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Umpolung of Amine Reactivity. Nucleophilic α-(Secondary Amino)-alkylation *via* Metalated Nitrosamines[**][***]

New synthetic methods (7)

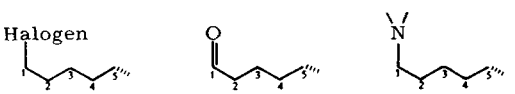
By Dieter Seebach and Dieter Enders[*]

There are basically two kinds of hetero atoms in organic molecules: one kind confers electrophilic character upon the carbon atom to which it is bound, and the other kind turns it into a nucleophilic site. The development of methods permitting transitions between the two resulting categories of reagents has become an important task of modern organic synthesis. The scope of such umpolung of the reactivity of functional groups is discussed for the case of amines as an example. A method of preparing masked α-secondary amino carbanions consists in nitrosation of the secondary amine, followed by metalation of the resulting nitrosamine α to the nitrogen, reaction with electrophiles, and subsequent denitrosation. Many examples are given for each of these steps which illustrate the wide scope of the overall synthetic operation (electrophilic substitution at the α-C atom of the secondary amine). Preliminary applications and a method for avoiding the handling of nitrosamines are presented, and the report concludes with a brief account of the significance of nitrosamines in the study of carcinogenesis and mutagenesis.

1. Introduction

1.1. Concept of Umpolung

We chemists are obliged to conform to certain simple rules dictated by Nature. Thus from the very beginning of our education in organic chemistry we learn—just how explicitly depends on the quality of our teacher—that heteroatoms such as halogen, oxygen, and nitrogen produce a certain reactivity pattern in a carbon skeleton: their electronegativity, being greater than that of carbon (−I effect), and their ability to stabilize an adjacent positive charge (+M effect) lead to the sites shown in Scheme 1 which are susceptible to attack by



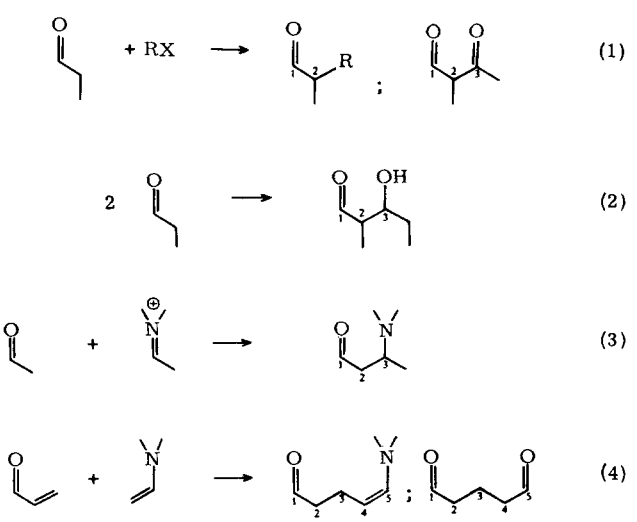
sites of $\frac{\text{electrophilic}}{\text{nucleophilic}}$ reactivity are C atoms $\quad \frac{1, 3, 5, \ldots}{2, 4, 6, \ldots}$

attack by $\frac{\text{nucleophiles}}{\text{electrophiles}}$ occurs at C atoms

Scheme 1. Polarity pattern in hetero-substituted carbon chains.

reagents possessing a given "philicity". Nucleophiles attack the odd C atoms ($N^{1,3,\cdots}$ attack)[*] whereas electrophiles attack the even C atoms ($E^{2,4,\cdots}$ attack) of the chain (for examples see Table 1).

In C—C linking reactions of two or more heterosubstituted carbon compounds it is thus established what synthetic opera-



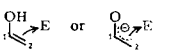
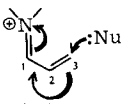
[*] Prof. Dr. D. Seebach and Dr. D. Enders [**]
Institut für Organische Chemie der Universität
63 Giessen, Ludwigstrasse 21 (Germany)

[**] This report draws extensively on the Dissertation of *D. E.*

[***] Attempts to find an English equivalent of the term "*Umpolung*" have yielded none so concise as the original German word. Its general adoption into English has therefore been proposed (see Chem. Ind. (London) *1974*, 910).

[*] Wherever there is a danger of confusion with a nitrogen atom the nucleophile will be designated "Nu".

Table 1. Examples for the typical reactivity of halogen compounds, carbonyl compounds, and amines with nucleophiles and electrophiles.

Attack by Nu or E at atom *n*	Halogen compound	Carbonyl compound	Amine
N^1			
	S_N substitution	addition or substitution at carbonyl C	aminoalkylation
E^2			
	HX′ addition	substitution at α-carbonyl C	enamine reactions
N^3			
	$S_{N'}$ substitution	1,4- or Michael addition	vinylogous Mannich reaction

tions are possible and the *distance* between the functional groups in the product is predetermined. A carbonyl compound is alkylated at position 2 by a halide [eq. (1)]; acylation, the aldol reaction, and the Mannich reaction [eqs. (1)—(3)] afford products having the heteroatoms in a 1,3 arrangement; additions of enamines to α,β-unsaturated carbonyl compounds furnish 1,5-bifunctional compounds [eq. (4)] (*odd* distance!).

Any "trick" by which the polarity pattern shown in Scheme 1 is contravened will be termed umpolung of the normal reactivity in the broadest sense. The price to be paid for an umpolung invariably involves a synthetic detour, *i.e.* we must reckon with additional steps such as introduction and removal of protecting and masking groups or with having to perform rearrangements. On the other hand, we are then able to attach a synthon possessing a given reactivity, E or N, at atypical sites of a carbon chain and to synthesize molecules having *even* instead of *odd* distances between the functional groups.

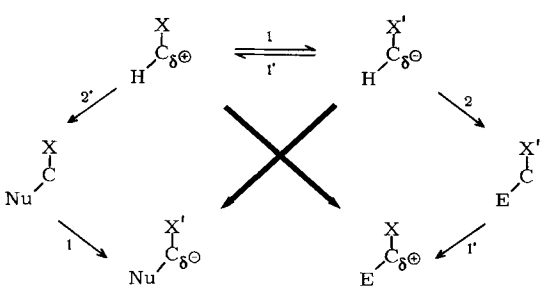
Umpolung is as old as organic synthesis itself, as is apparent from the first examples listed in Table 2. However, a systematic search for umpolung methods was only initiated by the enormous advances made in carbanion and carbocation chemistry during the past twenty years. Another contributing factor has been the full realization of the advantages offered by reagents of reversed charge affinity. The lower part of Table 2 gives some examples of carbonyl umpolung which we have described in detail elsewhere[1-3].

Table 2. Examples for umpolung of carbonyl compounds and amines. Newly formed bonds are shown in bold print.

Attack	Reagent	Equivalent	Product type	Ref.
E^1				[3, 4]
E^1	*(9)*			[4–6]
E^1				[3, 6]
E^1	*(8)*			[3, 6]
N^2				[3–5]
N^2				[5, 6]
E^1				[7]
E^1				[1–3]
N^2				[8]
E^3				[1–3, 8–11]
N^4				[3, 12]

1.2. Reversible Umpolung

Of greatest synthetic value is *reversible umpolung*. The concept is shown for a simple $E^1 \rightleftharpoons N^1$ example in Scheme 2. A compound having a C atom rendered positive is transformed,



Scheme 2. General principle of reversible umpolung.

by modification of the heteroatom from X to X′ in step 1, into a derivative in which the originally electrophilic C atom has now become nucleophilic. Reaction with an electrophile in step 2 is followed by reversal of step 1, *i.e.* by reinstitution of the original reactivity in step 1′. The net result (bold arrow from upper left to lower right) is introduction of an *electrophile* at a *positively* charged C atom.

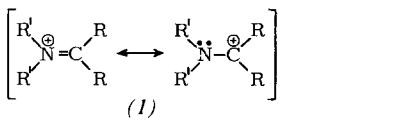
Attack by a nucleophile on a nucleophilic C atom (bold arrow from upper right to lower left) is feasible *via* the sequence 1′, 2′, 1. After temporary umpolung the C atom is in both cases finally available with normal reactivity again. A fre-

quently exploited example of the former case is umpolung of carbonyl compounds with thioacetal derivatives[1-3], and the latter case is illustrated by the masking of α-carbonyl cations by means of chloronitrones[8] (see also Table 2). In the following, the methods available for umpolung of amines will by briefly considered and a new reversible umpolung for secondary amines will be described in detail.

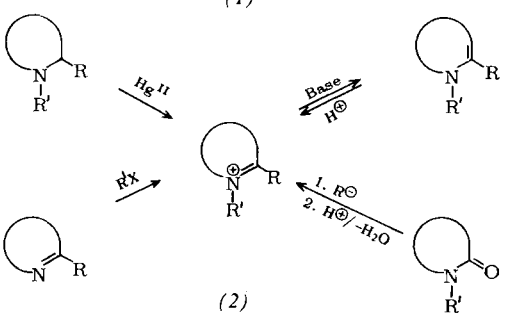
2. Possibilities of Umpolung of Amine Reactivity

2.1. α-Amino Carbocation *versus* α-Amino Carbanion

Amines display a "notorious" electrophilic reactivity at the α-C atom: the Mannich[13-15], Vilsmeier-Haak[16], Bischler-Napieralski, and Pictet-Spengler[17] reactions proceed *via* immonium ions of type *(1)*; salts of *(1)* are isolable[18-21],



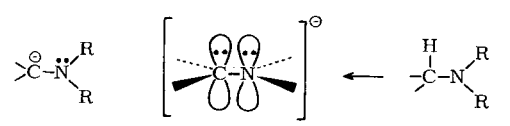
(1)



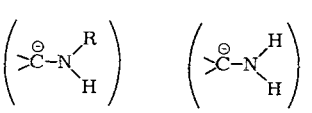
(2)

and even commercially available[22], and the dichloro derivative *(1)*, R=Cl[16] and a vinylimmonium ion *(1)*, R—R= $=C(CH_3)_2$[23] have recently been introduced into organic synthesis. Just how easy it is to come by immonium ions is obvious from the four routes shown for formation of the cyclic derivatives *(2)*. *Electrophilic* α-aminoalkylations are thus common events in organic synthesis and in biochemistry.

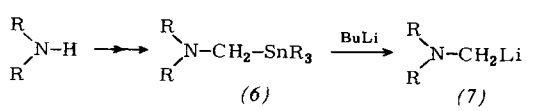
The situation is completely different with *nucleophilic* α-aminoalkylations, *i.e.* regarding the availability of α-amino carbanionic derivatives *(3)—(5)*; neither the relatively small electronegativity of the amino nitrogen nor the electronic configuration comparable with that in a ketyl[24] or ethylene



(3) *(3a)*



(4) *(5)*



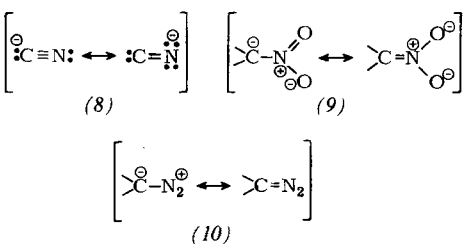
(6) *(7)*

dianion [see *(3a)*] favor the formation of a carbanion derivative, as may be seen from the extremely slow H/D[25] and H/Li exchange[26-28] in tertiary aliphatic amines. Once they have been formed, *e.g.* by transmetalation of the tin compounds *(6)*, α-aminomethyllithium compounds *(7)* display sufficient thermodynamic stability—*e.g.* toward Wittig rearrangement[29]—at 0 °C in hydrocarbons or ethers to act as reagents for nucleophilic α-*tertiary*-aminomethylation[26, 27]. Anions *(4)* and *(5)* of *secondary* and *primary* amines can be envisaged only if strong anion-stabilizing groups are bound to the carbon since tautomerization affording an amide anion would otherwise occur.

Since amines number among the most important classes of substances in organic chemistry and since at most *tertiary* α-aminoalkylating agents such as *(7)* are directly accessible, the use of *masked* synthons of anions *(3)—(5)* with reversed reactivity at the α-N-carbon atom is highly significant. Thus the question arising is: (a) what factors favor formation of a negative charge adjacent to nitrogen? and (b) which of these factors can be exploited in the sense of Scheme 2 for temporary umpolung of reactivity?

2.2. Dipolar and/or Resonance-Stabilized α-N-Carbanions

As is obvious from the "classical" α-N-carbanions *(8)* and *(9)* listed in Table 2, and from the diazo compounds *(10)*, which are likewise nucleophilic at the carbon, there exist bonding states of the nitrogen in which adjacent C atoms bear a negative charge, owing to endowment of the nitrogen



(8) *(9)*

(10)

with a positive charge (inductive effect), hybridization effects at the carbon (stability series $sp\text{-}C^{\ominus} > sp^2\text{-}C^{\ominus} > sp^3\text{-}C^{\ominus}$, increase in electronegativity of the carbon with increasing s character), and/or resonance stabilization of the negative charge.

A literature search reveals that the generation of negative charges on C atoms adjacent to nitrogen in derivatives of types *(11)—(17)* is favored, as can be deduced from H/D exchange, condensation, or metalation reactions. Remarks on the various types and references are given under the relevant formulas in Table 3. It is trivial that any substitution at the negative C atom leading to additional delocalization, such as incorporation of allyl ($\overset{\ominus}{C}$—C=C), benzyl ($\overset{\ominus}{C}$—C_6—H_5, in general $\overset{\ominus}{C}$-aryl or $\overset{\ominus}{C}$-heteroaryl), enolate ($\overset{\ominus}{C}$—C=O), or iminoenolate resonance ($\overset{\ominus}{C}$—C=N, $\overset{\ominus}{C}$—C≡N) will further enhance the stability, and in the ultimate case will suffice to generate an ambident, fully masked α-N anion. Lithiated α-amino ester derivatives *(18)* represent an example[127] which should be termed lithium enolates rather than nucleophilic

Table 3. Structures *(11)*—*(17)* with negative charges on the C atoms adjacent to nitrogen.

(11)

X=C:	isocyanides [7]
X=C<	Schiff bases [30—34], imines of pyridoxal phosphate [35]
X=C=S	isothiocyanates [36]
X=NR	azo compounds [37]; anion with R=C_6H_5 reacts with carbonyl compounds at C, and with alkyl halides at N
$X=N_2$	azides [38]
X=O	oximes; oximates react with electrophiles at O or N, not at C [39], exception in intramolecular reactions [40]

(12)

X=C<, X'=C<	azomethine ylides [41, 42], pyridinium ylides [43]
X=C<, X'=O$^{\ominus}$	nitrones [38]
X=NR, X'=O$^{\ominus}$	azoxy compounds [44, 45]
X=X'=O$^{1/2\ominus}$	nitro compounds [4, 39]; anions do not react with alkylating agents at C

(13)

unstabilized [46—49], allyl- [50, 51], benzyl- [52], and enolate stabilized [53—56] nitrogen ylides [57]; cf. Stevens-Sommelet-Hauser rearrangement [58]; metalated amine oxides [38, 59—61]

(14)

X=$^{\ominus}$	dianions of Schiff bases [62]
X=C_6H_5	benzylic and/or allylic stabilization of anions necessary [29, 63, 64]
X=COR	R should not contain [65] α-carbonyl hydrogens [66], anion stabilization necessary, *e.g.*, by C_6H_5 [67, 68] or C≡N [69, 70], Reissert compounds; cyanamines cannot be metalated to *(14)*, X=C≡N [71]
X=N=C<	hydrazones [38], 1-methylpyrazole [72], 1-methylindazole [103]
X=N=NR	triazenes (not yet accomplished [73])
X=N=O	nitrosamines [71, 74—90]
$X=NO_2$	nitramines [89, 91]
$X=POR_2$	phosphonic amides [26, 92]

(15)

X=C<	imidazoles, 2-methylindazole [103], 1,3-dimethylpyrazole [104], nitroolefins [125, 126]
X=O	formamides [3, 93—97]
X=S	thioformamides [71, 93, 97, 98]

(16)

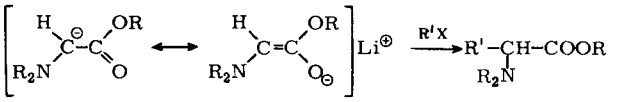
aldimines [99—102], heteroaromatics like pyrazoles, imidazoles [103, 105—108], triazoles [106—109], thiazoles [103, 110, 111], and pyridines [112—114]

(17)

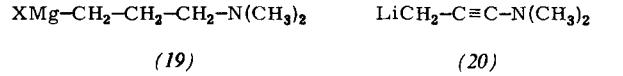
X=X'=C<	pyridinium, quinolinium ylides [115—117]
X=C<, X'=O$^{\ominus}$	nitrones [118], pyridine *N*-oxides [119—121]
X/X'=N$^{\ominus}$	diazomethanes [122—124]

α-aminoalkylating agents. Although they possess considerable preparative significance, these cases will be excluded from the present discussion, as will reagents with E^3-umpolung of the amine skeleton (see Scheme 1 and Tables 1 and 2), such as *(19)*[128-130] and *(20)*[131].

Among the numerous α-N anion systems *(11)*—*(17)* there are several which cannot be utilized as masked amino carb-



(18)



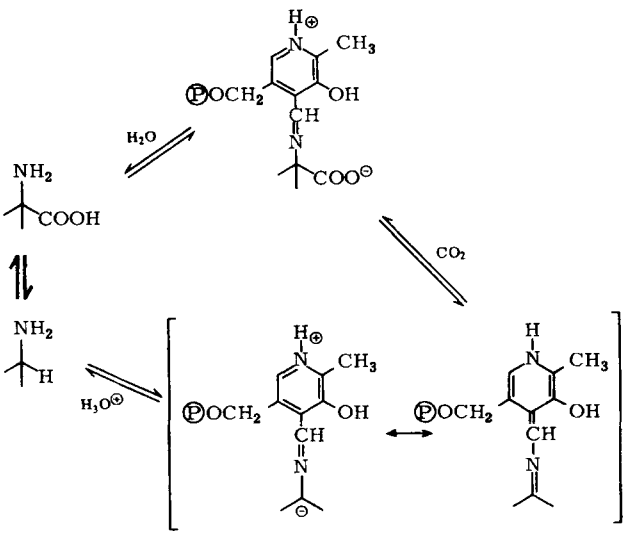
(19) *(20)*

anions *(3)*—*(5)*; some have long been employed for the umpolung of amines[132] [Table 2 and Systems *(8)*—*(10)*], while others have only recently been exploited for the purpose. However, only very few of them are suitable for reversible umpolung according to the general Scheme 2.

2.3. Reversible Umpolung at the α-Position of Primary, Secondary, and Tertiary Amines

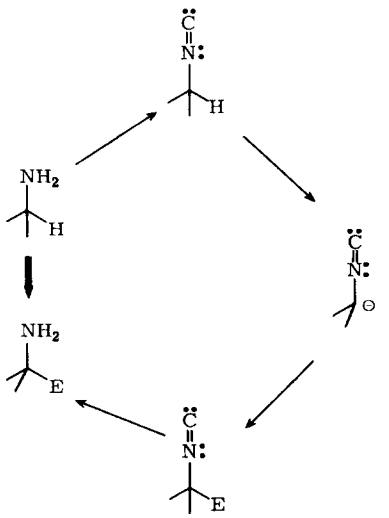
As may be seen from Scheme 2, reversible umpolung essentially involves the following three steps: Masking of the compound exhibiting normal reactivity with umpolung; reaction with "opposite sign"; "demasking".

The elegant way in which Nature has solved this problem for *primary amines* is apparent from Scheme 3 which outlines the interconversion of amino acids and biogenetic amines with the aid of a pyridoxal phosphate derivative[35]; the electrophiles $H^{\oplus}$ and CO_2 undergo mutual exchange at the α-amino C atom.



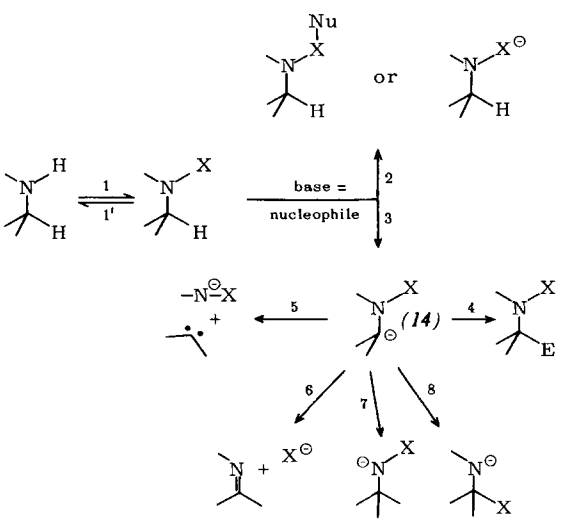
Scheme 3. Reversible umpolung of primary amines in Nature. Ⓟ = phosphate.

Those derivatives *(11)*, which can readily be prepared from primary amines, and nitro compounds of type *(12)* appear to be most suitable for imitation of this process *in vitro*. So far the best solution having a broad scope is probably the isocyanide method developed by *Schöllkopf* and his group[7] (Scheme 4): A variety of mild methods is available for conversion of primary amines into isocyanides; subsequent metalation and reaction with electrophiles proceed excellently and demasking is a hydrolytic step. In comparison, masking *via* nitro compounds (>CH—NH_2→>CH—NO_2) requires an oxidation[133], the nitro anions (>$C^{\ominus}$—NO_2) only react with certain electrophiles at the C atom[4, 39, 134], and reductive demasking succeeds only under quite drastic conditions[135].



Scheme 4. Reversible umpolung of primary amines *via* isocyanides.

The derivatives *(14)* suggest themselves for reversible umpolung of *secondary amines*. The following conditions must be



Scheme 5. Conditions for reversible umpolung of secondary amines *via* anions of type *(14)*.

fulfilled (see Scheme 5):

a) X must be readily attached (masking, step 1);

b) X must be removable under mild conditions, *i. e.* replaceable by H (eventual "demasking", step 1');

c) X should neither contain CH acidic groups nor be subject to easy attack by a nucleophile (step 2);

d) X must impart sufficient acidity to the α-amino CH group [step 3, →*(14)*];

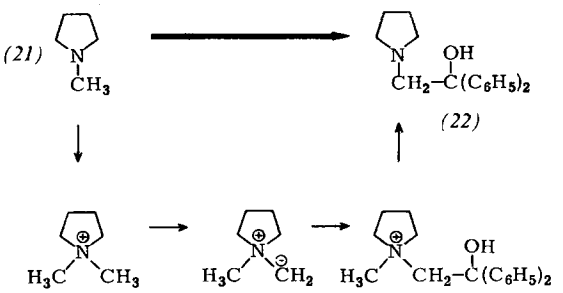
e) *(14)* must be strongly nucleophilic at the $C^{\ominus}$ atom (step 4);

f) *(14)* should not decompose by α- or β-elimination (steps 5 and 6); and

g) *(14)* should not rearrange (steps 7 and 8).

In the course of the last three years we have found only one substituent X which satisfies these requirements: the nitroso group[71, 79–81, 83, 88–90]. Thus we have used it to develop the first practicable method for reversible umpolung of secondary amines. The remaining sections of this progress report are devoted to its detailed description.

No general procedure for reversible α-anionization of *tertiary amines* has yet been developed. Ammonium ylides[46, 47] and amine oxides *(13)*[59, 60] should prove suitable for this purpose, as demonstrated by the—conceptual—conversion of 1-meth-



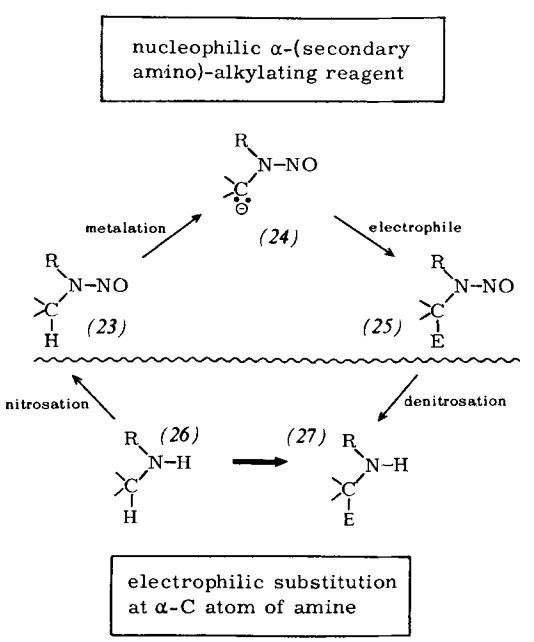
ylpyrrolidine *(21)* into the amino alcohol *(22)*. Of the steps involved, quaternization is trivial, hydroxyalkylation of the ammonium ion with benzophenone *via* the ylide is possible in 52% yield according to *Wittig*[46, 47], and mild and selective methods are nowadays available for removal of the methyl group to give *(22)*[136, 137].

Amines can also be functionalized by free-radical processes[138].

3. Metalated Nitrosamines as Masked Nucleophilic α-(Secondary Amino)alkylating Reagents

3.1. Concept

If it proves possible to convert nitrosamines *(23)* having at least one α-hydrogen atom into metal derivatives of the anion *(24)*, and if *(24)* is stable and sufficiently reactive to give good yields of the substituted nitrosamines *(25)* with



electrophiles, then a secondary amine *(26)* has effectively been subjected to electrophilic substitution at the α-C atom to form *(27)*. Nitrosation of amines, *(26)*→*(23)*, and the denitrosation of nitrosamines, *(25)*→*(27)*, are actually well-

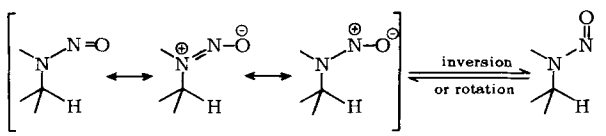
proven methods of organic synthesis. We cannot go into details of these steps here; mention should however be made of the extensive literature on this topic[139-146] and of the fact that we have performed the nitrosations[139, 140] primarily in glacial acetic acid and found either hydrogen chloride in inert solvents (benzene, ether[141]), or Raney nickel[143] in THF, most suitable for removal of the nitroso group[140-146]. In many cases both steps proceed in yields of more than 95%.

The wavy line in the reaction scheme is intended not only to separate the net electrophilic substitution from the individual steps but also to signalize an area of hazard: it is hoped that nitrosamines are generally known to be *carcinogens*. This aspect and the precautions they demand are considered in Section 3.7.

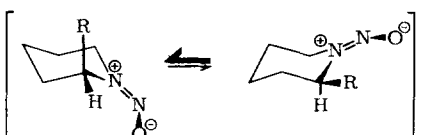
The following sections are devoted to the metalation of nitrosamines, the stability of lithionitrosamines and their reactions with electrophiles, as well as a number of examples of overall reactions *(26)*→*(27)*.

3.2. Metalation of Nitrosamines [Step *(23)*→*(24)*]

On consideration of the three resonance formulas of a nitrosamine *(23a)*↔*(23b)*↔*(23c)*, several analogies with carbonyl compounds become apparent. Besides the "neutral" formula *(23a)*, the dipolar electronic configurations *(23b)* and *(23c)* are very important. This may be deduced form the coplanarity of the nitrosated nitrogen[147], which is compatible with *(23b)*, and from the high ON—N rotational or O—N inversional



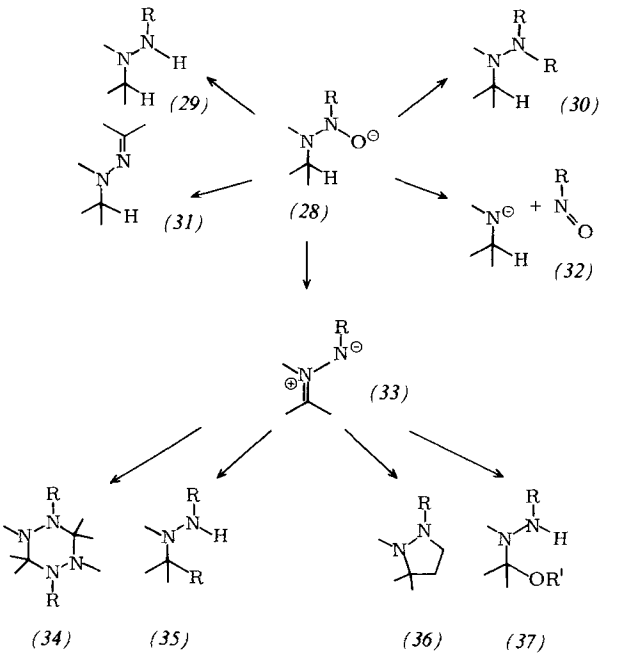
(23a) *(23b)* *(23c)* *(23')*



(23")

barrier *(23)*⇌*(23')*, which amounts to about 23 kcal/mol in dialkylnitrosamines[139, 148-150]. The marked axial preference of the substituent R in 1-nitrosopiperidines *(23")* can also be interpreted in the same way[151-156]. Electron-withdrawing groups or those that can engage in conjugation, such as CF_3 or C_6H_5, considerably lower the N—N rotational barrier when attached to the nitrosated nitrogen[157, 158]. CNDO calculations show the nitroso-N atom to bear a partial positive charge[159]. Hence this atom will be attacked readily by nucleophiles (see also pathway 2 in Scheme 5). Since the H atom adjacent to the positively charged nitrogen can be acidified, as in a carbonyl derivative [cf. *(23b)*], however, each Lewis base reacting with a nitrosamine therefore has a choice of attacking the nitroso nitrogen as a nucleophile or the α-CH group as a base.

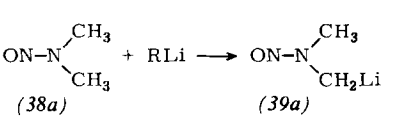
Until recently only the former reaction type was known. The primary adduct *(28)* has an unusually large range of secondary reactions from which to choose. All the products isolated



(29) *(30)* *(31)* *(28)* *(32)* *(33)* *(34)* *(35)* *(36)* *(37)*

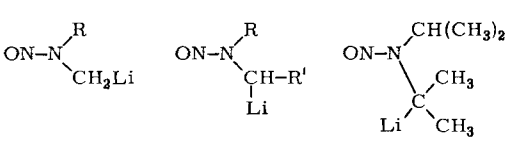
(29)—*(32)* and *(34)*—*(37)* can be explained in terms of *(28)*. Depending upon the nature of the group R and the conditions of reaction and work-up complicated mixtures[71, 79, 160-163] of these products are sometimes formed in reactions with RMgX and RLi (R = alkyl, aryl, R_2N). The hydrazines *(29)* and *(30)* apparently arise from attack of a second mol of $R^{\ominus}$ with loss or replacement of the oxygen[160-162]. Hydrazones *(31)* can result [160, 161] if R contains an α-hydrogen atom. A transnitrosation product *(32)* may be released by β-elimination[71, 79, 161]. Finally an azomethinimine *(33)*[42, 164] may be formed, either in the reaction mixture or during work-up; this species can dimerize to hexahydrotetrazine *(34)*[79, 161], react with a second $R^{\ominus}$ to yield *(35)*[161], be trapped by dipolarophiles to form *(36)*[162] or be "neutralized" on work-up with alcohols, yielding *(37)*[161, 162].

Unequivocal proof of the acidity of nitrosamines *(23)* not bearing an additional acidifying group[74, 165] was probably first established by *Rademacher* and *Lüttke*[75, 77] by base-cata-

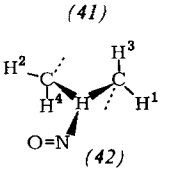


(38a) *(39a)*

R = CH_3	60%
R = n-C_4H_9	45%
R = t-C_4H_9	10%
R = C_6H_5	80%
R = $N[CH(CH_3)_2]_2$	>95%



(39) *(40)* *(41)*

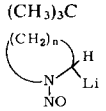
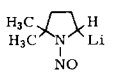
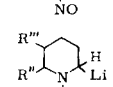
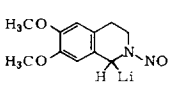
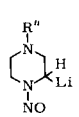
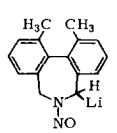


(42)

lyzed perdeuteration of dimethylnitrosamine. In 1970, *Keefer* and *Fodor* succeeded in methylating dimethylnitrosamine *(38a)* with sodium hydride/methyl iodide to give a low yield of ethylmethylnitrosamine. Two years later we reported[79] the quantitative metalation of the same nitrosamine to *(39a)* with lithium diisopropylamide (LDA) in tetrahydrofuran at $-80\,^{\circ}C$ and reactions with various electrophiles. Other metalating agents generally gave poorer yields of *(39a)* owing to competing attack at the nitroso group.

Since metalation of dimethylnitrosamine *(38a)* also succeeds in the presence of excess dimethyl sulfoxide, the pK_a value of *(38a)* must lie below 34[167]. Meanwhile, we have been able to show that other primary, as well as secondary and tertiary, Li derivatives *(39)*, *(40)*, and *(41)* can be produced from nitrosamines and LDA and reacted with a variety of electrophiles (see Sections 3.4 and 3.5). Table 4 reveals the broad scope of metalation of nitrosamines! The examples *(39b)*, *(39c)*, *(39e)*, *(39f)*, and *(40m)* show the acidity to follow the usual series $-CH_3 > -CH_2- > \geqslant CH$. Owing to the enhanced thermodynamic stability of the benzylic Li derivative the series is violated in the case of benzylmethylnitrosamine [*(39g)*, *(40d)*, Table 4].

Table 4. Primary and secondary lithium derivatives *(39)* and *(40)* of nitrosamines [71, 79—81, 83, 88—90] prepared with lithium diisopropylamide (LDA) at $-80\,^{\circ}C$.

Nr.	Li derivative R	R′	Yield [a] [%] of type *(25)*
primary			
(39a)	CH_3		100
(39b)	C_2H_5		90
(39c)	$(CH_3)_2CH$		95
(39d)	$(CH_3)_3C$		100
(39e)	cyclohexyl		95
(39f)	menthyl		90
(39g)	$C_6H_5CH_2$		60 [b]
(39h)	C_6H_5		58 [c]
secondary			
(40a)	C_2H_5	CH_3	90
(40b)	n-C_6H_{13}	n-C_5H_{11}	100
(40c)	$(CH_3)_3C$	$C_6H_5CH_2$	70
(40d)	CH_3	C_6H_5	65 [b]
(40e)	$C_6H_5CH_2$	C_6H_5	99 [78]
(40f)	$(CH_3)_3C$	SCH_3	95
(40g)	$(CH_3)_3C$	$Si(CH_3)_3$	95
(40h)		n = 2	75
(40i)		n = 3	90
(40j)		n = 4	90
(40k)		n = 5	90
(40l)[87]			
(40m)		R″ = n-C_5H_{11}, R‴ = H	70
(40n)		R″ = H, R‴ = OLi	50
(40o)			50
(40p)			60
(40q)		R″ = CH_3	45
(40r)		R″ = C_6H_5	73 [78]
(40s)			98 [78]

[a] The yields given are the highest yet obtained with the Li derivatives *(39)* and *(40)* on reaction with electrophiles (see Tables 5—8). In most cases they have not been optimized.

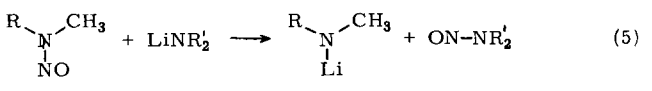
[b] Kinetically controlled metalation (5 min) at CH_3, thermodynamically controlled metalation (> 60 min) at CH_2.

[c] Metalated with cyclohexylisopropylamide at $-110\,^{\circ}C$.

The rate at which the nitrosamines are metalated by LDA at $-80\,^{\circ}C$ is extremely fast: with methylnitrosamines the electrophile can be added a few minutes after the metalating agent; hexamethylphosphoric triamide (HMPA) further accelerates this step, as we were able to show for 1-nitrosopiperidine[88]. According to our experience, its Li derivative *(40j)* is formed the most slowly of all the compounds listed in Table 4; 3—4 h are required. In the presence of four equivalents of HMPA this time can be reduced to 1 h. At the same time HMPA enhances the stability of lithionitrosamines[88] (see Section 3.3).

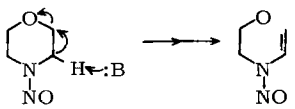
The stereochemistry of nitrosamine deprotonation was established by *Fraser et al.*[78] for the dibenzoazepine derivative *(40s)*: of the four hydrogens present in the precursor, of which two are quasi-axial and two are quasi-equatorial as indicated in *(42)*, the *syn*-axial one, H^4, is preferentially replaced by D on treatment with bases. This is in accord with our findings[88] in the metalation of nitrosopiperidines to yield *(40j)*, *(40m)*, *(40n)*, and *(40o)* (Table 4).

Difficulties arising from the side- and secondary reactions discussed in Scheme 5 occur only in special cases when our metalation procedure is employed. Transnitrosation according to eq. (5) becomes the principal reaction if R has a pronounced anion-stabilizing effect[71], as in nitrosamides and nitrososul-

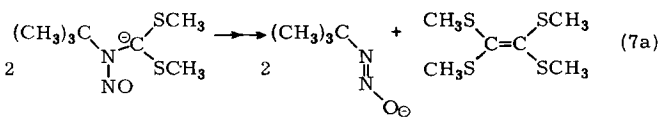


(5)

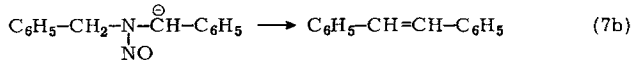
R = Ar, COR, COOR, Tos



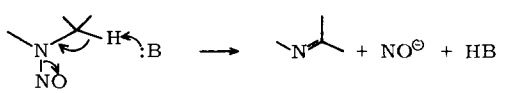
(6)



(7a)



(7b)

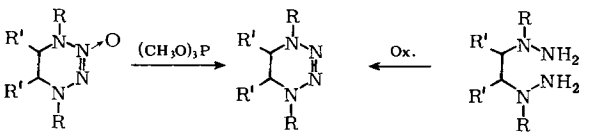


(8)

fonamides; with nitrosomorpholine, elimination according to eq. (6) takes place[71]; and the thioacetal derivative[90] shown in eq. (7a) undergoes α-elimination, which is presumably also responsible for the formation of stilbene from metalated dibenzylnitrosamine [eq. (7b)][89]. So far, in our metalation experiments with dialkylnitrosamines, we have not obtained unequivocal evidence for the $NO^{\ominus}$ elimination, described in eq. (8) and also observed with other bases[74, 165].

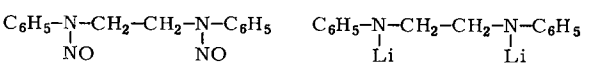
3.3. Dimerization of Lithionitrosamines to Tetrahydro-*v*-tetrazine Derivatives[71, 79, 83, 88, 89]

Even at −80 °C the lithium derivatives *(39)*—*(41)* are only short-lived reagents. Thus the lithiated dimethylnitrosamine *(39a)* decomposes with a half-life of two hours in HMPA-free THF solution (8 h in the presence of four equivalents of the



(43) *(44)* *(45)*

(a), R = CH_3, R' = H [from *(39a)*]
(b), R = Cyclohexyl, R' = H [from *(39e)*]
(c), R-R' = -$(CH_2)_3$- [from *(40i)*]
(d), R-R' = -$(CH_2)_4$- [from *(40j)*]
(e), R-R' = -$(CH_2)_5$- [from *(40k)*]
(f), R-R' = -CH_2-CH_2-N(CH_3)-CH_2- [from *(40q)*]



(46) *(47)*

amide), as we have shown by trapping with benzaldehyde as electrophile. So far we have isolated up to 55% yields of the tetrazine oxide *(43a)* as the sole decomposition product. Other derivatives *(39)* and *(40)* correspondingly afford compounds *(43b)*—*(43f)*. The structure of these novel heterocycles was confirmed by spectroscopy and by reduction to the oxygen-free tetrahydro-*v*-tetrazines *(44)*, which are meanwhile also accessible in low yield, by oxidation of bis-hydrazines *(45)*[168, 169]. After decomposition of lithiated methylphenylnitrosamine *(39h)* (see Table 4) we isolated the dinitroso derivative *(46)* (15%) and secondary products of the dianilide *(47)* (30%). The products *(43)*, *(46)*, and *(47)* are apparently formed by C—C linkage between the formerly anionic C atoms of the lithionitrosamines; *(43a)*—*(43f)* are

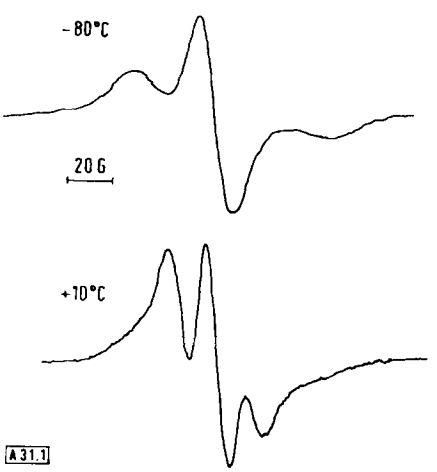
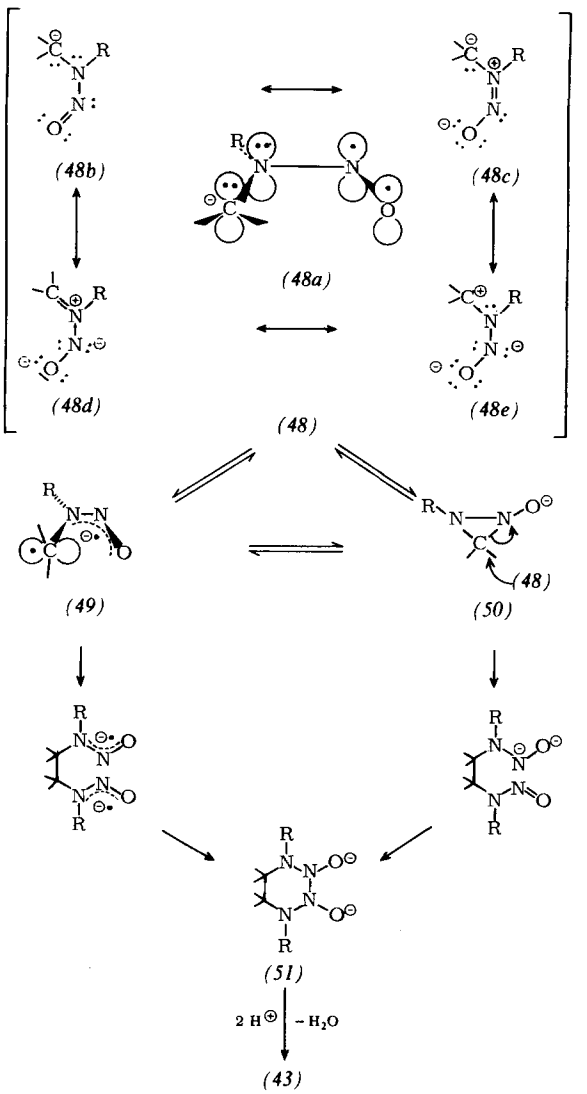


Fig. 1. ESR spectra of a lithiodimethylnitrosamine solution at −80 and +10 °C. The changes occurring on going to the higher temperature are reversible. The metalation mixture (THF/hexane/lithium diisopropylamide) does not give a signal prior to addition of the nitrosamine. Perdeuterated dimethylnitrosamine affords the same spectrum (recorded with a Varian E4 spectrometer).

dimers minus H_2O, *(46)* is a dimer minus H_2 of the original nitrosamines.

Concerning the course of this reaction one can indulge at most in interesting speculations, which are closely related to the important question of the structure of the lithionitrosamines *(39)*—*(41)*. If it is deduced from the stereochemistry of deprotonation [see *(42)*][78] that the resulting anion prefers the planar *cis* form *(48)*, then the π-system *(48a)* occupied by six electrons should be present: this system can be described by four resonance formulas *(48b)*—*(48e)*. Dimerization of *(48)* as a 1,3-dipole should not proceed *via* the head-to-head product *(51)* to the observed tetrazine *(43)*. However, a 90° rotation of the C atom with decoupling of the π-system[170]



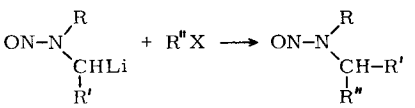
giving *(49)* or a ring closure to *(50)*, for which there is experimental evidence[165], would explain the formation of the tetrazine oxides *(43)*, as may be seen from the flow chart. Nitrosamine radical ions such as are formulated therein are formed very readily by alkali metal reduction[171]. Corroborating evidence for the presence of radicals in solutions of lithionitrosamines comes from ESR spectra of lithiodimethylnitrosamine (Fig. 1). An interpretation of the spectra and a definite mechanistic concept of *v*-triazine formation have not yet been produced.

3.4. Reactions of Lithionitrosamines with Electrophiles [Step (24)→(25)]

It is clear from the foregoing Section that all reactions of nitrosamine lithium derivatives with electrophiles must be carried out at or below −80°C. Only when the reaction of the lithium compounds with the electrophile is faster than their decomposition can good yields of products having the general structure *(25)* be expected. Hence it is hardly surprising that, for instance, epoxides, which are also relatively inert towards other lithium reagents[172], cannot be utilized as electrophiles. In contrast, additions to carbonyl groups proceed exceedingly rapidly (see Section 3.4.2, α-hydroxyalkylations and preparation of aminoethanols) and succeed even at temperatures of about 0°C under conditions of base catalysis (tBuOK)[71,85,88,89] or at even higher temperatures with α-tin-substituted nitrosamines[71] (see Section 3.4.2).

3.4.1. Alkylation

Alkylations of primary and secondary lithionitrosamines *(39)* and *(40)* accomplished so far are summarized in Table 5. The substituted derivatives *(52)* with R′=H [from *(39)*] and R′=alkyl and aryl [from *(40)*] are formed in yields ranging from 60 to 95% and higher. However, the reactions with primary alkyl iodides, especially in the case of the lithiated cyclic nitrosamines *(40i)*, *(40j)*, *(40m)*, *(40n)*, and *(40r)* give yields at the lower limit of this range, while allylation, methoxymethylation, and benzylation proceed almost quantitatively.



(39), R′ = H
(40), R′ ≠ H

(52)

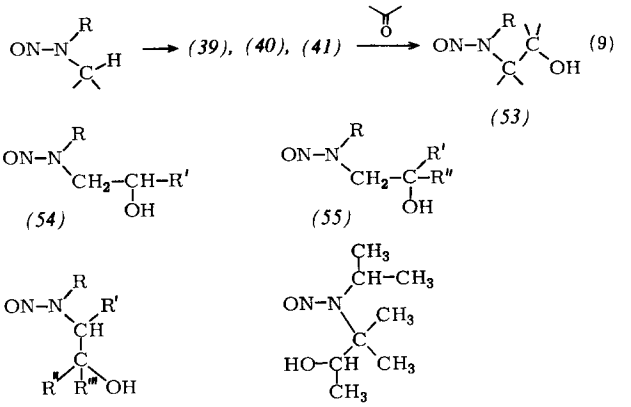
Table 5. Alkylation of lithionitrosamines *(39)* and *(40)* of Table 4 to form the products *(52)* [general type *(25)*].

No.	R″X	Yield [%] of *(52)*	Ref.
(39a)	CH_3I	75	[79]
(39a)	n-C_4H_9I	75	[79]
(39a)	$H_2C{=}CH{-}CH_2Br$	90	[88]
(39a)	$C_6H_5CH_2Br$	>95	[79]
(39c)	$C_6H_5CH_2Br$	95	[80]
(39d)	$C_6H_5CH_2Br$	>95	[71]
(39d)	$CH_3{-}O{-}CH_2Cl$	93	[71]
(40b)	$C_6H_5CH_2Br$	>95	[80]
(40c)	$C_6H_5CH_2Br$	70	[71]
(40e)	CH_3I	91	[78]
(40e)	n-C_3H_7I	85	[78]
(40f)	$C_6H_5CH_2Br$	95	[90]
(40i)	n-C_3H_7I	60	[88]
(40i)	$C_6H_5CH_2Br$	90	[80]
(40j)	n-C_3H_7I	60	[88]
(40j)	n-$C_5H_{11}I$	60	[88]
(40j)	$CH_2{=}CH{-}CH_2Br$	60	[88]
(40j)	$C_6H_5CH_2Br$	60	[80]
(40m)	n-$C_5H_{11}I$	60	[88]
(40p)	$C_6H_5CH_2Br$	60	[89]
(40n)	n-C_3H_7I	40	[88]
(40r)	CH_3I	46	[78]
(40s)	CH_3I	98	[78]

Cyclizations are also possible *via* alkylation with dihaloalkanes and are mentioned in Section 3.5.4.

3.4.2. Reactions with Aldehydes and Ketones (α-Hydroxyalkylation)

There are about 50 examples of this reaction, which corresponds to the aldol addition: it is formulated in general terms in eq. (9). Depending upon the nitrosamine and carbonyl



(53)

(54)

(55)

(56a), R/R′ not linked
(56b), R-R′ cyclic

(57)

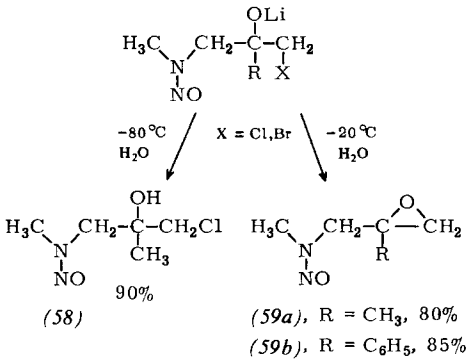
components employed, the structure of the products of type *(53)* can vary within wide limits. The primary and secondary lithionitrosamines *(39)* and *(40)* react with aliphatic and aromatic aldehydes, and with aliphatic, cycloaliphatic, and aromatic ketones to give adducts of types *(54)*, *(55)*, and *(56)* listed in Tables 6 and 7 (Section 3.5.3). The α-branched

Table 6. Reactions of primary and secondary lithionitrosamines *(39)* and *(40)* with aldehydes and ketones involving hydroxyalkylation to the products *(54)*—*(56)* [71, 79, 80, 88—90] (further examples will be found in Table 7, Section 3.5.3). The yields refer to distilled or recrystallized products [general type *(25)*].

No.	Carbonyl derivative	Product type	Yield [%]
(39a)	n-butanal	*(54)*	80
(39a)	benzylaldehyde	*(54)*	>95
(39a)	acetone	*(55)*	70
(39a)	3β-hydroxy-16α,17α-epoxy-5-pregnen-20-one	*(55)*	80 [a]
(39a)	cyclohexanone	*(55)*	95
(39a)	cyclohexenone	*(55)*	85
(39a)	*d,l*-camphor	*(55)*	70
(39a)	(−)-fenchone	*(55)*	80 [b]
(39b)	acetaldehyde	*(54)*	75
(39c)	acetaldehyde	*(54)*	85
(39d)	acetaldehyde	*(54)*	95
(39d)	diphenylacetaldehyde	*(54)*	80
(39d)	3,4-methylenedioxy-benzaldehyde	*(54)*	95
(39d)	acetone	*(55)*	90
(39e)	benzophenone	*(55)*	95
(39g)	acetaldehyde	*(54)*	60 [c]
(39h)	acetaldehyde	*(54)*	60
(40d)	acetaldehyde	*(56a)*	65 [c]
(40e)	benzaldehyde	*(56a)*	62 [78]
(40f)	benzaldehyde	*(56a)*	90
(40f)	cyclohexenone	*(56a)*	80
(40j)	acetaldehyde	*(56b)*	90
(40j)	propionaldehyde	*(56b)*	90
(40j)	benzaldehyde	*(56b)*	70
(40j)	acetone	*(56b)*	78
(40n)	benzophenone	*(56b)*	50
(40n)	acetone	*(56b)*	50
(40o)	benzophenone	*(56b)*	50
(40p)	3,4-dimethoxybenzaldehyde	*(56b)*	60
(40q)	acetaldehyde	*(56b)*	45

[a] Mixture of diastereoisomers exhibiting an unsharp melting point; no evidence for epoxide ring shift from the NMR spectrum.
[b] Optical purity of starting fenchone 82%.
[c] See Table 4, footnote [b].

derivatives *(56)* having two chiral centers are obtained as mixtures of diastereomers. Linkage to a methine carbon atom in the nitrosamine moiety leads to the product shown in formula *(57)* [from *(41)* and acetaldehyde]. Enolate formation plays a subordinate role to carbonyl addition, even on reaction with readily enolizable carbonyl compounds like diphenylacetaldehyde, acetone, cyclohexanone, 3β-hydroxy-16α,17α-epoxy-5-pregnen-20-one, and camphor. Carbonyl groups subject to pronounced steric hindrance, such as that of fenchone, react with ease. Halo ketones like chloroacetone and bromoacetophenone are attacked exclusively at the carbonyl; if the initially formed lithium alkoxides are protonated at the reaction temperatures then nitrosaminohalohydrins like *(58)* are obtained. On warming lithium halide elimination occurs, furnishing the epoxynitrosamines *(59)*. Thus the lithionitrosamines can be described as powerful *carbonylophiles* (cf. also acylation, Section 3.4.4).

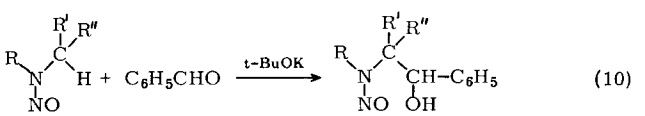


(58)

(59a), R = CH_3, 80%

(59b), R = C_6H_5, 85%

Examples[85, 88] of *in-situ* generation of nitrosamine anions and addition to a non-enolizable aldehyde are given in eq. (10). The comparison between nitrosamines and carbonyl compounds already mentioned above (see Section 3.2) comes once

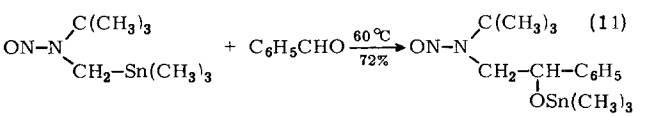


(10)

R = CH_3, R' = R'' = H >95%

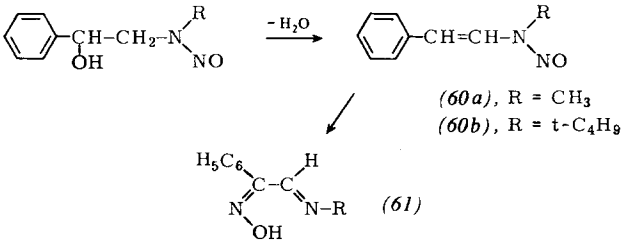
R = p-Cl-C_6H_4, R' = R'' = H 69%

R-R' = -$(CH_2)_4$-, R'' = H 80%



(11)

more to mind on consideration of the carbonyl addition [eq. (11)] accomplished by merely mixing the components and warming to 60 °C[71]. This reaction type has long been known in the case of α-silyl[173] and α-stannyl[174] carbonyl derivatives[175]. Use of this modification should permit nucleophilic aminoalkylation [see *(26)* → *(27)* and Section 3.5] of carbonyl derivatives that are sensitive to aggressive organolithium compounds; moreover, the reactivity of aldehydes, ketones, and esters towards α-stannylnitrosamines should vary widely, thus rendering *selective* reaction with polyfunctional molecules possible.



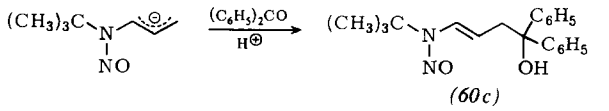
(60a), R = CH_3

(60b), R = t-C_4H_9

(61)

Adducts of type *(54)* with aromatic aldehydes can be dehydrated to the interesting but scarcely known[176, 177] enenitrosamines *(60)*. Compounds *(60a)* and *(60b)*, formed almost quantitatively in the *trans* form, undergo 1,3-nitroso shift to give iminooximes *(61)* on heating, irradiation, or treatment with gaseous hydrogen chloride in benzene[71].

An enenitrosamine *(60c)* is also obtained on reaction of metalated allyl-*tert*-butylnitrosamine with benzophenone. All

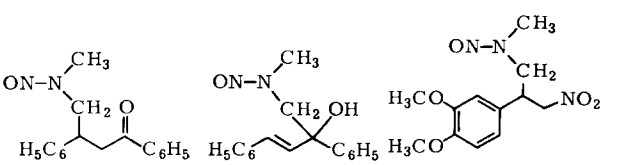


(60c)

other electrophiles we have used so far add to this allyl anion α to the heteroatom[88].

3.4.3. Reaction with α,β-Unsaturated Ketones and with Nitroolefins (Michael Addition)

As can be seen from Table 6, reaction of the lithionitrosamines *(39a)* and *(40f)* with cyclohexenone affords 85 and 80%, respectively, of the 1,2-adduct after hydrolysis[79, 90]. NMR and IR analytical comparison of the starting materials and the crude and pure products rules out the formation of more than traces of the 1,4-adduct. The situation is different with benylideneacetophenone which is even found to yield somewhat more Michael product *(62)* than allyl alcohol *(63)* on reaction with lithiodimethylnitrosamine; the overall yield is almost quantitative. From β-nitro-3,4-dimethoxystyrene and



(62), 55%

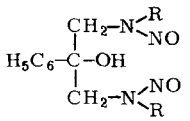
(63), 45%

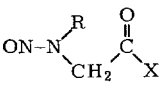
(64)

the same nitrosamine we could finally isolate the product *(64)* of conjugated addition in 75% yield[89].

3.4.4. Acylation and Carboxylation (Nitrosated α-Amino Ketones and Amino Acid Derivatives)

The pronounced *carbonylophilic* nature of lithiated nitrosamines can interfere when they are to be acylated with acyl chlorides: 1:1 reaction of benzoyl chloride with lithiodimethylnitrosamine furnished an 80% yield (based on the latter) of the bisadduct *(65a)*[79] [similarly, *(39d)* afforded *(65b)* in 45% yield[71]]. On modification of the reaction conditions

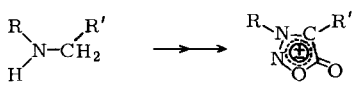




(65a), R = CH_3
(65b), R = t-C_4H_9

(66a), X = OH, R = t-C_4H_9, 80%
(66b), X = OCH_3, R = t-C_4H_9, 95%
(66c), X = NHC_6H_5, R = CH_3, 85%
(66d), X = CH_3, R = CH_3
(66e), X = C_6H_5, R = CH_3
(66f), X = C_6H_5, R = t-C_4H_9
} 40-50%

(initial excess of acyl chloride, reverse addition) and use of other acylating agents (methyl carboxylates, carbon dioxide, phenyl isocyanate, phenyl isothiocaynate), however, moderate to very good yields of α-amino acid or α-amino ketone derivatives *(66)*[71] are obtained. Carboxylation with CO_2 has been described for a further series of nitrosamine anions [*(40e)*[78], *(40i)*[80], *(40r)*[78], and *(40s)*[78]]. Removal of the nitroso group[71, 78], which is also employed as a protecting group in peptide synthesis[178], thus provides an entry to *N*-substituted amino acids. This constitutes a first example of electrophilic substitution at a secondary amine, *(26)*→*(27)*, with E = COOH, and an imitation of the biochemical interconversion of amino acids and primary amines according to Scheme 3 (see also applications, Sections 3.5). Since nitroso amino acid derivatives are readily transformed into sydnones[179, 180], the metalated nitrosamine route provides access to this class of compounds from secondary amines [eq. (12)].

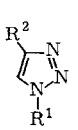


(12)

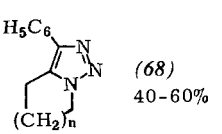
The esters and ketones *(66)* are formally analogs of 1,3-dicarbonyl compounds and should undergo base-catalyzed condensation reactions at the CH_2 group.

3.4.5. *v*-Triazoles by Reaction with Nitriles[71, 81, 89]

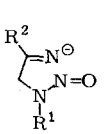
Apart from the carboxylic acid derivatives mentioned in the previous Section, nitriles also represent potential acylating agents. We were unable to react enolizable aliphatic nitriles such as acetonitrile with nitrosamine anions. In contrast, aromatic nitriles afford the *v*-triazoles *(67)* and *(68)* in the yields shown, provided that the metalated nitrosamine is employed



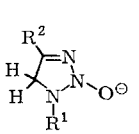
(67a), R^1 = CH_3, R^2 = C_6H_5, 83%
(67b), R^1 = CH_3, R^2 = *p*-CH_3-C_6H_4, 57%
(67c), R^1 = CH_3, R^2 = *p*-Br-C_6H_4, 84%
(67d), R^1 = CH_3, R^2 = β-Naphthyl, 80%
(67e), R^1 = $CH(CH_3)_2$, R^2 = C_6H_5, 90%
(67f), R^1 = $C(CH_3)_3$, R^2 = C_6H_5, 99%



(68)
40-60%
n = 1, 2, 3



(69)

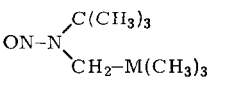


(70)

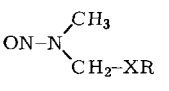
in a twofold excess. A 1:1 reaction furnishes only 35—55% of these heterocycles. By analysis of aliquot samples from the reaction mixtures we were able to show that the nitrile reacts sluggishly. If acetic acid is added at −78 °C after 30 min during the preparation of *(67a)*, 25% of triazole and 6% of the acylation product *(66e)* are isolated along with 65% of unreacted benzonitrile. After prolonged reaction only the decomposition products *(43)* and *v*-triazoles are obtained. Hence the triazoles are probably formed *via (69)* and *(70)*. It is still an open question whether the improved yields obtained from the 2:1 reaction are merely a consequence of competitive decomposition (see Section 3.3) or are due to proton abstraction at the CH_2 group of *(70)* by the excess of lithium derivative. This *v*-triazole synthesis is suitable for the preparation of novel triazoles such as *(68)*.

3.4.6. Reactions with Hetero-Electrophiles[71, 90]

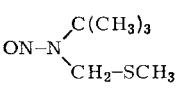
A number of hetero-substituted nitrosamines have already been mentioned [see Table 4: *(40f)*, *(40g)*; Tables 5 and 6: reactions of *(40f)*; eqs. (7) and (11)]. We obtained the derivatives *(71)*—*(73)* in high yields by reaction of the corresponding nitrosamine anions with trimethylchlorosilane, trimethylchlorostannane, disulfides, or diselenides. The sulfoxide *(74)* is accessible quantitatively by metaperiodate oxidation of *(73)*. A use of the tin derivative *(71b)* is shown in eq. (11). The sulfur- and selenium-substituted nitrosamines *(72)*—



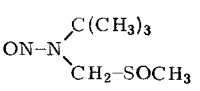
(71a), M = Si, 80%
(71b), M = Sn, > 95%



(72a), RX = SCH_3, 85%
(72b), RX = SC_6H_5, 85%
(72c), RX = SeC_6H_5, 70%



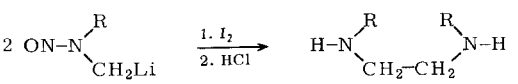
(73), 90%



(74)

(74) may be regarded as *N,S*- and *N,Se*-acetals of formaldehyde. *N,O*-Acetals of this type have recently been prepared by a completely different method[181, 184].

So far we have been unable to isolate α-halo nitrosamines on reaction of metalated nitrosamines with chlorine, bromine, and iodine[71]. Iodine leads to oxidative coupling which can be exploited in the synthesis of ethylene diamines—relevant examples are shown in eq. (13)[71, 79, 89].

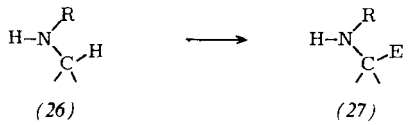


(13)

R = CH_3, 95%
R = t-C_4H_9, 50%

3.5. Applications

The two foregoing Sections (3.3 and 3.4) have demonstrated the feasibility of preparing the nitroso derivatives of higher substituted secondary amines *via* metalated nitrosamines. It has already been mentioned in Section 3.1 that secondary amines and nitrosamines can be readily interconverted. This property opens the way for a simple electrophilic substitution *(26)*→*(27)* [eq. (14)] at the α-C atom of secondary amines.

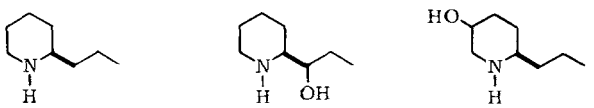


(26) (27) (14)

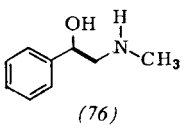
Examples of applications for the synthesis of amino acids and ethylenediamines have already been presented in Section 3.4.4 and in eq. (13).

3.5.1. Denitrosation of Products Listed in Tables 5 and 6 to Yield Simple Alkaloids

Some of the products of alkylation and hydroxyalkylation of lithionitrosamines *(39)* and *(40)* listed in Tables 5 and 6 are nitroso derivatives of simple alkaloids. We have prepared[71,88] the hemlock alkaloids *(75)*[185] and halostahine *(76)*[186] by denitrosation[140-146]. In the formulas, and also



(75a) coniine *(75b)* conhydrine *(75c)* ψ-conhydrine

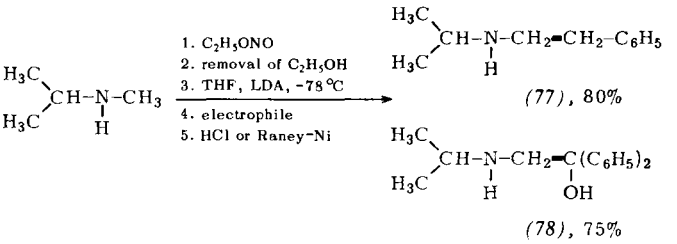


(76) halostahine

in the following discussion, the newly formed C—C bonds are emphasized by bold print. The simplicity of the new method can be demonstrated for compound *(75c)* which we have prepared from the commercially available compounds 3-hydroxypiperidine and *n*-propyl iodide[88] (40% overall yield); synthesis by "classical" methods is far more complicated and less productive[187]. Numerous applications of metalated nitrosamines can be envisaged in the field of alkaloid synthesis (see also Section 3.5.4).

3.5.2. "One-Pot" Substitution According to Equation (14)

Successful application of this method for electrophilic substitution α to the nitrogen of secondary amines requires that the handling of carcinogenic (see Section 3.7) nitrosamines is completely avoided in order to reduce the hazard to a minimum. We have therefore developed a technique by which a secondary amine is weighed into a flask and a substituted secondary amine is isolated on work-up. The method involves preparation of a standard solution of ethyl nitrite in anhydrous tetrahydrofuran, of which an aliquot is added to the amine destined for nitrosation in a flask under an inert gas. Quantitative formation of the nitrosamine is complete within 10—50 h at 20 °C. The co-product ethanol is removed together with solvent under reduced pressure. Dissolution in THF is followed by metalation in the usual manner (Section 3.2; LDA = lithium diisopropylamide), and treatment of the lithium derivative with the electrophile. After warming, the nitrosamine is denitrosated in the reaction mixture, *i.e.* without prior isolation, by gaseous hydrogen chloride or Raney nickel; only then is the product worked up[188]. In this way we have obtained phenethylisopropylamine *(77)* and the amino alcohol *(78)* in high yields from methylisopropylamine and benzyl bromide and benzophenone, respectively.



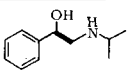
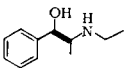
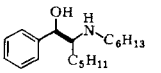
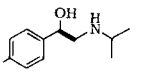
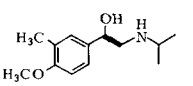
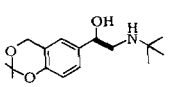
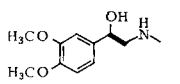
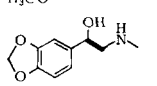
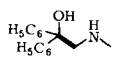
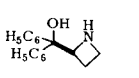
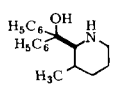
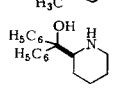
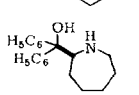
(77), 80%

(78), 75%

3.5.3. 2-Amino-1-arylethanols from Aromatic Carbonyl Compounds and Secondary Amines

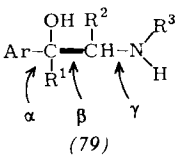
This modification can be employed for preparing numerous 2-amino-1-arylethanols, a class of compounds having an extre-

Table 7. Arylaminoethanols of types *(79)* and *(80)*. The yields given are total yields based on the original amount of carbonyl component and thus include the addition *and* denitrosation steps [71, 88].

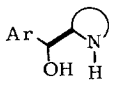
Starting components	Product	Yield [%]	M.p. [°C] [a]
benzaldehyde, isopropylmethyl-nitrosamine		74	
benzyldehyde, diethylnitrosamine		72	162–166 [b]
benzaldehyde, di-*n*-hexylnitrosamine		80	162–164 [b]
p-methylbenzaldehyde, isopropylmethyl-nitrosamine		64	157–159
4-methoxy-3-methyl-benzaldehyde, isopropylmethyl-nitrosamine		65	127–129
acetone acetal of 3-hydroxymethyl-4-hydroxybenzaldehyde, *tert*-butylmethyl-nitrosamine		88	155 [c]
3,4-dimethoxy-benzaldehyde, dimethylnitrosamine		66	118–124
3,4-methylenedioxy-benzaldehyde, dimethylnitrosamine		66	138 [c]
benzophenone, dimethylnitrosamine		70	
benzophenone, 1-nitrosoazetidine		75	195 [c]
benzophenone, 1-nitrosopiperidine		40	84 [d]
benzophenone, 1-nitroso-3-methylpiperidine		35	103 [d]
benzophenone, 1-nitrosoperhydroazepine		77	271 [c]

[a] M.p. of the hydrochloride. [b] Mixture of diastereoisomers.
[c] Decomposition point. [d] M.p. of amine.

mely wide spectrum of pharmacological activity[189]. On preparation of compounds of type *(79)*, the α-bond to the aromatic ring is normally coupled by acylation; some of the acylating agents used already contain the N-function[191,192]; however, in most cases this function is introduced subsequently by linkage of the γ-C—N bond[193-196]. Compounds of type *(79)* can be produced from metalated nitrosamines and aromatic aldehydes and ketones with formation of the β-C—C bond. Some examples and overall yields, based on the carbonyl component used, are listed in Table 7; this procedure is clearly also suitable for preparing cyclic derivatives *(80)* whose production by other methods is invariably more complicated[197,198].

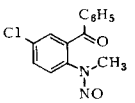
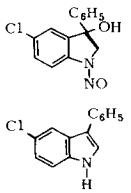
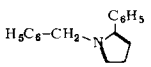
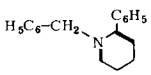
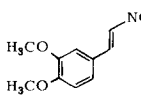
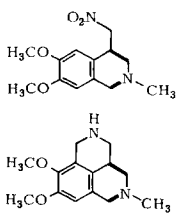
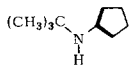


(79)

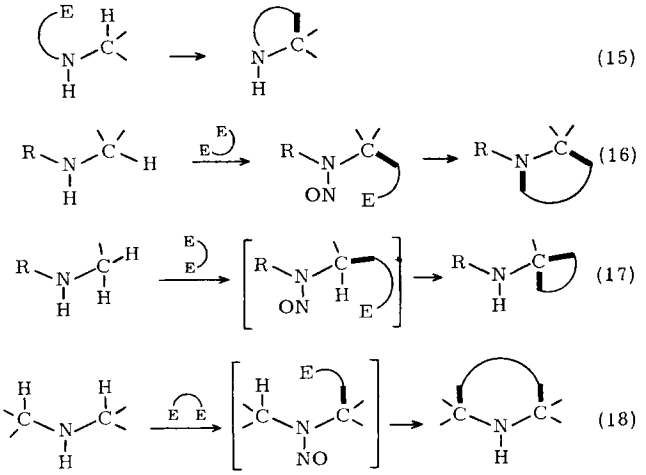


(80)

Table 8. Cyclizations *via* metalated nitrosamines according to the general equations (15)—(18).

Starting material	Eq.	Product(s)	Ref.
	(15)		[85]
dibenzylnitrosamine, 1,3-dibromopropane	(16)		[78]
dibenzylnitrosamine, 1,4-dibromobutane	(16)		[78]
1-nitrosopyrrolidine, 1-brom-3-iodopropane	(16)		[88]
1-nitrosopiperidine, 1-chloro-4-iodobutane	(16)		[88]
dimethylnitrosamine,  [see *(64)*] [a]	(16)		[89]
methyl-*tert*-butylnitrosamine, 1-chloro-4-iodobutane	(17)		[88]
dimethylnitrosamine, 1-bromo-3-iodopropane	(18)		[88]

[a] Denitrozation of *(4)* and Pictet-Spengler reaction with the resulting nitro amine initially afford the bicyclic compound, which is converted into the tricyclic compound by reduction of the nitro group and renewed Pictet-Spengler cyclization (*V. Ehrig* [89]).



(15)

(16)

(17)

(18)

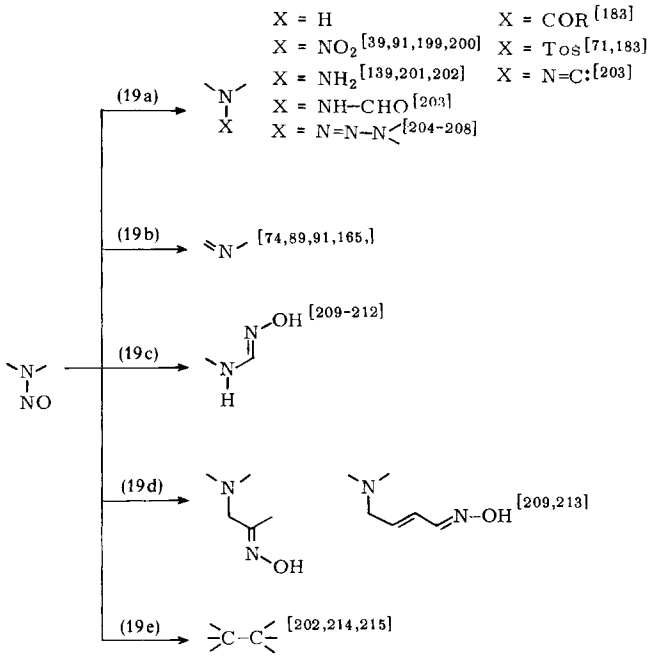
3.5.4. Cyclizations *via* Metalated Nitrosamines

In principle, heterocyclic or nitrogen-substituted carbocyclic compounds should be accessible *via* metalated nitrosamines according to the generalized equations (15)—(18). The boldly printed bonds in the rings are each newly formed. Cyclization as shown in eq. (15) is possible only with electrophilic centers E that survive the metalation conditions applied on removing the CH proton adjacent to the α-nitrogen. The same clearly applies to the cyclization steps in eqs. (17) and (18). Reactions with bifunctional electrophilic compounds according to eqs. (16)—(18) are favored if the two electrophilic centers differ in their reactivity, as for example in the case of 1-chloro-*n*-iodoalkanes or ω-halo aldehydes and ω-halo ketones. In reaction (16) the initial open-chain adduct is denitrosated, whereupon the nitrogen of the secondary amine, which has now become nucleophilic, forms a C—N bond with the electrophilic function in the incorporated side chain and thereby closes the ring.

First examples of the preparation of cyclic compounds with participation of at least one nitrosamine C—C linking step α to the nitrogen are shown in Table 8. The yields, which have not yet been optimized, lie between 30 and 80%.

3.6. Chemistry of Nitrosamines

Not only can nitrosamines be denitrosated to their parent secondary amines [eq. (19a), X=H[139,139-146]]; they also undergo many other reactions. Reactions with bases and nucleophiles have already been mentioned in Section 3.2 [products *(29)*—*(32)* and *(34)*—*(37)*]. Several other conversions of synthetic value[139] are depicted in equations (19a)—(19e). As may be seen from eq. (19a), oxidation leads to nitramines, reduction to hydrazines or their derivatives, replacement of the NO group by COR and RSO_2 gives carboxamides and sulfonamides respectively. Basic elimination of HNO or, after oxidation to the nitramine, of HNO_2 affords azomethines according to eq. (19b); photolysis according to eq. (19c) furnishes hydroximamides; photoaddition to olefins or 1,3-dienes according to eq. (19d) yields amino oximes. Finally, in certain cases it is possible to formally eliminate N_2O as shown in eq. (19e) to give compounds devoid of nitrogen. Thus substitution α to nitrogen in nitrosamines *via* the metal derivatives *(39)*—*(41)* has a preparative significance ranging well beyond the production of amines.

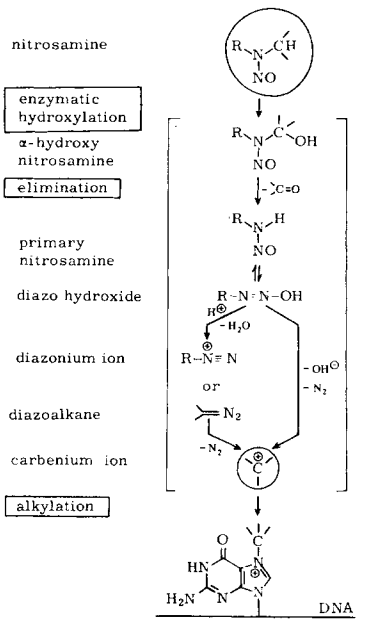


3.7. Carcinogenic and Mutagenic Action of Nitrosamines[216-222]

Most of the nitrosamines tested so far are extremely potent carcinogens and/or mutagens. Their occurrence in the environment[223], *e.g.* in cigarette smoke, in nitrite-preserved meat, and in smoked fish, is well established. Such activity is limited to those nitrosamines which bear at least one hydrogen atom on the carbon situated α to the nitrogen atom. Animal experiments show that, in contrast to other dangerous compounds encountered in everyday laboratory work, nitrosamines have a relatively low toxicity. However, these tests also reveal that in certain cases a single large dose can produce cancer. Tissue changes resulting from a single dose, or on administration over a prolonged period followed by complete cessation, become manifest only after an induction period. In experimental animals having an average life expectancy of about 800 d, the induction period can be as long as several hundred days. Treatment of pregnant animals can lead to their progeny developing carcinomas in later life without ever having been exposed to nitrosamines after birth[224].

Compared with other classes of carcinogens and mutagens, including those of similar activity, nitrosamines are characterized by showing a pronounced organospecific or organotropic effect. Depending upon its structure, a given nitrosamine will give a high "yield" (as the cancer experts say) of carcinoma in a particular organ, irrespective of how it is applied (inhalation, intravenous or subcutaneous injection, oral incorporation, or diffusion through the skin) while even closely proximate tissues remain unaffected. This structure/organ correlation places nitrosamines among the most important reagents of cancer and mutagenesis research. On the one hand they are employed for purely experimental reasons, *i.e.* for the study of morbid changes in a certain type of tissue which can also become cancerous "naturally", this work being important for the development of new methods for early diagnosis and therapy. On the other hand, it is hoped that elucidation of the mechanism underlying the organ specificity of nitrosamines might bring us one step closer to answering the question of how cancer arises. Furthermore, precisely this observed organ specificity suggests that it might be possible to find nitrosamine derivatives which specifically mutate cancerous tissue and thus exert a carcinostatic effect. In fact, nitroso derivatives, especially nitroso-amides, are presently undergoing clinical tests as anti-cancer drugs in several countries.

The currently preferred theory of carcinogenesis and mutagenesis by nitrosamines is outlined in Scheme 6.



Scheme 6. Alkylation theory of carcinogenesis by nitrosamines.

The nitrosamines are assumed to be α-hydroxylated by hydroxylases. The resulting 2-hydroxy nitrosamine decomposes to a carbonyl compound and a diazo hydroxide[225], a precursor of diazo and diazonium derivatives which like all other alkylating agents, even such "everyday" synthetic reagents as methyl iodide and dimethyl sulfate, are carcinogens.

Recent studies on the metabolism of nitrosamines *in vivo* show that the alkyl chains are also subject to ω oxidation yielding alcohols and carboxylic acids, to β-oxidation affording ketones, and to chain shortening[226-229].

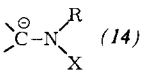
The results of animal experiments cannot be applied *a priori* to humans. After lectures on this topic we have often been approached by older colleagues who enjoy the best of health, although at one time they had worked with large amounts of nitrosamines and nitrosamides without any precautionary measures (for a time low molecular weight nitrosamines were used, *e.g.* as polar solvents on an industrial scale[230]).

What does this mean for the chemist working with nitrosamines? The chemist is accustomed to working with dangerous substances with a minimum of risk, and such work should be part of his training. He must always adapt his techniques to avoid incorporation of chemicals. We cannot even guess how many of the compounds in daily laboratory use might exert dangerous long-term effects. All our work with nitrosamines is performed in a specially reserved fume hood contain-

ing a full complement of equipment and an HBr/glacial acetic acid bath for washing all apparatus[231]. The extractors are fitted with extra-powerful motors. Disposable gloves are worn during all manipulations. Low molecular volatile nitrosamines, which possess only limited synthetic potential, are commercially available and must always be stored in a fume hood[232]. Liquids and solutions are handled with syringes. Whenever possible the "*one-pot*" procedure described above is used (Section 3.5.2).

4. Conclusions

In spite of intense searching, no other acidifying group has yet been found which permits reversible transformation of secondary amines into nucleophilic aminoalkylating agents *via* anions of type *(14)*. It requires little imagination to predict



(14)

that further searching for novel reagents with inverse reactivity will bring in a rich harvest of valuable results and additional knowledge, which might even bring us nearer to the virtuosity of analogous biochemical processes demonstrated in Scheme 3, and show us how to reach our goal in a more intelligent and less brutal way.

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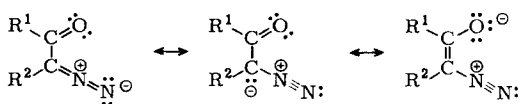
The Wolff Rearrangement of α-Diazo Carbonyl Compounds

By Herbert Meier and Klaus-Peter Zeller[*]

The readily accessible α-diazo carbonyl compounds are distinguished by their high reactivity, which opens up a variety of preparative applications under modified conditions. Wolff rearrangements of these compounds, induced thermally, photochemically, or catalytically, afford ketenes. Free and complexed carbenes, 1,3-dipoles, 1,3-diradicals, and the antiaromatic oxirenes have been considered as intermediates or transition states. The present progress report attempts to integrate preparative and theoretical aspects.

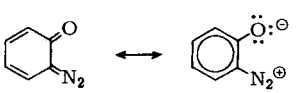
1. Introduction

α-Diazo carbonyl compounds *(1)* contain the CO—CN_2 group, which is capable of resonance, as characteristic structural unit.



(1)

The C—C bond can be part of a carbon chain or of a cyclic system. If it belongs to an aromatic ring then an inner diazonium phenoxide ("*o*-quinone diazide") *(2)* is present.

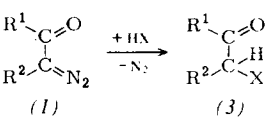


(2)

Key positions in the attached groups may also be occupied by heteroatoms. In this context, the α-diazo carboxylic acid derivatives *(1)*, $R^1 = OR$, NH_2, NHR, NR_2, *etc.*, warrant special attention.

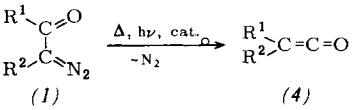
Apart from the CO stretching vibration, a simple analytical feature of the open-chain α-diazo carbonyl structure is the diazo band lying between 2090 and 2190 cm^{-1} (usually at 2130 cm^{-1}) in the IR spectrum. Mutual interaction between the diazo and the carbonyl group lowers the CO frequency and raises the N_2 frequency.

α-Diazo carbonyl compounds are particularly reactive substances. Reactions involving loss of the N_2 group are generally induced thermally, photochemically, catalytically, or by (Lewis) acids. Whereas the decomposition by acids is applic-



(1) *(3)*

able to all diazoalkanes, in the other three processes one observes a rearrangement that is specific for α-diazo carbonyl compounds and is known after its discoverer as the Wolff



(1) *(4)*

rearrangement[1, 2]. The preparative value of the Wolff rearrangement is due to the ready accessibility of the α-diazo carbonyl compounds[3] and to the wide range of reactions of the resulting ketenes *(4)*.

[*] Univ.-Doz. Dr. H. Meier and Dr. K. P. Zeller [**]
74 Tübingen 1, Auf der Morgenstelle (Germany)

[**] European Science Exchange Program Fellow.