with the aid of which the presence of the R_FNO^- radical-anions in the reaction mixture has been detected.[128]



(9)

The ionic mechanism apparently operates in the reaction of nitroso-compounds with the anions of the *N*-chloroamides of sulphonic acids[120–122] and dihaloamine derivatives in the presence of bases.[99,112,113,118]



(10)

X = F, Cl; R^2 = O_2SAr, Cl, F.

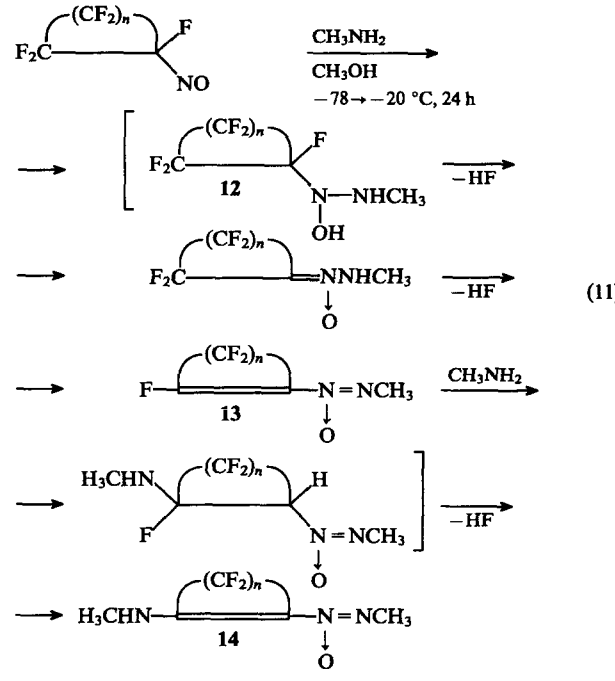
The "nitrene" mechanism of the reactions of nitroso-compounds with *N*-haloamines, *N*-haloamides, and *N*-halohydrazines, involving the formation of the nitrenes $R_2\dot{N}$ and their addition to the N=O bond, is least probable in view of the absence of the characteristic products of the rearrangement and insertion of the nitrenes in the C–H bonds of the solvent.[113,114]

Thus the reaction of nitroso-compounds with amino-derivatives containing N–halogen bonds constitutes a convenient selective method of synthesis of asymmetrically substituted azoxy-compounds. The principal deficiency of the method is associated with the difficulty of isolation, the low stability, and the risk of explosion of the initial *N*-halo-compounds containing two and more N–halogen bonds. An additional restriction of the application of the reaction is the inability of *N*-haloamines to form the diazene *N*-oxide group in the reaction with *N*- and *O*-nitroso-compounds.[128]

c. Reactions of nitroso-compounds with compounds containing the NH_2 group

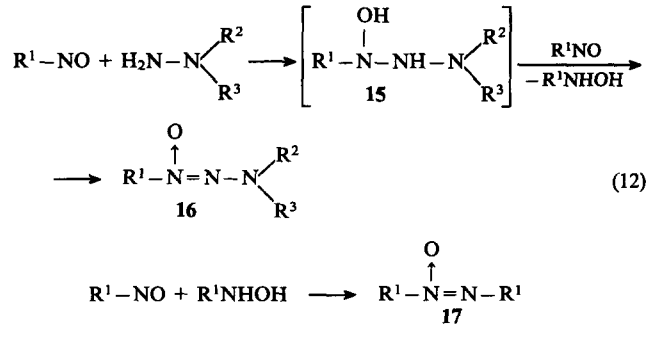
In view of the low stability of *N*-hydroxy- and *N*-halo-derivatives of amines, which limits their wide scale application, the direct synthesis of diazene *N*-oxides from nitroso-compounds and amino-derivatives containing an unsubstituted amino-group is extremely attractive. The reaction of nitroso-compounds with mono-substituted amines is known to entail usually the formation of asymmetrically substituted diazenes.[135–139] however, in a number of instances (when use is made of the characteristic features of the structures of certain types of starting compounds or when the reaction is carried out in the presence of oxidants), it is possible to drive the process towards the formation of diazene *N*-oxides.

Thus the products of the reaction of perfluoronitrosocyclobutane and cyclopentane with methylamine are methylazoxyperfluorocycloalkenes **14**. The reaction probably proceeds via the nucleophilic addition of methylamine to the N=O bond. The resulting adduct **12** is stabilised under these conditions by eliminating a HF molecule and by the addition of methylamine to the activated double bond of the azoxyalkene **13**.[140] The dehydrofluorination process is preferred to the usual process involving the dehydration of type **12** intermediates apparently because of the thermodynamic stability of the conjugated π-system forming part of compound **13**.



n = 2, 3

The reaction of nitroso-compounds with 1,1-dialkyl-,[96,144] 1-alkyl-1-aryl-,[96,141–144] and 1,1-diaryl-hydrazines,[96,142,143] leading to triazene 1-oxides, also takes place with retention of the NO bond (Table 6). Various nitrosoarenes, including those containing substituents in the aromatic ring,[141–144] and tertiary nitrosoalkanes[96] enter into this reaction. The latter probably proceeds via a stage involving the formation of the 1-hydroxy-triazane **15**, which is oxidised to the product **16** by the excess nitroso-compound.[96,144]



(12)

The side products of this oxidation-reduction reaction are hydroxy-aminoderivatives R^1NHOH and the products of their condensation with R^1NO — symmetrically substituted diazene *N*-oxides **17**.[96] The necessity for the use of an appreciable excess of the nitroso-compound (completion of the reaction requires 3 moles of the nitroso-compound per mole of hydrazine) and the marked dependence of the yields of triazene 1-oxides on the structure of the starting materials (Table 6) are serious disadvantages of the method, which lowers its preparative value.

In order to intensify the reactions leading to the formation of the diazene *N*-oxide group, the reactions of nitroso-compounds with primary amino-derivatives are carried out in the presence of compounds capable of oxidising the nitrogen atoms of the amino-groups but inert with respect to the nitroso-compound present in the system (Table 7). Mercury oxide,[96,145] diethyl azodicarboxylate,[144] lead tetraacetate,[96–98,148,150,151] phenyl iodosoacetate,[98,116,146,152,153,155] as well as halogenating agents [sodium hypochlorite,[113] bromine,[156] dibromoisocyanurate (DBI),[157–161]] and the *tert*-butyl hypochlorite–iodine[154] and *tert*-butyl hypochlorite–sodium methoxide[158] systems have been used as

Table 6. Reaction conditions and the yields of the products of the reactions of nitroso-compounds with 1,1-disubstituted hydrazines in the absence of an oxidant.

R^1	R^2	R^3	Solvent	$\frac{(R^1NO)}{(H_2NNR^2R^3)}$	Reaction temperature/ °C	Reaction time/h	Yield (%)[a]	Ref.
$-C_6H_5$	$-C_6H_5$	$-C_6H_5$	C_2H_5OH	3:1	−5 – +5	0.45	79	96, 143
$-C_6H_5$	$-CH_3$	$-CH_3$	C_2H_5OH	3:1	−5 – +20	0.45	74	96
$-C_6H_5$, $-C_6H_4-Br$-*p*	$-C_6H_5$	$-CH_3$	C_2H_5OH	3:1	−5 – +20	0.45	75	96, 143
$-C_4H_9$-t	$-C_6H_5$	$-C_6H_5$	C_2H_5OH	3:1	20	580	10	96
$-C_6H_3Cl_2$-2,6	$-CH_2C_6H_5$	$-CH_2C_6H_5$	THF	2:1	20	24	50	144
$-C_6H_3Cl_2$-2,6	$-CH_3$	$-CH_3$	THF	2:1	20	24	24	144
$-C_6H_4-Cl$-*p*	$-C_6H_5$	$-CH_3$	THF	1:1	−60 – +20	1.0	14	144
$-C_6H_4-N(CH_3)_2$-*p*	$-C_6H_5$	$-CH_3$	THF	1:1	−60	1.0	5	144

Note. The table does not include the results of studies in which the experiment was not described and no information was given about the yields of products (references to these investigations can be found in a monograph[95]).
[a] The yield calculated relative to the hydrazine component is quoted.

such substances. The promising nature of the reaction of nitroso-compounds with amino-derivatives in the presence of oxidants is indicated by the finding that it was possible to involve in this reaction aliphatic,[96–98, 146, 148, 150, 152, 157–159, 161] aromatic,[96, 113, 116, 145, 146, 152–154, 156, 158–161] and heterocyclic[98, 152, 153, 155, 158, 161] *C*-nitroso-compounds as well as *N*-nitroso-compounds.[147]

Among amino-derivatives, alkyl- and cycloalkyl-amines,[113, 146, 154, 157] cyanamide,[116, 146, 152, 153, 155, 158, 228–231] urethane,[152, 158] urea,[158] the amides of phosphoric[161] and sulphonic[146, 152] acids, 1,1-disubstituted derivatives of hydrazine,[96, 144–147, 156, 160] and alkoxyamines[97, 98, 148, 150, 151] were used. Such a wide range of substances involved in the given reaction ensures the synthesis with its aid of a wide range of carbo- and hetero-substituted azoxy-compounds whose diazene *N*-oxide group is linked to carbon,[113, 116, 146, 152–154, 157–159] oxygen,[97, 98, 148, 150, 151] nitrogen,[96, 144–147, 156, 160] and sulphur[146, 152] atoms.

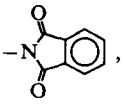
$$R^1-NO + H_2N-R^2 \xrightarrow{Ox} R^1-\overset{\overset{O}{\uparrow}}{N}=N-R^2 \qquad (13)$$

The majority of reactions of the given type take place readily under exceptionally mild conditions (at room or lower temperatures in inert organic solvents) and can be used to obtain azoxy-products containing various, including labile, functional groups.

The regiospecificity of the method is valuable. Regardless of the structure of the nitroso- and amino-compounds involved in the process and of the oxidant employed, the nitrogen atom forming part of the initial nitroso-compound is oxidised. The chemistry of the process is determined by the structure of the amine component and by the chemical nature of the oxidant. The mechanism of reaction (13) in the presence of oxidants such as mercury oxide or ethyl azodicarboxylate (a three-component reaction) is apparently similar to that of the corresponding two-component reaction (12) with the sole difference that in the given instance the intermediate **15** is dehydrogenated to the corresponding triazene 1-oxide by the oxidant present in the system.[96, 144] The synthetic result of the use of the oxidant is an increase in the effectiveness of the process, which can be carried out in the absence of an excess of the nitroso-compound.

When $Pb(OAc)_4$ and $C_6H_5I(OAc)_2$ are used as oxidants, the reaction of nitroso-compounds with amino-derivatives probably proceeds via a different pathway. Here the role of the oxidant consists in the formation of an electron-deficient centre of the nitrene type at the nitrogen atom of the amino-group, which subsequently interacts with the nitroso-compound to form the required diazene *N*-oxides.[96, 97, 147, 148, 151, 152]

$$R^2NH_2 \xrightarrow[\text{or } C_6H_5I(OAc)_2]{Pb(OAc)_4} [R^2N:] \xrightarrow{R^1NO} R^2-\overset{\overset{O}{\uparrow}}{N}=N-R^1 \qquad (14)$$

$R^2 =$  , $-OAlk$, $-CN$, $-CO_2C_2H_5$, $-SO_2C_6H_5$.

In the case of $C_6H_5I(OAc)_2$, a coordination process mechanism involving the formation and dissociation of the bond between the nitrogen atom of the amine component and the hypervalent iodine atom, has also been proposed.[146] When $Pb(OAc)_4$ and $C_6H_5I(OAc)_2$ are used, it is useful to involve in the reaction amino-derivatives capable of forming fairly stable nitrenes on treatment with oxidants: *N*-aminophthalimide, alkoxyamines, and cyanamide.[162, 163] Reactions with participation of the amides of arenesulphonic acids and urethane, whose nitrene derivatives are less stable, are characterised by a lower effectiveness.[152] The use of 1,1-dialkylhydrazines, incapable of forming stable nitrenoids in neutral media,[164] as amino-derivatives leads to the formation of 1,1,4,4-tetraalkyltetrazenes — the products of the oxidative dimerisation of the initial amino-compounds — instead of the expected triazene *N*-oxides.[96]

$$PhNO + H_2N-N(CH_3)_2 \xrightarrow{Pb(OAc)_4} \begin{cases} Ph-\overset{\overset{O}{\uparrow}}{N}=N-N(CH_3)_2 \\ (H_3C)_2NN=NN(CH_3)_2 \end{cases} \qquad (15)$$

Finally, in the presence of halogenating agents,[113, 154] the reactions of nitroso-compounds with amino-derivatives probably proceed via a stage involving the formation of *N*-halo-derivatives

Table 7. Reaction conditions and the yields of the products of the reactions of nitroso-compounds with primary amino-derivatives in the presence of oxidants.

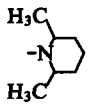
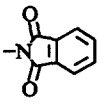
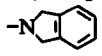
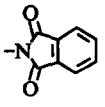
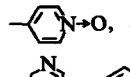
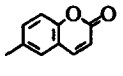
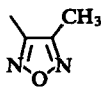
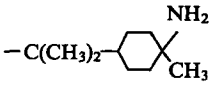
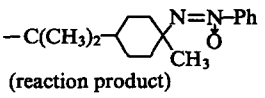
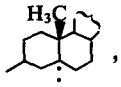
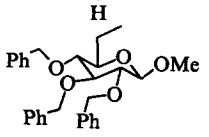
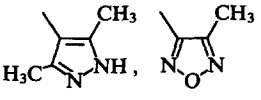
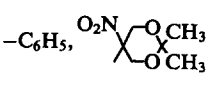
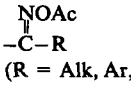
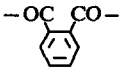
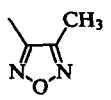
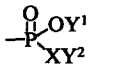
R^1	R^2	Oxidant (Ox)	Solvent	Reaction temperature/ °C	Reaction time/h	Yield of product (%)	Ref.
$-C_6H_4-N(CH_3)_2$-*p*	$-N(CH_3)_2$	HgO	C_2H_5OH	25	16.0	25	145
$-C_6H_5$		HgO	$CH_3CO_2C_2H_5$	25	16.0	71	145
$-C_6H_5$		HgO	$CH_3CO_2C_2H_5$	25	16.0	74	145
$-C_6H_4-F$-*o*	$-N(CH_3)_2$	HgO	$CH_3CO_2C_2H_5$	25	16.0	12	145
$-C_4H_9$-t	$-N(CH_3)_2$, $-N(C_6H_5)_2$	HgO	C_2H_5OH	20	1.0	29–46	96
$-C_6H_4-Cl$-*p*	$-N(CH_3)C_6H_5$	$(H_5C_2O_2CN{=})_2$	THF	−60	1.0	30	144
$-C_6H_4-N(CH_3)_2$-*p*	$-N(CH_3)C_6H_5$	$(H_5C_2O_2CN{=})_2$	THF	−60	1.0	75	144
$-C_4H_9$-t, $-C_6H_4-X$ (X = H, *o*, *p*-CH_3, *p*-$N(CH_3)_2$, *p*-CO_2CH_3)		$Pb(OAc)_4$	CH_2Cl_2 (K_2CO_3)	20	0.5–1.0	79–94	96
		$C_6H_5I(OAc)_2$	CH_2Cl_2	20	18.0	60–68	146
$-N(CH_3)_2$, , 		$Pb(OAc)_4$	CH_2Cl_2 (K_2CO_3)	0→20	0.5–1.0	69–79	147
$-C_4H_9$-t, $-C(CH_3)_2CH_2CH_3$	$-OC_nH_{2n+1}$ ($n = 1-4$), $-OCH_2CH{=}CH_2$	$Pb(OAc)_4$	CH_2Cl_2 (K_2CO_3)	−45 +20	1.0 0.5	60–70 60–70	97, 148 97, 148
$-CH(C_6H_5)_2$ [a]	$-OCH(C_6H_5)_2$	$Pb(OAc)_4$	CH_2Cl_2	0	0.2	32	150
$-N(CH_3)_2$, $-N(C_2H_5)_2$	$-OC_nH_{2n+1}$ ($n = 1-3$)	$Pb(OAc)_4$	CH_2Cl_2 (K_2CO_3)	−45	–	13–47	151
$-C(CH_3)_2NO_2$, $-C(NO_2)-(CH_2)_4-CH_2$	$-OCH_3$	$Pb(OAc)_4$	CH_2Cl_2 (K_2CO_3)	−45 +20	1.0 0.5	8–16 8–16	98 98
$-C_4H_9$-t, $-C_6H_4-X$ (X = H, Cl, $N(CH_3)_2$, NHAc, C(O)NHAr, $-O_2S-N$)	$-CN$	$C_6H_5I(OAc)_2$	CH_2Cl_2, $CHCl_3$, DMF	30	~1.0	85–95	152, 228–230
$-C_6H_4-COOH$-*o*, *p*	$-CN$	$C_6H_5I(OAc)_2$	Py	30	1.0	50–77	116
 (X = CH, N), , , , 	$-CN$	$C_6H_5I(OAc)_2$	CH_2Cl_2	30	~1.0	35–90	146, 153, 155, 231
$-C_6H_4-X$-*o* (X = H, CH_3)	$-O_2S-Ar$, $-CO_2C_2H_5$	$C_6H_5I(OAc)_2$	CH_2Cl_2	30	4.0	~30–50	146, 152
$-C_6H_4-X$-*o* (X = H, CH_3), $-C_4H_9$-t	$-C_4H_9$-t, 	$C_6H_5I(OAc)_2$	CH_2Cl_2	20	18.0	55–67	146
$-C(NO_2)-(CH_2)_4-CH_2$, $-C(CH_3)_2OC(O)CH_3$ [b],	$-OCH_3$	$C_6H_5I(OAc)_2$	CH_2Cl_2	35	4.0	17–53	98
$-C_6H_5$, 							

Table 7 (cont.).

R^1	R^2	Oxidant (Ox)	Solvent	Reaction temperature/ °C	Reaction time/h	Yield of product (%)	Ref.
$-C_6H_5$	$-C_4H_9$-t	NaOCl	$CH_3OH - H_2O$	20	2.0	83	113
$-C_6H_5$	 (initial compound)	NaOCl	$CH_3OH - H_2O$	20	2.0	75	113
	 (reaction product)						
$-C_6H_5$	$-C_4H_9$-n, $-C_6H_{11}$-cyclo,  , 	t-$C_4H_9OCl - I_2$	C_6H_6	20	16.0	62–97	154
$-C_6H_5$	$-N(R)CH_3$ ($R = CH_3$, CH_2CH_2CN)	Br_2	HBr – $(C_2H_5)_2O$	−20 – +15	4–10	63–75	156
	$-CH_3$, $-CH_2CH_2NH_2$	DBI	CH_2Cl_2	0–20	24	86–92	157
($R = CH_3$, Br)							
$-C_6H_5$, $-C(CH_3)_2NO_2$	$-CN$, $-CO_2C_2H_5$	DBI	CH_2Cl_2	−20 – +20	3.0	32–95	158
$-C(CH_3)_2Br$, $-C(CH_3)BrNO_2$ [c], 	$-C(O)NH_2$	t-$C_4H_9OCl - CH_3O^-$	CH_3OH	−60 – +20	5.0	29–56	158
$-C_6H_5$, 	 (R = Alk, Ar, $CO_2C_2H_5$)	DBI	CH_2Cl_2, $CHCl_3$	20	5.0	14–65	159
$-C_6H_5$	$-NR'R''$ (R', R'' = CH_3, CH_2CH_2CN, $-CO(CH_2)_2-$, 	DBI	CH_2Cl_2, THF – $(C_2H_5)_2O$	−40 – +20	5.0	57–98	160
$-C_6H_5$, $-C(CH_3)_2NO_2$, $-C(CH_3)_2Br$, 	 (Y^1, Y^2 = Alk, Ar; X = O, NR^3)	DBI	CH_2Cl_2	20	12.0	47–92	161, 232

[a] The nitroso-compound was obtained *in situ* by oxidising $H_2NOCHPh_2$.

[b] The nitroso-compound is formed *in situ* from acetone oxime.

[c] The nitroso-compound was obtained *in situ* by brominating a salt of ethanenitrolic acid.

of amines[157, 158, 161] or hydrazines,[160] which interact with nitroso-compounds via one of the pathways examined in section I.3 [via a radical pathway[154] — reaction (8), with participation of diazenium cations[156] — reaction (9), or with participation of the anions of *N*-haloamines[158] — reaction (10)].

Reaction (16) is superior to reaction (7) since in this case there is no necessity to isolate and purify the intermediates with the N–halogen bond, generated *in situ*, which makes it possible to involve successfully in the reaction amino-compounds whose halo-derivatives are distinguished by an extremely low stability (cyanamide,[158] 1,1-disubstituted hydrazines,[156, 160] ethers of amidoximes,[159] etc.).

$$AlkNH_2 \xrightarrow[X = Hal]{X^+} \begin{bmatrix} AlkNHX \\ AlkNX_2 \end{bmatrix} \xrightarrow{R^1NO} AlkN{=}N(O){-}R^1 \qquad (16)$$

Overall, the oxidative condensation of nitroso-compounds with substances containing a primary amino-group constitutes one of the most promising approaches to the formation of C-, N-, P-, and O-substituted diazene *N*-oxides of different structure.

V. Interaction of anions containing the N_2O_2 structural fragment with electrophiles

A specific method of synthesis of asymmetrically substituted azoxy-compounds in which the nitrogen atoms of the diazene *N*-oxide group are linked to two oxygen atoms involves the reaction of anions containing the N_2O_2 structural fragment (salts of N-substituted *N*-nitrosohydroxylamines, primary *N*-nitroamines, *N*-nitroamides of hyponitrous acid) with electrophiles. This reaction is accompanied by the formation of the C–O bond the elements of which do not form part of the diazene *N*-oxide group and is therefore considered separately from the chemically related reaction involving the alkylation of *syn*-diazotates [see section III, reaction (2)]. The early studies of reaction (17) and the general principles governing the alkylation of ambient anions with N–N bonds were described in another review.[35] This review deals with the present state of the problem and considers primarily studies carried out in recent years which have greatly expanded the applications and preparative possibilities of the method.

$$R^1{-}N(O^{\ominus}){-}\dot{N}{-}O \; Cat^{\oplus} + XR^2 \longrightarrow R^1{-}N(O){=}N{-}OR^2 \; (\mathbf{18}) + R^1{-}N(N{=}O){-}OR^2 \; (\mathbf{19}) \qquad (17)$$

The alkylation (sulphonylation, stannylation) of salts of N-substituted *N*-nitrosohydroxylamines, which makes it possible to synthesise regiospecifically azoxy-products in which the alkoxy-substituent is linked to the distal nitrogen atom of the diazene *N*-oxide group, has come to be most widely used in synthetic practice among reactions of the type considered (Table 8). The range of *N*-nitrosohydroxylamine salts involved in this reaction is fairly wide: these are the salts of aliphatic and aromatic *N*-nitrosohydroxylamines, including those containing different functional group substituents in the molecule. The cations of alkali[166, 167, 172, 173, 176, 178–182] and alkaline earth metals,[170] silver,[165, 166, 168, 169, 185] ammonia,[165–167, 181, 182, 184] and organic bases[174] were used as counterions. The electrophiles were alkyl halides, dialkyl sulphates, oxirans, toluene-*p*-sulphonyl chloride, and anhydrides of trifluoromethanesulphonic acid, and compounds with the Sn–Cl bond (Table 8).

The reactions are carried out in hydroxylated solvents,[165–167, 170–173, 175–177, 179, 181, 183] dimethyl sulphoxide,[166, 175, 176, 178–180, 186] chlorohydrocarbons,[182] ether,[166, 168, 169, 185] acetonitrile,[174] and sulphur dioxide[184] at −10 to +80 °C.

A favourable effect is achieved by carrying out the reaction in the presence of a base, which neutralises the products of the side processes. An important advantage of the reaction is the possibility of synthesising with its aid *N'*-alkoxydiazene *N*-oxides containing different functional groups in the hydrocarbon fragments of the molecule. Thus alkylation of salts of *N*-nitrosohydroxylamines containing carbonyl[175–177] or ester[178, 180] groups proceeds with retention of the above substituents and makes it possible to synthesise in one stage the corresponding *N*-alkyl-*N'*-alkoxydiazene *N*-oxides. Further-more, the formation of the diazene *N*-oxide fragment proceeds smoothly also in the presence in the anion being alkylated of a carboxy-group, which is transformed into an alkoxycarbonyl group under the reaction conditions.[179, 180]

N'-Alkoxydiazene *N*-oxides containing functional groups in the alkoxy-component of the molecule are formed in the reaction of salts of *N*-nitrosohydroxylamines with alkylating agents containing functional groups.[166, 168, 172–174] The involvement of oxirans in the reaction is accompanied by the regioselective opening of the oxiran ring and the formation of hydroxylated *N'*-alkoxydiazene *N*-oxides, in which the diazene *N*-oxide fragment is linked to the most hydrogenated carbon atom of the given compound.[172, 173]

The interaction of salts of *N*-nitrosohydroxylamines with sulphonic acid chlorides[181–184] and tin halides[185, 186] makes it possible to synthesise azoxy-products (unavailable by other methods) containing a fragment comprising several directly linked heteroatoms: $-N{=}N(O){-}E-$ (E = S, Sn). The products of the alkylation of nitrosohydroxylamines by tin dihalides have a unique structure. In this case the reaction proceeds with participation of both halogen atoms and leads to the formation of bisdiazene *N*-oxides in which the heteroatomic chain consists of nine heteroatoms (Table 8).[185]

Azoxy-compounds containing two diazene *N*-oxide groups can be obtained also by the reaction of salts of *N*-nitrosohydroxylamines with epibromohydrin[172, 173] (Table 8) and by alkylating the dianions of 1,1-bis(*N'*-nitrosohydroxyamine)alkanes (Table 9).[167, 187, 188] The 1,1-bis(*N'*-alkoxy-*N*-oxodiazeno)-alkanes **20** proved unexpectedly stable. Such compounds can be purified by heating with acids and alkalis.[167, 169]

$$R^1{-}CH(N(O^{\ominus}){-}\dot{N}{-}O)_2 \cdot 2Cat^{\oplus} + XR^2 \longrightarrow R^1{-}CH(N(O){=}N{-}OR^2)_2 \; (\mathbf{20}) \qquad (18)$$

Kinetic studies have shown that the alkylation reactions of salts of mono- and bis-(*N*-nitrosohydroxyamino)alkanes with dimethyl sulphate are first order with respect to each component and proceed via a bimolecular nucleophilic substitution mechanism.[171, 190] The stringent requirements which must be met by the transition state of the process are confirmed by the high negative entropies of activation for the reaction (−63 to −127 J mol^{-1} K^{-1})[171, 190] and by the decrease in the yield of the azoxy-products with increase in the three-dimensional branching of the alkylating agent.[165]

The alkylation reaction is complicated in many instances by the low stability of the salts of the initial *N*-nitrosohydroxylamines and the associated impossibility of isolating them in a pure state. The salts obtained by nitrosating the corresponding hydroxyamino-derivatives,[181] Grignard reagents,[170, 181, 183] or carbonyl compounds[175–178, 180] in an alkaline medium are as a rule highly contaminated by side products, which lower appreciably the yields of the *N'*-alkoxydiazene *N*-oxides synthesised from them. The appreciable influence of the quality

Table 8. Reaction conditions and yields of the products of the reactions of salts of N-substituted *N*-nitrosohydroxylamines with electrophiles.

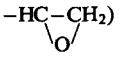
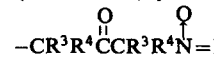
R^1	R^2	Catalyst	X	Solvent	Reaction temperature/°C	Reaction time/h	Yield of **18** (%)[a]	Ref.
$-C_6H_5$	$-CH_3$, $-C_2H_5$, $-C_3H_7$-i $-C_4H_9$-n, $-C_4H_9$-i, $-C_4H_9$-t, –Ad-1	NH_4, Ag	Br, SO_4CH_3	C_3H_7OH, H_2O	60	2–12	5–60	165–167
$-C_6H_5$, $-CH_3$	$-C_2H_5$, $-CH_2OR^3$ (R^3 = CH_3, C_2H_5, C_3H_7-i, $C(O)CH_3$)	Ag	Cl, Br, I	$(C_2H_5)_2O$	20–36	6–15	47–82	168, 169
$-C_2H_5$, $-C_3H_7$-i, $-C_4H_9$-n, $-CH_2C_4H_9$-t	$-CH_3$	MgBr, MgCl	SO_4CH_3	CH_3OH (H_2O)	65–90	2–3	18–43[b]	170
$-CH_3$, $-C_4H_9$-n, $-CH_2C_4H_9$-t	$-CH_3$	K, Na	SO_4CH_3	H_2O	60–90	1–2	71–80	170, 171, 189
$-C_6H_5$	$-CH_2Y$ (Y = $-CH=CH_2$, $-C_6H_5$, $-C\equiv CH$, 	Na, Ag	Cl, Br	$(C_2H_5)_2O$, DMSO, $(CH_3)_2CO$–H_2O, C_2H_5OH	20–78	1.5–36	20–47	166, 167, 172, 173
$-C_6H_5$	$-CH_2CH_2Y$ (Y = Br, OH, OAc)	Na	Cl, Br	DMSO, $(CH_3)_2CO$–H_2O, C_2H_5OH–H_2O	54–80	4–20	15–27	166
$-C_6H_5$	 (R^3 = H, CH_3; R^4 = H, CH_3, CH_2OH, CH_2OCH_3, $CH_2OC_6H_5$, $CH_2ON=N(O)C_6H_5$)	Na	[c]	$(CH_3)_2CO$–H_2O	50–60	8–18	19–48	172, 173
$-CH_3$	$-CH_2CH=CH_2$	NEt_4	Br	CH_3CN	20	2.0	34 (yield of **19**: 55%)	174
$-CHR^3R^4$ (R^3, R^4 = Alk, cyclo-Alk)	$-CH_3$, $-C_2H_5$, $-C_3H_7$-n, $-C_4H_9$-n	Na	Br	DMSO	55	1.5	25–30[d]	175, 176
$-CR^3R^4-C(O)C_6H_5$ (R^3, R^4 = Alk, cyclo-Alk)	$-CH_3$	Na	I	CH_3OH	55	3–5	54–62[e]	175, 176
$-CR^3R^4-C(O)CHR^3R^4$ (R^3, R^4 = Alk, cyclo-Alk)	$-CH_3$, $-C_2H_5$, $-C_4H_9$-n	Na	I	CH_3OH	60	3.0	50–85[e]	176, 177
 (R^3, R^4 = Alk, cyclo-Alk)	$-CH_3$	Na	I	CH_3OH	60	3.0	45–50[e]	177
$-CH(CO_2CH_3)_2$	$-CH_3$, $-C_2H_5$, $-C_3H_7$-i	Na	I	DMSO	50–60	2.0	10–15[e]	178
$-CH(R)COONa$ (in initial compound) $-CH(R)COOR^2$ (in product) (R = H, Alk, cyclo-Alk)	$-CH_3$, $-C_2H_5$, $-C_3H_7$-i, $-C_4H_9$-n	Na	I, SO_4CH_3	DMSO, H_2O	60–65	1–10	12–25	179–180
$-CH(R)COOCH_3$ (R = Alk, cyclo-Alk)	$-CH_3$	Na	I	DMSO	60	4.0	45–50[f]	180
$-CH_3$, $-CH_2C_3H_7$-i	$-O_2S-C_6H_4CH_3$-*p*	Na, K	Cl	H_2O, CH_2Cl_2	20	12	27–52[j]	181, 182
$-C_6H_{11}$-cyclo $-(CH_2)_n-C_6H_5$ (n = 1,2)	$-O_2S-C_6H_4CH_3$-*p*	Na, NH_4	Cl	$(CH_3)_2CO$–H_2O, CH_2Cl_2	20	0.5	4–20[b]	182, 183
$-C_6H_4-Cl$-*p*	$-CH_3$, $-O_2S-C_6H_4CH_3$-*p*	Na	Cl, SO_4CH_3	H_2O, $(CH_3)_2CO$–H_2O	20	0.6–0.8	24–32[h]	167, 181
$-C_6H_4-Y$-*p* (Y = H, CH_3)	$-O_2S-C_6H_4CH_3$-*p*	NH_4	Cl	H_2O	20	12	55–63	181

Table 8. (cont.).

R^1	R^2	Catalyst	X	Solvent	Reaction temperature/°C	Reaction time/h	Yield of **18** (%)[a]	Ref.
$-CH_3$	$-O_2SCF_3$	NH_4	OSO_2CF_3	SO_2	−10	0.25	not quoted	184
$-C_6H_5$, $-C_6H_{11}$-cyclo	$-SnR_3$ (R = Alk, C_6H_5)	Ag, K	Cl	$(C_2H_5)_2O$, DMSO	20	20	87–90	185,186
$-C_6H_5$	$-SnR_2-$ (R = Alk)	Ag	Cl	$(C_2H_5)_2O$	–	–	~90[i]	185

[a] The product **19** was not isolated.
[b] Yield calculated relative to R^1X (X = halogen).
[c] The compounds $H_2C-CR^3R^4$ (O) where used as alkylating agents.
[d] Yield calculated relative to $R^1C(O)X$.
[e] Yield calculated relative to R^1H.
[f] Yield calculated relative to $CH(R)(CO_2CH_3)_2$.
[j] Yield calculated relative to R^1MgBr.
[h] Yield calculated relative to R^1NHOH.
[i] The reaction product is $(PhN(O)=NO)_2SnR_2$.

of the initial compounds on the effectiveness of the alkylation reaction is confirmed by the increase in the yields of the azoxy-products when purified salts of *N*-alkyl-*N*-nitrosohydroxylamines are involved in the reaction.[170,181]

Another factor which complicates the alkylation reaction is the ambident nature of the anions of *N*-nitrosohydroxylamines. Both oxygen atoms of the RN_2O_2 group can participate in the process, which leads to the formation, together with the required *N'*-alkoxydiazene *N*-oxides **18**, of isomeric O,N-disubstituted *N*-nitrosohydroxylamines **19** [reaction (17)]. There is virtually no quantitative information in the literature about the ratio of the isomeric products of the alkylation of salts of *N*-nitrosohydroxylamines. This is due to the low chemical and thermal stabilities of compounds **19**, which usually decompose under the reaction conditions. It is only known[174] that the main product of the alkylation of the tetraethylammonium salt of *N*-methyl-*N*-nitrosohydroxylamine with allyl bromide is *O*-allyl-*N*-methyl-*N*-nitrosohydroxylamine **19**, whereas the yield of the required *N*-methyl-*N'*-allyloxydiazene *N*-oxide **18** does not exceed 34% (Table 8). The lack of systematic data precludes the estimation of the influence of the structure of the interacting compounds and the reaction conditions on the mode of alkylation, which hinders deliberate regulation of the process.

On the basis of general considerations, the formation of *N'*-alkoxydiazene N-oxides might have been expected in the reaction of salts of hyponitrous acid, containing the ambident anion $N_2O_2^{2-}$, with alkylating agents. However, only one example of the reactions of hyponitrites accompanied by the formation of the diazene *N*-oxide group has been described in the literature. This involves the alkylation of silver hyponitrite with diphenylmethyl chloride. The reaction is carried out in a benzene–hexane mixture at 20 °C for 3.5 h; the yield of *N*-diphenylmethyl-*N'*-diphenylmethoxydiazene *N*-oxide **21** does not exceed 11%.[191]

$$2Ph_2CHCl + Ag_2N_2O_2 \longrightarrow \underset{\mathbf{21}}{Ph_2CHN(O)=N-OCHPh_2} \qquad (19)$$

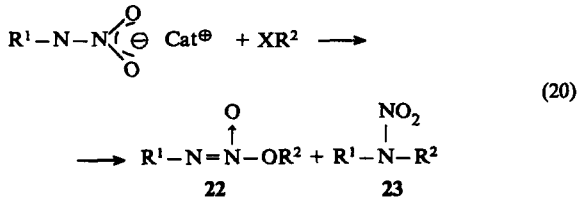
In the remaining cases the products of the alkylation of the ambident anions $N_2O_2^{2-}$ are unstable esters of *trans*-hyponitrous acids.[192]

Whereas the synthesis of *N'*-alkoxydiazene *N*-oxides is extremely widely represented in the chemical literature, less attention has been devoted to the synthesis of isomeric azoxy-

Table 9. Reaction conditions and yields of the products of the reactions of salts of 1,1-bis(*N'*-hydroxy-*N*-oxodiazeno) alkanes with alkylating agents.

R^1	R^2	Catalyst	X	Solvent	Reaction temperature/°C	Reaction time/h	Yield of **20** (%)	Ref.
H	$-CH_3$, $-C_2H_5$	NH_4	SO_4R^2	H_2O (8% NH_3)	20	31	9–33	167
H	$-CH_2CH_2Cl$	Ag	I	C_2H_5OH	20	120	37	167
CH_3	$-CH_3$	Na	SO_4CH_3	H_2O	20 60	31 1–2	20 20	187 187
H	$-CH_3$, $-C_2H_5$, $-C_3H_7$, $-C_4H_9$-n	Na	SO_4CH_3 Br	H_2O, DMSO	60	1–5	25–36	188
H	$-C_6H_{11}$-cyclo $-CH_2C\equiv CH$	Na	Cl, I	DMSO	60	5	2–4	188
H	$-C_4H_9$-t	Ag	Br	$(C_2H_5)_2O$	20	8	3	188

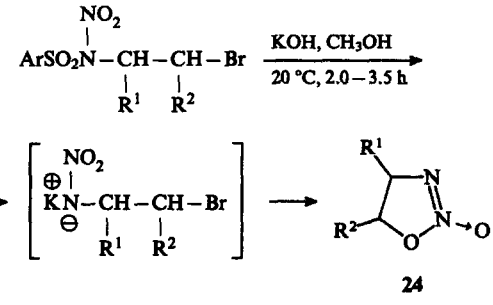
compounds **22** (Table 10), in which one of the nitrogen atoms of the diazene *N*-oxide groups is linked to two oxygen atoms. A general approach to the synthesis of structures of this type involves the interaction of salts of *N*-nitroamines and *N*-nitroamides with alkylating and acylating agents or the interaction of the corresponding CH acids with diazomethane (Table 10).



(20)

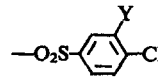
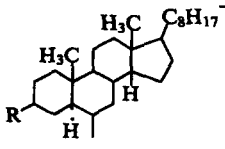
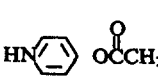
Like other reactions involving the alkylation of ambident anions containing the N_2O_2 fragment, the above processes are complicated by the formation, together with the azoxy-compounds **22**, of the isomeric products which in the given instance are secondary nitroamines **23**. The involvement in the reaction of the silver salts of nitroamines[169,193] and nitroamides[197–199] and increase in the size and degree of branching of the groups R^1 and R^2 in the interacting compounds[196,198,200] help to drive the process towards the preferential formation of the diazene *N*-oxide group. A decrease in the polarity of the solvent also promotes an increase in the yield of the *O*-alkylation products.[198]

When the initial compound contains a nitroamino-group and a halogen atom in vicinal positions, the reaction takes place intramolecularly[201] with the selective formation of cyclic azoxy-products **24**.



R^1 = H, CH_3; R^2 = H, CH_3.

Table 10. Reaction conditions and the yields and ratios of the products of the reactions of salts of *N*-nitroamines with alkylating agents.

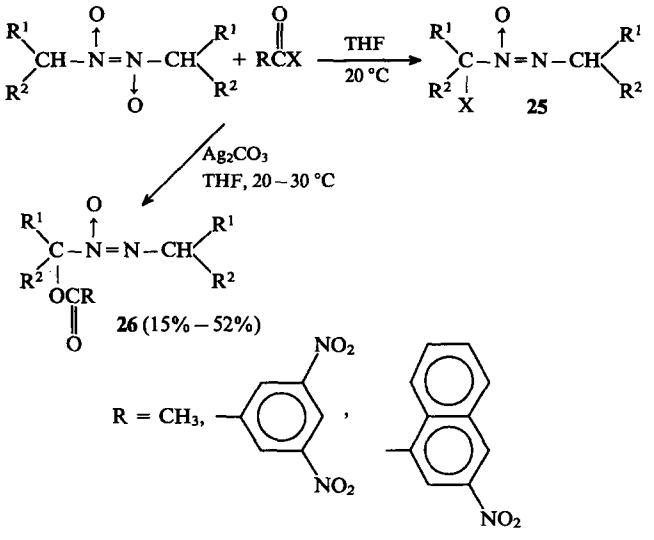
R^1	R^2	Catalyst	X	Solvent	Reaction temperature/°C	Reaction time/h	Yield of **22** (%)	Yield of **23** (%)	Ratio **22**/**23**	Ref.
$-CH_3$	$-C_2H_5$	Ag	I	–	–	–	Mixture of *cis*- and *trans*-isomers (1 : 4)	[a]	–	169
$-C_3H_7$-i	$-CH_3$	K	I	C_2H_5OH	20	48	9	60	0.15	193
		Ag	I	$(C_2H_5)_2O$	36	1.5	45	4	12.5	193
		K	SO_4CH_3	H_2O	20		21	18	1.20	193
		H	[b]	$(C_2H_5)_2O$	20		20	54	0.38	193
$-CH_3$, $-C_5H_{11}$-i	$-C_3H_7$-i	Ag	I	$(C_2H_5)_2O$	36	4–6	39–51	<4	>12.5	193
$-CH_3$, $-C_2H_5$, $-C_3H_7$, $-C_6H_{11}$-cyclo, $-C_4H_9$-t	$-CH_3$, $-C_2H_5$, $-C_3H_7$-i	Ag	Br, I	$(C_2H_5)_2O$	36	4.12	–	[a]	–	194
$-CH_3$, $-C_2H_5$	$-CH_2OCH_3$	Na	Cl	CH_3CN	70	0.3	28–38	23–36	0.77–1.39	195
					20	12.0	28–38	23–36	0.77–1.39	195
$-CH_3$	$-CH_3$	H	[b]	$(C_2H_5)_2O$	0	12.0	22	38	0.58	196
$-C_2H_5$, $-C_3H_7$-i, $-C_4H_9$-t	$-CH_3$	H	[b]	$(C_2H_5)_2O$	0	12.0	53–60	10–24	2.2–6.5	196
$-O_2S-C_6H_4-CH_3$-*p*	$-CH_2C_6H_5$	Ag	Cl	$(C_2H_5)_2O$	20	170	37	10	3.7	197
	$-CH_3$	Ag	Br	$(C_2H_5)_2O$	20	48–72	9–15	61–66	0.15–0.22	198
	$-C_2H_5$	Ag	Br	$(C_2H_5)_2O$	20	48–72	34–46	28–35	1.20–1.31	198
	$-C_3H_7$-n	Ag	Br	$(C_2H_5)_2O$	20	48–72	52	26	2.0	198
	$-C_3H_7$-i	Ag	Br	$(C_2H_5)_2O$	20	48–72	71	18	4.0	198
(Y = H, NO_2)	–Ad	Ag	Br	$(C_2H_5)_2O$	20	48	65	0	>100	198
$-O_2S-C_6H_4-CH_3$-*p*	$-Si(CH_3)_3$, $-B(C_2H_5)_2$	Ag	Cl	CH_2Cl_2	–30–20	1	~100	0	>100	199
	$-CCH_3$			$(CH_3CO)_2O$–Py	20	0.5	73	0	>100	200
(R = H, Cl, OH)										

[a] The product was not isolated.
[b] CH_2N_2 was used as the alkylating agent.

Thus the alkylation of ambident anions containing the N_2O_2 structural fragment is a fairly common method of synthesis of asymmetrically substituted azoxy-compounds, in which the diazene *N*-oxide group is linked directly to an oxygen atom. Linear and cyclic azoxy-products, including those with different functional groups, can be obtained by means of this reaction. The principal disadvantage of the method is the uncertainty in the course of the reactions due to the dual reactivity of the alkylated anions and hence the low yields of the target azoxy-compounds.

VI. Other methods of synthesis of asymmetrically substituted diazene *N*-oxides

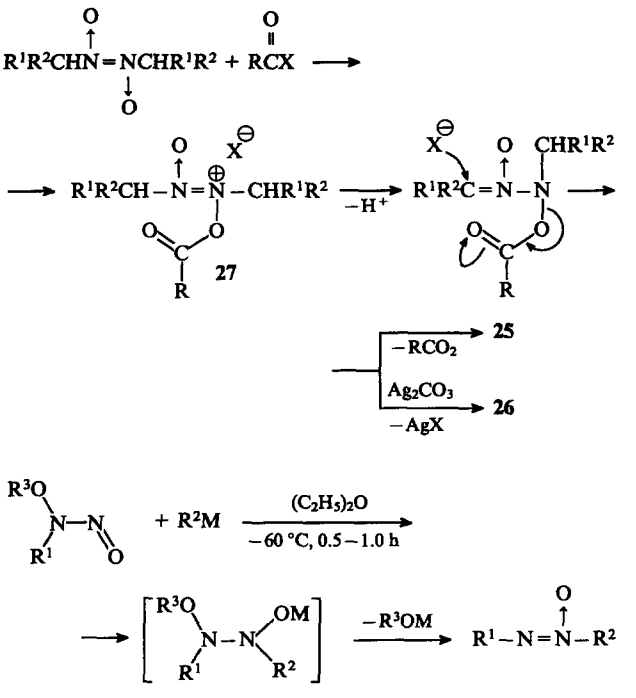
Apart from the alkylation of anions containing the N_2O_2 fragment, a number of other special methods of synthesis of asymmetrically substituted diazene *N*-oxides, used to obtain a narrow range of azoxy-products with specific structures, have been described in the literature. However, these methods have not found extensive applications in synthetic practice because of their limited applicability, low availability of the initial compounds, and also the inconvenient preparative aspect of the process. We shall consider some of these reactions. Thus the reaction of the dimers of primary and secondary nitrosoalkanes with acid halides leads to the formation of α-haloalkyldiazene *N*-oxides **25** containing a halogen atom in the α-position relative to the oxidised nitrogen atom of the diazene *N*-oxide fragment.[202]
When the reaction is carried out in the presence of Ag_2CO_3, its products are the corresponding α-acyloxyalkyldiazene *N*-oxides **26**.



R^1	R^2	X	Yield of **25** (%)
$-C_3H_7$-i	H	Cl	65
$-C_3H_7$-i	H	Br	41
$-(CH_2)_5-$		Cl	25
$-CCl(CH_3)_2$	H	Cl	74

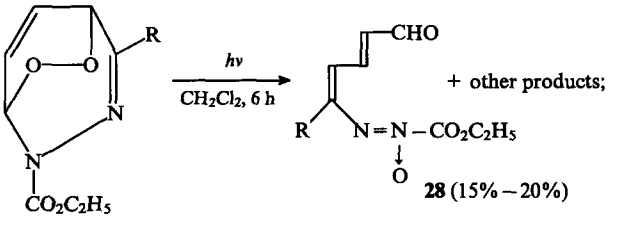
It has been suggested that the process proceeds via a stage involving the formation of *O*-acyl derivatives of diazene *N,N'*-dioxides **27**, which are stabilised by conversion into the final reaction products via the addition of a halide anion or (in the presence of Ag_2CO_3) via a rearrangement.[202]

The regiospecific formation of the azoxy-group is observed in the reaction of *N*-nitroso-*O,N*-dialkylhydroxylamines with certain organometallic reagents, but the yields of the asymmetrically substituted azoxyalkanes do not as a rule exceed 20–30% in this case and the reaction has no preparative value.[203]



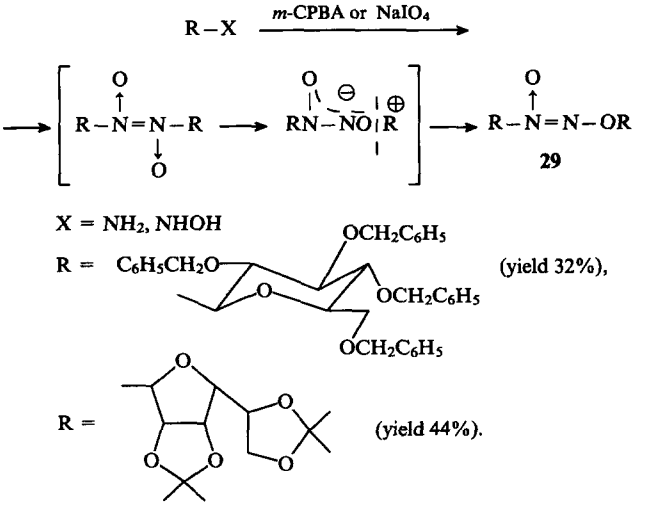
R = H, CH_3

The photolysis of 1*H*-diazepine 1,2-epidioxides leads to the formation of a mixture of products,[204] one of which is the azoxyalkene **28** with functional group substituents.



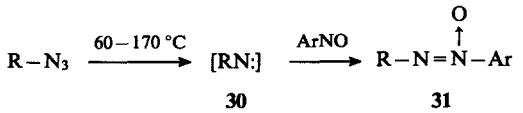
R^1, R^3 = Alk; R^2 = Alk, Ar; M = Li, MgBr.

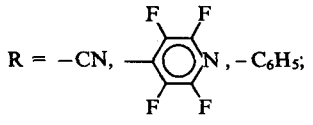
The reaction of the amino- and hydroxyamino-derivatives of glucopyranose and mannose with oxidants results unexpectedly in the formation of the azoxy-derivatives **29** of the corresponding carbohydrates, containing the $-N{=}N(\rightarrow O)-$ structural fragment.[205]



The authors explained this unusual mode of reaction by the heterolytic cleavage of the N–R bond in the dimeric nitroso-compounds (primary oxidation products) and the subsequent recombination of the ion pair, which leads to the product **29**. The driving force of the process is in this case the thermodynamic stability of the anions of the nitrosohydroxylamines and the cyclic oxonium cations.

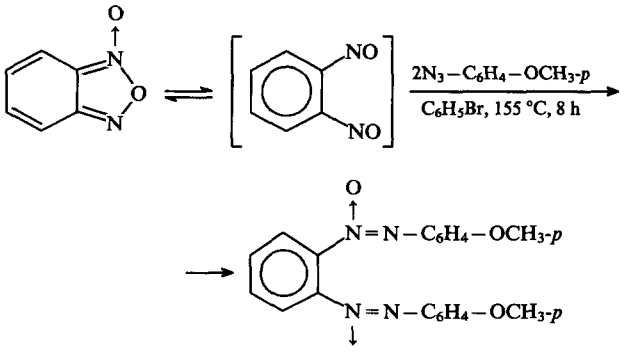
The formation of the diazene *N*-oxide group has been noted in the reaction of aromatic nitroso-compounds with cyanazides,[59,60] aryl azides,[206] and heteroaryl azides.[53] The most probable reaction pathway involves the addition of cyano-, aryl-, and heteroaryl-nitrenes **30**—the products of the thermal decomposition of the corresponding azide-derivatives—to nitrosoarenes with formation of the final reaction product **31**.





Ar = $-C_6H_4X$ (X = H, NO_2, $N(CH_3)_2$).

Together with nitroso-compounds, benzofuroxan can be made to react with aryl azides. It recyclises under the reaction conditions to *o*-dinitrosobenzene.[207]



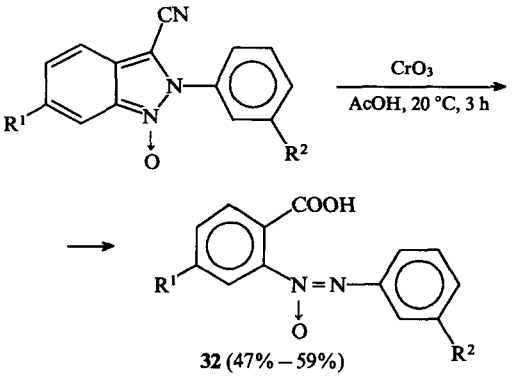
In view of the severe conditions in the thermolysis of the azides and the associated risk of explosion in the process as well as the low yields of the azoxy-products, this reaction cannot be regarded as a preparative method of synthesis of asymmetrically substituted diazene *N*-oxides.

A specific method of synthesis of *N,N'*-diaryldiazene *N*-oxides **32** with various substituents in the aromatic rings involves the oxidation of 2-aryl-3-cyanoindazole-1-oxides with chromium trioxide.[208,209]

Despite its regiospecificity, the reaction has not found wide scale application in synthetic practice, apparently owing to the low availability of the initial compounds.

VII. Conclusion

The data examined in this review show that studies designed to expand the applications of the known regioselective methods of synthesis of asymmetrically substituted diazene *N*-oxides and to develop new ones have been actively prosecuted in recent years in both our own and foreign scientific centres. A wide range of asymmetrically substituted azoxy-compounds, whose diazene *N*-oxide group is linked to carbon, oxygen, sulphur, nitrogen, and phosphorus atoms, has become available as a result. The range of the possible practical applications of these substances is extremely wide. Thus many of the newly synthesised asymmetrically substituted diazene *N*-oxides can be regarded as potential medicinal drugs (antibacterial,[7,10,12–16,59–61,63,122,153,214–217] antimicrobial,[218,219] antitumour,[12–16,63,122,153,220] anti-inflammatory,[145,221] immunodepressant,[222–224] anticonvulsive,[225,226] and analgesic[227]) as well as chemical plant protecting agents (nematocides,[19,20] fungicides,[16–18,186,228–231] and insecto-acaricides[161]), as components of liquid crystal compositions,[21–30] as gas-generating substances,[213] and as high-performance phases for gas–liquid chromatography.[30,210–212]



R^1, R^2 = H, NO_2

Bearing in mind the dynamics of the development of the synthetic and applied studies in this field, one may expect the preparation in the next few years of new diazene *N*-oxides which can find wide scale applications in various branches of science, industry, medicine, and agriculture.

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