# The chemistry of vinyl nitroxides

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Abstract - Vinyl nitroxides (VNs) generated by oxidation of nitrones or the corresponding hydroxylamines are very reactive radicals. In contrast to VNs di-substituted at the ß-position of the vinyl group those which are mono-substituted could not be observed directly by ESR with a few exceptions. Instead, their spin adducts with the precursor nitrones were detected. Dimerization of VNs occurs usually by bond formation between the two ß-carbon atoms, frequently followed by a secondary reaction step. An unsymmetrical dimer formed by bonding between the oxygen and the ß-carbon atom could be isolated in a single case. However, such OC-dimers are frequently formed in a kinetically controlled reaction. Being usually less stable compared to the CC-dimers, their intermediate formation becomes conspicuous if they can undergo a subsequent reaction that gives a thermodynamically stable product. ß-Acyl-ß-aryl-disubstituted VNs form either bi- or tricyclic dimers. The latter dissociate in solution, usually even at room temperature, regenerating the VNs by breaking of four bonds.

INTRODUCTION

Di-tert-alkyl nitroxides are usually very stable radicals since steric effects as well as the high delocalization energy of about 30 kcal/mol (ref. 1) prevent them from dimerization or disproportionation. In view of the considerable electronic stabilization dimerization by OO-bonding, that would be sterically unhindered, is energetically too unfavorable. In contrast, nitroxides substituted by a primary or secondary alkyl group are kinetically far less stable although the thermodynamic stabilization of their nitroxide group is the same. Such nitroxides can easily undergo disproportionation forming the corresponding hydroxylamines and nitrones (ref. 2). Consequently, primary or secondary alkyl-substituted nitroxides can be easily oxidized to yield nitrones.

For vinyl nitroxides (VNs) **1**, however, a high reactivity is expected as a consequence of the delocalization of the unpaired electron to the vinyl group. Since now bond formation with the ß-carbon atom of the vinyl group is possible, the loss of delocalization energy of the nitroxide group can be more than compensated by dimerization or similar reactions. On the other hand, the reactivity of VNs should be lowered by appropriate substitution at the ß-position. Thus, VNs substituted at ß-position by various groups R(2) and R(3) were generated by oxidation of either nitrones **3** or the corresponding hydroxylamines **2** with lead dioxide. The formation of either VNs or spin adducts formed with the precursor nitrones was studied by ESR spectroscopy. Isolation and identification of their dimerization products gave informations about their reaction pathways.
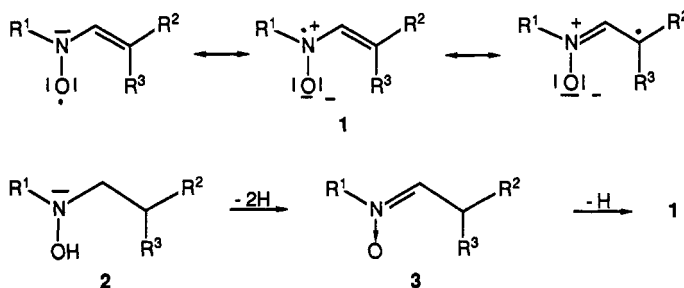

ESR SPECTROSCOPIC STUDIES

Spin-trapping of vinyl nitroxides by their precursor nitrones

With a very few exceptions VNs substituted by only one substituent at ß-position (**1** R(3)=H) are too reactive to be directly observed. Usually they add immediately to their precursor nitrones **3** which act as spin traps (ref. 3). Thus spin adducts **4** or **6** may be formed. Furthermore, adduct **4** may undergo an intramolecular spin trap reaction affording nitroxide **5** (ref. 4). Due to the electron-attracting effect of the oxygen atom at ß-position radicals **5** and **6** should have smaller nitrogen coupling constants as compared to **4**. Nevertheless, a distinction between these three types of spin adducts is frequently difficult because the

differences of a(N) are only about 1 G or less and a(H) for the proton at the α-C atom varies considerably (ref. 4). In particular, in borderline cases if only one adduct is formed, the structure often cannot be ascribed unambigiously. In some cases the comparison of a(N) to the value of model compounds has been helpful (ref. 4,5). As an example, radical **5U** generated directly by oxidation of compound **7U** is converted to **4U** by ring opening after some minutes (ref. 4).

$a^N = 13.8\,G$ $a^N = 14,8\,G$

$a^H_{\alpha C} = 5.85\,G$ $a^H_{\alpha C} = 2,1\,G$

U : $R^1 = Me_2C\,(CN)$
        $R^2 = H$
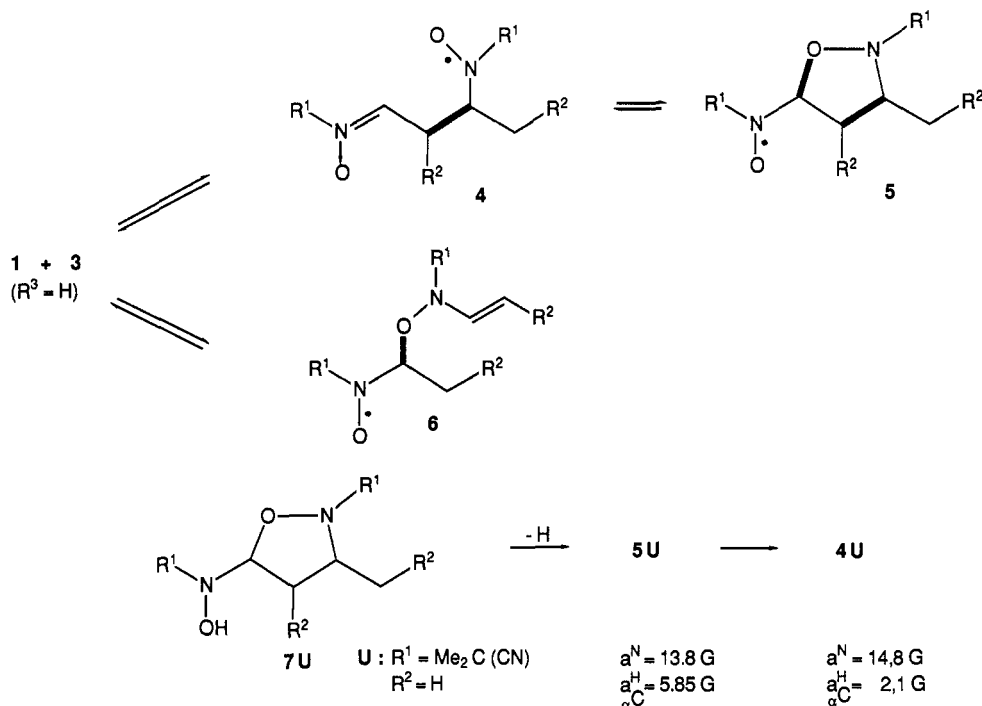
The detection of vinyl nitroxides

One of the few ß-monosubstituted VNs that could be detected is **1Da** (R(1)=tBu, R(2)=SO₂Ph, R(3)=H). Oxidation of nitrone **3Da** in chloroform solution affords **1Da**, which is characterized by its low nitrogen coupling constant (a(N) = 8.2 G) and by the coupling of the proton or deuteron, respectively, at the ß-carbon atom (a(H-ßC) = 7.3 G, a(D-ßC) = 1.0 G), whereas in diethyl ether the spin adduct **5Da** (a(N) = 12.7 G, a(H-αC) = 3.5 G) is formed (ref. 6). The spin density at the ß-C atom could be determined from a(H-ßC), whereas (17)O-labeling of **1Da** allowed the determination of ρ(O) from a((17)O). Delocalization of the unpaired electron into to sulfonyl group occurs only to a neglectable degree, if at all (ref. 6). As a comparison of the spin density distribution of **1Da** with that of di-tert-butyl nitroxide indicates, delocalization of the unpaired electron to the vinyl group of **1Da** occurs mainly at the expense of the spin density at nitrogen ρ(N) (see Table 1).

TABLE 1. Comparison of the spin-density distribution in VN **1Da** and di-tert-butylnitro-xide (DTBN) (ref. 7)

	$a^{(17)}O_{(G)}$	ρ^O	$a^N_{(G)}$	ρ^N	$a^H_{\beta C}$	$\rho_{\beta C}$	$a^H_{\alpha C}$	$\rho_{\alpha C}$
1Da	18.5 •	0.52	08.2	0.25	7.3	0.27	1.65	-0.06
DTBN	19.1	0.54	15.0	0.455	-	-	-	-

The various types of VNs detected by ESR are summarized in Table 2. In general, their kinetic stability seems to be due to the steric congestion of the ß-C atom as well as to the presence of an electron-attracting group. The coupling constants a(N) reveal that the spin density ρ(N) is in the same order of magnitude for most of them. (Values between 6.85 and 8.5 G correspond to a spin density ρ(N) of approximately 0.21-0.25 (ref. 7)). According to the more extended delocalization of the unpaired electron in **8S** and **8T** their coupling constants a(N) are of course considerably smaller. In principle, delocalization may also occur to the substituent R(2) and R(3), in particular to the phenyl groups. As the different coupling constants of the phenyl protons indicate (a(H-R(2)): 1.32 (3H), 0.54 (2H) - a(H-R(3)): 0.83 (3H), 0.49 G (2H) (ref. 4) the two phenyl groups of **1C** are twisted to a different degree. In **1Ga** and **1Ha** the protons of the phenyl group R(2) contribute to the splitting of the ESR spectrum, but those of the benzoyl group do not (ref. 5). The relatively small value for a(N) of **1R** is believed to be mainly due to a shift of spin density from N to O within the nitroxide group, caused by the electron-withdrawing effect of the two carbonyl groups.

TABLE 2. Coupling constants a^N (in Gauß)
of various types of VN

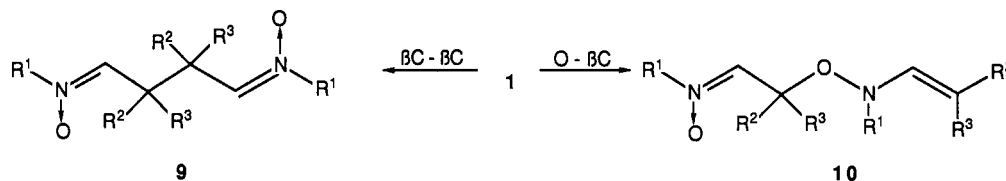|	R^1	R^2	R^3	a^N
1C	tBu	Ph	Ph	8.4
1Da	tBu	SO_2Ph	H	8.2
1Ga	tBu	COPh	Ph	8.8
1Ha	Ph	COPh	Ph	8.1
1O	tBu	SMe	CN	6.85
1P	tBu	SePh	CO_2Me	7.25
1K	tBu	a	a	7.55
1R	tBu	a	a	4.7
8S	a	a	a	5.8
8T	a	a	a	4.03^b
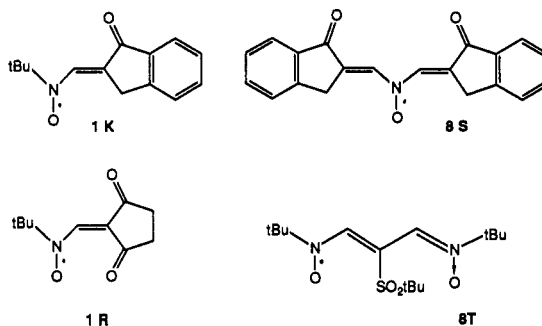
a) see formulas; b) 2N at $+65°C$

For the vinylogous nitronyl nitroxide **8T** the two NO groups are expected to be equivalent. However, this is not true at $-38°C$ as the different coupling constants for the two nitrogen atoms as well as those for the two protons at the α-carbon atoms indicate (ref. 8). Thus, the sterically crowded molecule must be twisted, so that delocalization to the second CH=N(O) subunit is somewhat restricted. Since the two coupling constants become equivalent at $+65°C$ although some line broadening is still observed, a dynamic process must take place by which the two NO groups interchange their positions (ref. 8). Possibly, this process is caused by rotation of the tert-butyl sulfonyl group which alternately pushs the two CH=N(O) groups away from the molecular plane.

THE DIMERIZATION OF VINYL NITROXIDES

As a consequence of the large gain in bond energy by the formation of CC- or OC-bonds compared to the formation of OO-bonds VNs are expected to form either CC-dimers **9** or OC-dimers **10** or both of them. In fact, such dimers undergo frequently secondary reactions. Table 3 reflects the substituent effects on the course of dimerization.

TABLE 3. The dimerization products of VNs (starting compounds **3A** and **B**; **2D-I**)

Radical type	R^1	R^2	R^3	yield of dimer a)	(%)
1A	tBu	Ph	H	9A	85
1B	Ph	Ph	H	9B	19.5^b
1C	tBu	Ph	Ph	10C	30
1D	tBu	SO_2R'	H	11Da	71
1D	tBu	SO_2R'	H	11,12,13Db	c
1E	tBu	COR'	H	14Ea	82
1F	Ph	COR'	H	14Fa	61
1G	tBu	COR'	Ar	15Ga	91
1H	Ph	COR'	Ar	16Ha	93
1I	tBu	COR'	Me	15Ia	65

a) **a**: R' and Ar' = Ph; **b**: R' = CH_2-CH=CH_2; b) see ref. 9; c) see text

Phenyl groups as substituents at β-position

The formation of VN **1A** (R(1)=tBu, R(2)=Ph, R(3)=H) upon oxidation of nitrone **3A** could not be directly proved by ESR, however, two spin adducts, presumably **4A** and **5A**, were observed. Nevertheless, the oxidation of **3A** by lead dioxide afforded the CC-dimer **9A** in 85% yield (ref. 4). On the other hand, there is no indication of products arising from **4A** or **5A**. This means that formation of **4A** and **5A** is only an unproductive reaction path. Rather, the reaction proceeds via VN **1A** which exists only in a non-detectable concentration in equilibrium with the spin adducts. Oxidation of **3A** to yield **9A** occurs even by oxygen as was also found for the corresponding N-phenyl substituted nitrone **3B** by De Sarlo (ref. 9).

In contrast, oxidation of nitrone **3C** (R(1)=tBu, R(2)=R(3)=Ph) by lead dioxide proceeds very slow. After a reaction time of 63 hours only a 30% yield of OC-dimer **10C** could be isolated (ref. 10). Under these reaction conditions, however, decomposition products were also formed which at least partly arose from **10C**.

As these results reveal, the formation of the CC-dimers **9A** and **B** is obviously favored by electronic effects which may originate from the better stabilization of the second nitrone group in **9** compared to that of the enaminoxy group in **10**. For VNs substituted by R(2)=Ph, R(3)=H these electronic effects are dominating. For VN **1C** (R(2)=R(3)=Ph), however, the steric interaction in the CC-dimer **9C** would be so strong that now the steric effects dominate favoring the formation of the OC-dimer **10C**. This situation resembles the dimerization of the triphenyl methyl radical.
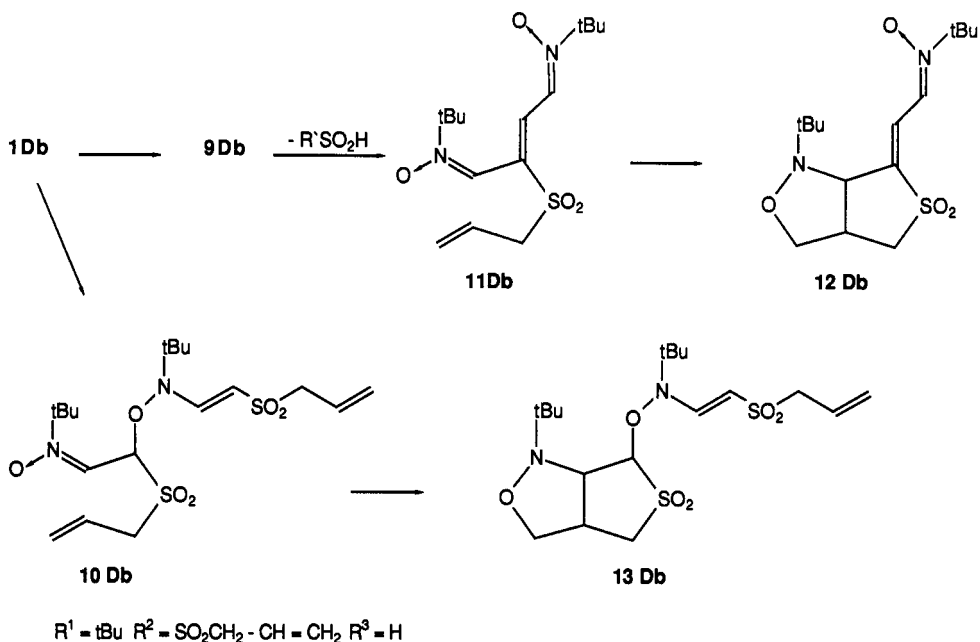
The sulfonyl group as substituent R²

Oxidation of nitrone **3Da** (R(1)=tBu, R(2)=SO₂Ph, R(3)=H) as well as oxidation of hydroxylamine **2Da** gave the dinitrone **11Da** (R'=Ph) (ref. 11). The same is true for the corresponding compound R'=nPr. In this case the CC-dimers **9D** could not be isolated since they undergo a facile elimination of sulfinic acid.
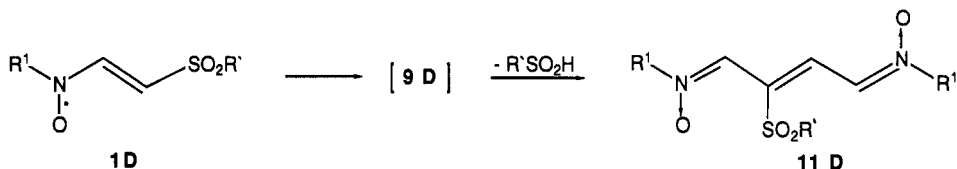

The oxidation of hydroxylamine **2Db** (R(1)=tBu, R(2)=SO₂-CH₂-CH=CH₂, R(3)=H), however, allows an interesting insight into the dimerization of VNs, because now intermediates can be trapped by intramolecular (3+2)cycloaddition reactions between the nitrone group and the allyl group provided that the cycloaddition proceeds fast enough. In fact, the main products formed from the intermediate VN **1Db** are the compounds **11Db** (10%), **12Db** (13%) and **13Db** (34%). Performing the reaction at -20°C we isolated **13Db** in approximately the same yield whereas only traces of **12Db** and no **11Db** were formed (ref. 12). These results reveal that the OC-dimers **10D** are the kinetically favored product.

Usually, however, **10D** is thermodynamically unstable, so that the reaction proceeds via CC-dimer **9D** to the more stable product **11D**. Only if there is a favorable pathway for a subsequent reaction step, giving rise to the formation of a stable secondary product, as it is the case for the conversion of **10Db** to **13Db**, the intermediate formation of OC-dimers becomes conspicuous.

$R^1 = tBu$ $R^2 = SO_2CH_2 - CH = CH_2$ $R^3 = H$

The acyl group as substituent R^2

Oxidation of the hydroxylamines **2E** and **2F** (R(3) = H) yields the dehydrodimers **14** arising from the CC-dimers **9E** and **9F**, respectively, by an additional dehydrogenation step (ref. 11). Whereas **1E** and **1F** could not be detected, the VNs **1G**, **1H** and **1I** formed by oxidation of the corresponding hydroxylamines **2** are stable in solution for some hours. Obviously, their dimerization is retarded by the increasing steric hindrance at the ß-position. Oxidation of **2G** and **2I** on a preparative scale yields the tricyclic dimers **15**, whereas from **2H** the bicyclic dimers **16H** are formed (ref. 13). The formation of dimers **15** is assumed to occur by CC-dimerization followed by an intramolecular (3 + 2 + 2) cycloaddition of **9G** and **9I** involving one of the nitrone groups and the two acyl groups. In contrast, dimers **16H** arise from the OC-dimer **10H** by an intramolecular (3 + 2) cycloaddition between the nitrone group and the alkene moiety.
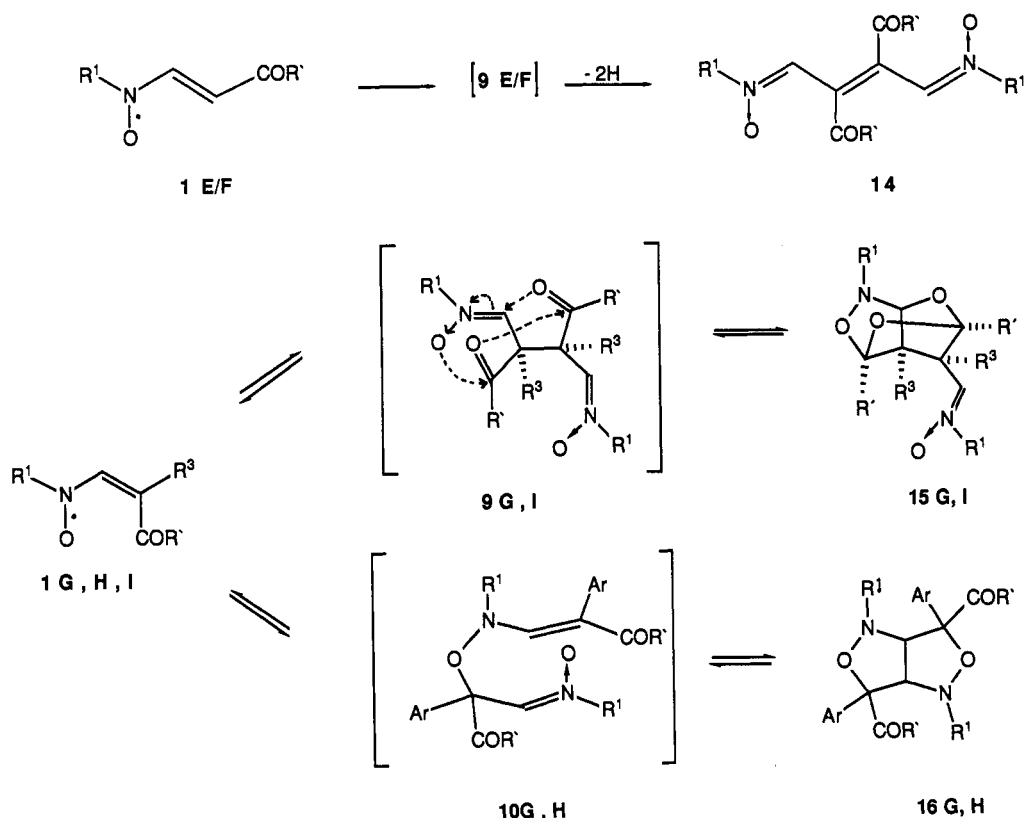

The dimers **15G** dissociate in solution breaking four bonds to give VNs **1G**, mostly already at room temperature. For the parent compound (R' = Ph, R(3) = Ph) the following values were determined: ΔH°(diss) = 22.3 ± 2 kcal/mol, ΔS°(diss) = 45.5 ± 3 eu at 49°C. If the acyl group is stabilized by an appropriate substituent R'(e.g. R' = 4-MeOPh or 2-thienyl) the dissociation of dimer **15G** is increased. The same is true for substituents R' that destabilize the dimer for steric reason (e.g. R' = 2-MePh). In contrast, neither dimer **15I** nor the bicyclic dimers **16H** dissociate up to 160°C (ref. 13).

The tricyclic dimers **15G** are rearranged at elevated temperatures (ref. 13). Thus, in refluxing benzene **15Ga** is converted to a tetracyclic dimer as main product and to compound **16Ga** as a minor product. The latter arises from a reaction sequence **15 -> 9 -> 1 -> 10 -> 16**. Thus, it may be concluded that the bicyclic dimers **16** are the thermodynamically favored compounds as compared to the tricyclic dimers **15**. With increasing stabilization of the aryl group R'CO (see also dissociation) the proportion of rearranged product **16** is increased.

It can be argued that the different dimerization pathways of VNs **1G** (R(1) = t-Bu) and **1H** (R(1) = Ph) may be caused by a delicate balance between electronic and steric effects of the corresponding CC-dimers **9** and OC-dimers **10** formed as intermediates. Thus, the better stabilization of the enaminoxy moiety in **10** by a N-phenyl group R(1) as compared to a N-tert-butyl group could turn the scale in favor of the formation of bicyclic dimer **16H**. However, the formation of intermediate **10** should be reversible as well as those of **9** is. More probably, the intramolecular (3 + 2) cycloaddition of **10** to give **16** is the crucial reaction step. Such cycloadditions proceed much more facile for N-phenylnitrones as compared to N-tert-butyl nitrones (ref. 12). Thus intermediates **10H** (R(1) = Ph) can undergo the intramolecular cycloaddition affording the thermodynamically favored **16H** even at room temperature, whereas this reaction path is blocked for **10G** (R(1) = tBu) under these conditions. Instead, VNs **1G** form the tricyclic dimers **15G** via CC-dimers **9G**. In

the highly substituted **9G** one conformation exists in which one of the nitrone groups and the two carbonyl groups are forced together at rather short distances. Once **9G** being formed the proximity effect should give rise to the unusual reaction generating **15G**.

Attempts to isolate some of the simple dimers **9** or **10** were only successful with radical **1K**. Oxidation of the corresponding nitrone afforded dimer **9K** as a mixture of dl and meso form (ref. 14). **9K** is not converted to **15K** because this compound would be severely strained. On the other hand, VN **1L** generated by oxidation of the corresponding nitrone afforded the bicyclic dimer **17L**, indicating that OC-dimer **10L** is still flexible enough to undergo an intramolecular (3+2) cycloaddition (ref. 15). VNs **1M** and **1N** prefer the same dimerization route yielding **17M** and **17N**, respectively (ref. 16). At present **1M** is the only known ß-acyl-substituted VN with a N-tert-butyl group R(1) that forms a stable dimer via the OC-bonded intermediate **10** at room temperature. Presumably, the ß-position of **1M** is sterically hindered too much by the menthon moiety to give a CC-dimer **9**. This is indicated by the exceptionally high coupling constant of **1M** (a(N) = 10.65 G) which points to a stronger distortion caused by steric congestion.
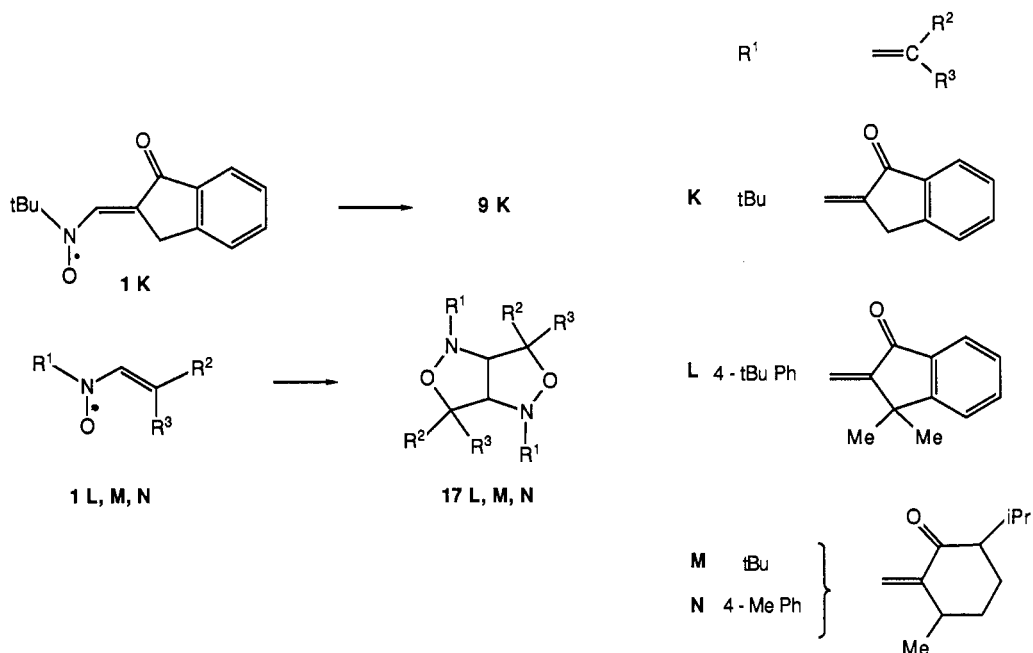
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