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Reactive Intermediates

4,5-Dihydro-1,2,3-oxadiazole: A Very Elusive Key Intermediate in Various Important Chemical Transformations

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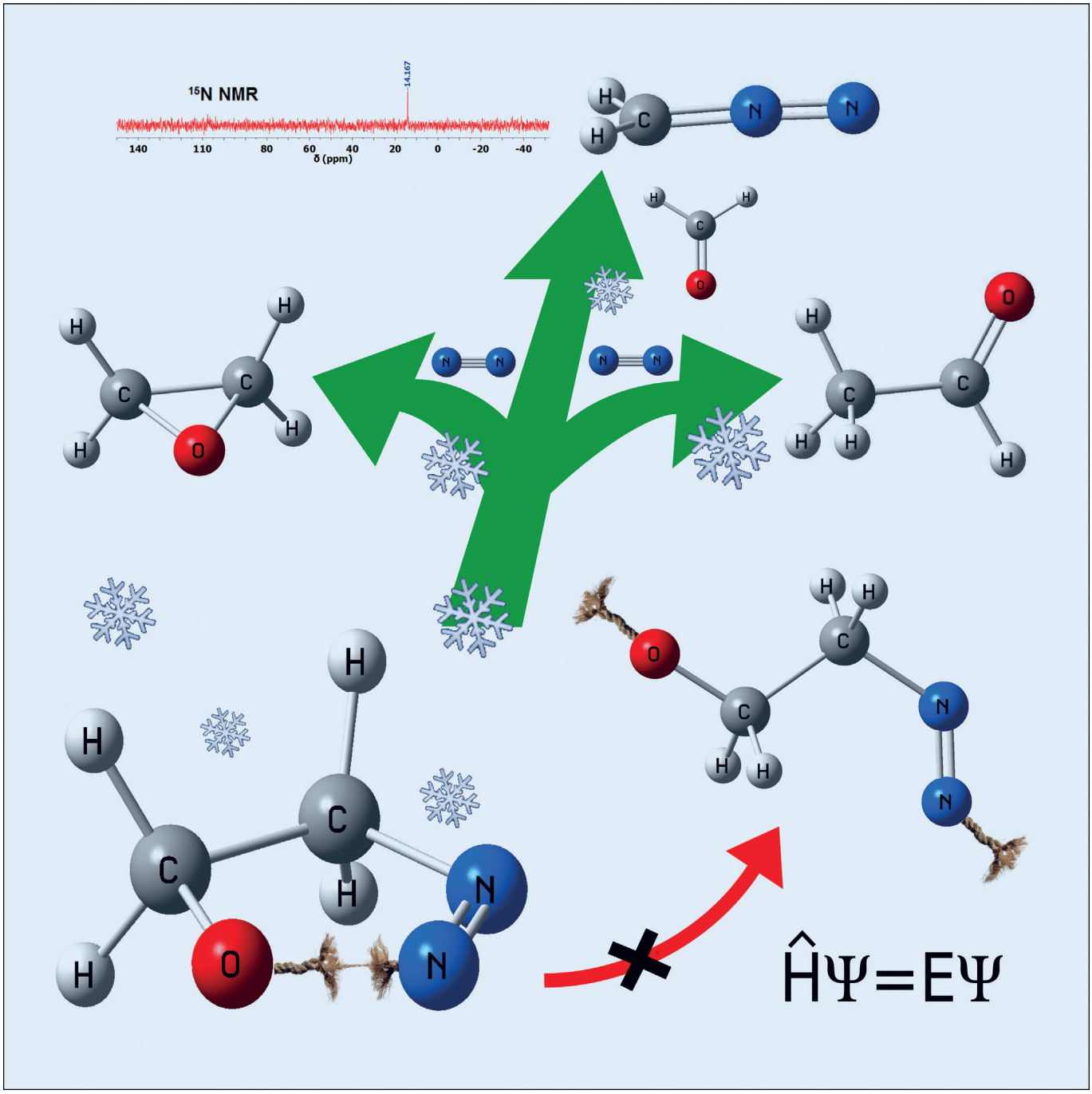
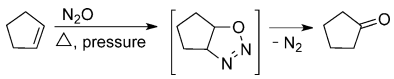
Dedicated to Prof. Harald Günther on the occasion of his 80th birthday

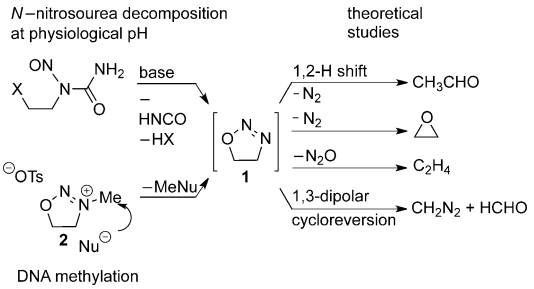


Abstract: 4,5-Dihydro-1,2,3-oxadiazoles are postulated to be key intermediates in the industrial synthesis of ketones from alkenes, in the alkylation of DNA in vivo, and in the decomposition of *N*-nitrosoureas; they are also a subject of great interest for theoretical chemists. In the presented report, the formation of 4,5-dihydro-1,2,3-oxadiazole and the subsequent decay into secondary products have been studied by NMR monitoring analysis. The elusive properties evading characterization have now been confirmed by ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy, and relevant 2D experiments at very low temperatures. Our experiments with suitably substituted *N*-nitrosoureas using thallium(I) alkoxides as bases under apolar conditions answer important questions on the existence and the secondary products of 4,5-dihydro-1,2,3-oxadiazole.

4,5-Dihydro-1,2,3-oxadiazoles[1] of type **1** are postulated to be intermediates in the synthesis of ketones from alkenes under drastic conditions,[2,3] the decomposition of *N*-nitrosoureas at physiological pH,[4] and the alkylation of DNA and other relevant molecules in vivo[5] (Schemes 1 and 2). We became interested in **1** from a process used by BASF Ludwigshafen wherein N_2O (a waste product and highly potent greenhouse gas) is utilized to synthesize cyclopentanone and ketones with twelve-membered rings[2c] (30000 tons per year) by means of 1,3-dipolar cycloaddition of N_2O to the alkene. Recently, Panov et al. described[2a,b] an alternative liquid-phase oxidation of cyclohexene and cyclopentene by nitrous oxide with nearly 100% selectivity. In these processes, 4,5-dihydro-1,2,3-oxadiazoles have been hypothesized to be intermediates that immediately, under the reaction conditions, extrude dinitrogen to give ketones in high yields. The use of N_2O in organic chemistry has been rather unexplored because of the relative chemical inertness and the high-energy input required. This low reactivity can be overcome by utilizing reaction partners with ring strain,[6] *N*-heterocyclic carbenes,[7] or metalorganic reagents.[8] Quantum chemical calculations performed on **1**[9,10] and similar heterocycles[3,11] predict various secondary products by different modes (Scheme 2), including the formation of diazomethane and formaldehyde as one of the most favorable routes on the basis of inherent weakness of the N–O bond.



Scheme 1. Industrial synthesis of cyclic ketones employed by BASF.[2c]



Scheme 2. Possible modes of formation and subsequent products of **1**.

On the other hand, the decomposition of suitably substituted *N*-nitrosoureas at physiological pH has also been postulated[4] to proceed via **1**. In these cases, quantum chemical calculations likewise predict the intermediacy and the secondary products of **1** (Scheme 2).[9] The role of 3-methyl-4,5-dihydro-1,2,3-oxadiazolium salts of type **2** in DNA alkylation and alkylation in general[5] also suggests the transient formation of **1**. There are reports on the methylation of nucleophilic compounds by **2** in very good to moderate yields.[5a] In spite of many discussions involving **2** as the methylating agent, no attempts have been made to characterize **1** or its secondary products directly.[5] However, contrary results with main or exclusive nucleophilic attack at C-5 of **2** have also been published.[5a,c,e,f,i,12]

Armed with such a great deal of information about the important role played by **1** in various branches of chemistry, we present our results regarding to the existence and the formation of secondary products of **1**.

Previous studies have been done on the decomposition of *N*-nitrosoureas in aqueous buffered solutions,[4] but these conditions are not conclusive to comment on the stability of **1** and the formation of its primary decay products. We chose thallium(I) alkoxides[13] as bases, because of their high solubility in various apolar solvents even at very low temperatures, which is quintessential for monitoring the reaction by NMR spectroscopy under such conditions. First, we utilized 2-chloroethyl-*N*-nitrosourea (**3**)[4d] as a substrate to investigate the formation of **1** in non-aqueous solutions (Scheme 3). Tosylate **4** was also synthesized for NMR studies, but it was not suitable owing to its limited solubility in dichloromethane at low temperatures. The generation of **1** was initially attempted by treating **3** with TlOEt (1.0 equiv) in CD_2Cl_2 within the range −40 to −20 °C under constant monitoring by NMR spectroscopy.[14] Immediately, we could observe the ^{1}H NMR signal of ethylene oxide (15% yield) and traces of acetaldehyde along with strong signals of 1-ethoxyethyl carbamate (**5**) (67% yield) and a trace signal of diazomethane (Table 1). The identity of ethylene oxide and **5** was further confirmed by their chemical shift values in the ^{13}C NMR spectrum. The observation of ethylene

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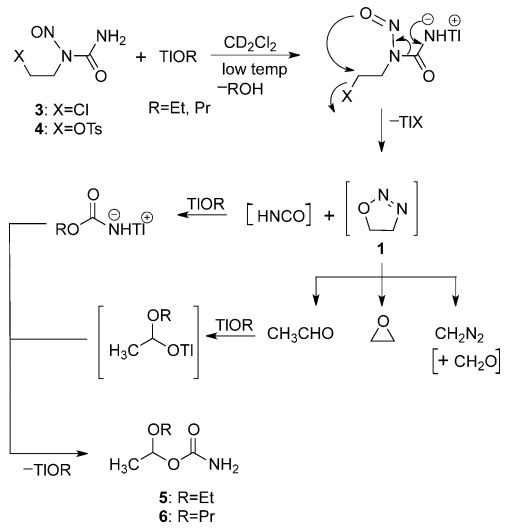


Scheme 3. Mechanisms to explain the formation of **1** and the experimentally observed secondary products.

Table 1. Yield[a] of the products formed from **3** or **14** and suitable bases in CD_2Cl_2.

Substrate	Base	T [°C]	CH_3CHO [%]	Ethene oxide [%]	CH_2N_2 [%]	Carbamates **5** or **6** [%]	*trans*-2-butenal [%]
3	TlOEt	−20	trace	15	trace	67	–
3	TlOPr	−20	32	28	3	trace	–
3	KOH	RT	6	9	–	–	–
3	Aq. KOH	−20	15	17	–	–	4
3	DIPA[c]	RT	3	4	–	–	–
3	TEMP[d]	RT	4	3	trace	–	–
14[b]	TlOPr	−20	7	19	4	–	–

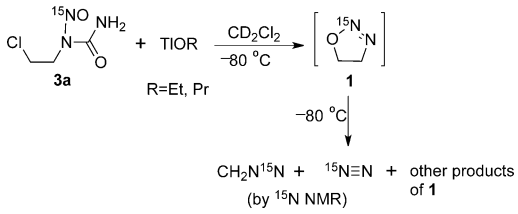
[a] Yields were measured by ^{1}H NMR spectroscopy using an internal standard. [b] Incomplete reaction because of the low solubility of **14**; yields are based on consumed **14**. [c] DIPA = diisopropylamine. [d] TEMP = 2,2,6,6-tetramethylpiperidine.

oxide and **5** can be understood by abstraction of an amide proton by ethoxide and subsequent release of isocyanic acid followed by an intramolecular S_N2 reaction, which leads to transient compound **1**. This species immediately loses dinitrogen to give ethylene oxide and acetaldehyde. Generation of diazomethane is rationalized by 1,3-dipolar cycloreversion of **1**. The formation of **5** can be explained by a nucleophilic attack of the thallium hemiacetal, resulting from the reaction of acetaldehyde and TlOEt, on the urethane, which originates from the reaction of isocyanic acid and TlOEt. Alternatively, **5** may be directly produced from isocyanic acid and the thallium-hemiacetal. Since most of the acetaldehyde is transformed into an acetal-type secondary product, it is not surprising that the even more electrophilic formaldehyde, which should be formed in small amounts by the cycloreversion of **1**, could not be detected in any experiment.

Doubling the amount of TlOEt did not make any appreciable change. Encouraged by the clean reaction, we decided to monitor the reaction from −90 °C to room temperature by NMR spectroscopy. However, even at −90 °C, we could easily detect the same secondary products in lesser yields along with unreacted **3**.[14]

To ensure that acetaldehyde was not directly resulting from TlOEt by transfer and loss of hydride (as in the Meerwein–Ponndorf–Verley reduction), we used thallium propoxide, TlOPr[13a] (1.1 equiv), and the reaction with **3** was monitored by NMR spectroscopy from −60 °C to room temperature. Here, we could clearly observe the signals of ethylene oxide, acetaldehyde, and diazomethane, whereas those of the carbamic acid derivative **6** were very weak. The higher yield of acetaldehyde and diazomethane in this reaction can be attributed to the different association nature[13a] of various thallium(I) alkoxides. We also utilized conventional bases such as potassium hydroxide, diisopropylamine, and 2,2,6,6-tetramethylpiperidine to study the formation and decomposition of **1** (Table 1).[14]

To confirm our results and especially the detection of diazomethane, we synthesized the ^{15}N-labeled substrate **3a** and monitored the reaction with TlOEt (1.1 equiv) in CD_2Cl_2 from −80 to −50 °C (Scheme 4) by ^{15}N NMR spectroscopy (Figure 1). Even at −80 °C, we could easily detect a signal of ^{15}N≡N at δ = −69.7 ppm[15] in the ^{15}N NMR spectrum. From −80 to −50 °C, we observed an increase in the intensity of ^{15}N≡N and a consequent decrease in the ^{15}NO signal of **3a**. Subsequently, we studied the reaction of **3a** with TlOPr in the temperature range of −80 to −10 °C.[14] In this case, we observed a clearly visible ^{15}N NMR signal of $CH_2N^{15}N$ at δ = 14.2 ppm (Figure 1) and the corresponding doublet with δ = 3.34 ppm and $^3J(^{15}N,^1H)$ = 1.1 Hz in the ^{1}H NMR spectrum,[16,17] which indicated a yield of diazomethane of about 3%. The identity of diazomethane was further confirmed by ^{15}N,^{1}H long-range correlation (gHMBCAD) 2D NMR spectroscopy and by the synthesis of $CH_2N^{15}N$ for comparison from ^{15}NO-labeled *N*-methyl-*N*-nitrosourea and KOH in $H_2O/CDCl_3$. The very different proportions of diazomethane in the experiments with **3**/**3a** and TlOEt or TlOPr might be attributed to the various association natures[13a] of thallium(I) alkoxides, or can be explained by the instability of diazomethane in the presence of TlOEt. In a ^{1}H NMR control experiment with diazomethane/$CDCl_3$ prepared from *N*-methyl-*N*-nitrosourea, addition of TlOEt led to 92% decay of the diazomethane after 15 min at −10 °C,



Scheme 4. Reaction of ^{15}N-labeled **3a** with TlOR.

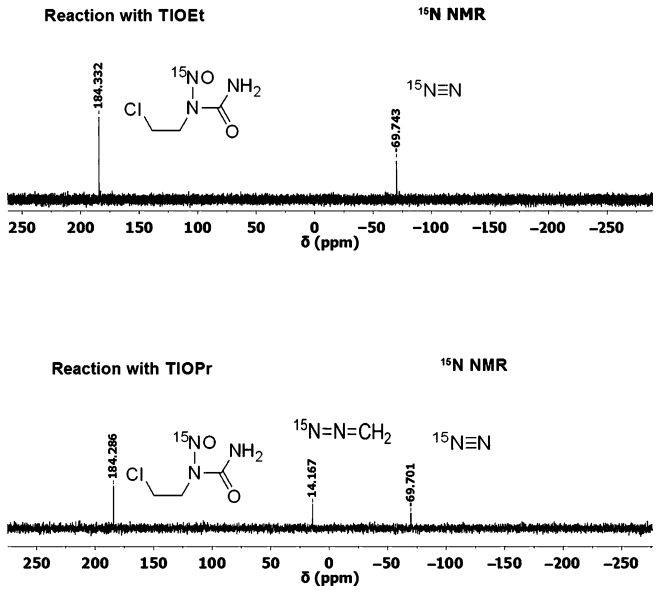


Figure 1. ^{15}N NMR spectra with detection of $^{15}N{\equiv}N$ and $CH_2N^{15}N$ after treatment of **3a** with TlOEt or TlOPr at −80 °C. $MeNO_2$ was used as external reference.

whereas an analogous sample without TlOEt showed negligible decomposition. In an additional control experiment, we confirmed that the stability of diazomethane in the presence of thallium propoxide is significantly greater than that with thallium ethoxide.

In our experiments with **3** or **3a** and TlOEt or TlOPr, we did not detect a ^{15}N NMR signal of $N^{15}NO$[15] or any NMR signal of ethene. Thus, the 1,3-dipolar cycloreversion of **1** to give these products is excluded. Although the transformation of **3**/**3a** in the presence of thallium(I) alkoxides already started at −90 °C, we were not able to detect any NMR signal of **1** in the range of −90 to −80 °C or at higher temperatures. Instead, only secondary products, such as dinitrogen, diazomethane, ethylene oxide, and acetaldehyde or its acetal-type succeeding products, were identified. This result seems to supply clear evidence of the inherent short-lived properties of the heterocyclic compound **1**. However, we cannot exclude that the fragmentation of **1** is efficiently catalyzed by thallium cations. On the other hand, monitoring the reaction of **3** with potassium hydroxide at −20 °C also did not lead to the observance of NMR signals of elusive intermediate **1**.

Although reports in medicinal chemistry on the possible role of salt **2**[5] in the methylation of nucleophilic molecules suggest the parallel formation of **1**, no attempts have been made to detect intermediate **1**, and no sequential products of **1** were identified (Scheme 2). For example, accounts of obtaining the corresponding methyl thioether from **2** and 3,4-dichlorothiophenol in >90% yield were explained by S_N2 attack of the sulfur nucleophile at the *N*-methyl group,[5a] which must lead to the demethylated heterocycle **1**. However, **1** or its decay products were not even mentioned in this case. There are also a few reports[5c,d,12] doubting the role of **2** as a methylating agent. The structure of **2** is an intriguing one and cannot be fully assigned by NMR spectroscopy alone. This is similar to

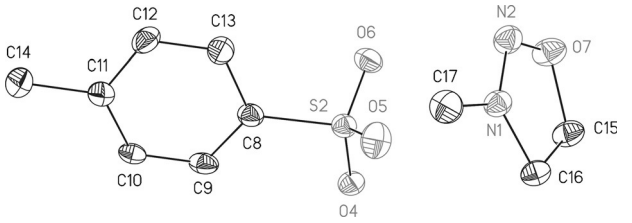
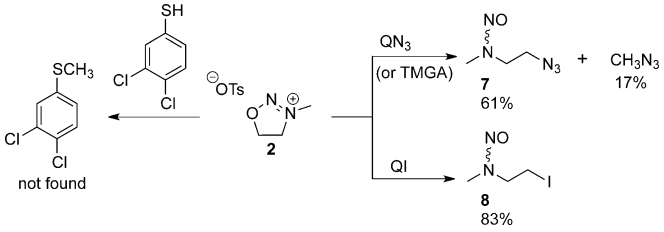


Figure 2. ORTEP representation (50% probability level) of the molecular structure of **2** with atom numbering scheme; hydrogen atoms and further co-crystallized species (H_3O^+, TsO^-) are omitted for clarity.[14,19]

other oxadiazole compounds,[18] for which XRD data were imperative for unambiguous structure elucidation. Therefore, to be sure of the structure and chemistry of **2**, we synthesized **2**[5c,i] and determined its structure by single-crystal XRD (Figure 2).[14,19]

When we repeated the treatment of **2** with 3,4-dichlorothiophenol, we did not detect even a trace of the methyl thioether, and the reaction gave a mixture of many different products, but none of the secondary products of **1** were observed (Scheme 5). We then utilized QN_3[20] (Q = *n*-hexadecyltributyl-

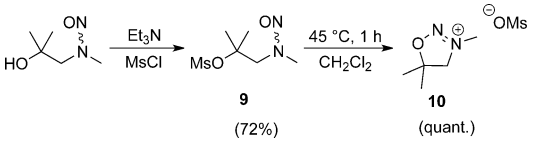


Scheme 5. Products of nucleophilic attack on **2**, Q = *n*-$C_{16}H_{33}Bu_3P$.

phosphonium), which is an azide salt with unique properties and especially useful in monitoring nucleophilic substitution reactions. Substrate **2** was treated with QN_3 (2.0 equiv) at −45 °C, and the reaction was monitored by NMR spectroscopy.[14] Immediately, we could identify the open-chain *N*-nitrosamine rotamers **7** along with CH_3N_3 (17% yield). The formation of **7** can be explained by S_N2 reaction at C-5 of **2**. The detection of methyl azide suggested that some of the needle-like azide nucleophile had probably attacked the *N*-methyl group of **2**. However, as we did not observe any of the secondary products of **1**, the generation of methyl azide was probably occurring through another mechanism. After complete consumption of **2** and additional 24 h at −20 °C, we measured the ^1H NMR spectrum again and found that the yield of methyl azide had increased to 23%. When the solvent and all volatile products, such as methyl azide, were removed in vacuum after total transformation of **2**, another treatment of the residue of **7** with $QN_3/CDCl_3$ at −30 °C slowly led to renewed formation of methyl azide, which was identified by ^1H and ^{13}C NMR spectroscopy. Owing to these results, we assume that the open chain rotamers **7** are not stable and slowly yield methyl azide in the presence of QN_3. Similar results were obtained with TMGA (tetramethylguanidinium azide), which indicate that the

size or the nature of the cation had little role to play. We also treated **2** with QI hoping that the polarizable nature and the large size of iodide would promote an S_N2 reaction at the *N*-methyl group of **2**. But also in this case, we observed a very clean reaction which gave only open chain rotamers **8** with no trace of CH_3I.[21]

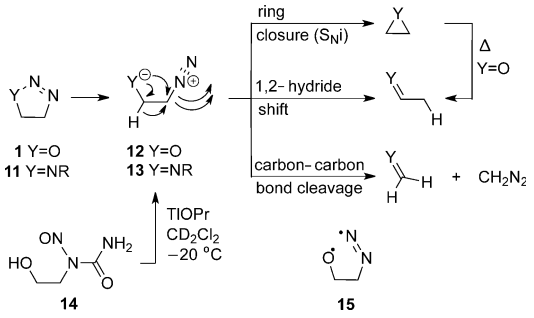
We then synthesized compound **10** as a yellow oil by mesylation of known[22] 2-methyl-1-[methyl(nitroso)amino]-2-propanol followed by thermal ring closure of mesylate **9** (Scheme 6).[14] The idea was that the two geminal methyl



Scheme 6. Synthesis of **10** (Ms = methanesulfonyl).

groups at C-5 would discourage the S_N2 reaction at that position and the direct displacement reaction at the *N*-methyl group of **10** might be feasible. However, **10** did not give any reaction with QN_3, QI, or other nucleophiles. Thus, our results do not confirm S_N2 attack at the methyl group of N-3, not only in the case of substrate **10**, but also for the reactions of salt **2**. Therefore, the methylation of DNA in vivo and methylation of other molecules by treatment with **2** certainly does not involve **1** as an intermediate and occurs by another mechanism.

The decay of short-lived heterocycle **1** can be compared with the well-known chemistry of 4,5-dihydro-1*H*-1,2,3-triazoles **11** (Scheme 7).[23] In the case of **1**, the decomposition is domi-



Scheme 7. Cleavage reactions of the intermediates **12** and **13** generated from the precursors **1**, **11**, and **14**.

nated by cleavage of the very weak N–O bond followed by loss of dinitrogen and ring closure to form a three-membered ring (S_Ni). Alternatively, 1,2-hydride shift leads to a carbonyl compound, or carbon–carbon bond cleavage generates another carbonyl compound with a lower number of carbon atoms and a diazo compound. All three types of reactions are also relevant in the thermolysis of nitrogen heterocycles **11**. After fission of the N–N single bond, simple 4,5-dihydro-1,2,3-triazoles mainly yield aziridines along with imines, which result from a 1,2-hydride shift.[23] However, formation of imines with less carbon atoms and diazo compounds through cleavage of the carbon–carbon bond is also known in the case of special heterocycles of type **11**.[24] However, there are also differences in the succeeding reactions of **1** and the known chemistry of **11**, that included 1,3-dipolar cycloreversion to produce azides RN_3 and alkenes.[25] We were not able to find any evidence of the analogous transformation of **1**, which should lead to the generation of N_2O and ethene. Whereas more than one thousand examples of stable 4,5-dihydro-1,2,3-triazoles are reported in literature, and even heterocyclic compounds **11** without substituents at C-4 and C-5 have been isolated at room temperature,[26] we have obtained evidence for the elusive properties of **1** that prevent direct detection of **1** even at low temperatures. We assume that the very weak N–O bond is responsible for the low stability of **1**.

Since we favor heterolytic cleavage of the N–O bond in **1** via zwitterionic intermediate **12**, we also investigated the base-induced decay of substrate **14** (Scheme 7). This reaction was previously studied in aqueous buffers at physiological pH and 37 °C.[27] Under these conditions, however, at least diazomethane, if formed, would not persist. Owing to its limited solubility, **14** cannot be reacted with thallium propoxide in CD_2Cl_2 at very low temperatures. Even at −20 °C, we had to use a suspension of **14**, and thus the consumption of this substrate was slower. Nevertheless, we were able to detect the products acetaldehyde, ethene oxide, and diazomethane (Table 1). We assume that these compounds are formed via betain **12**. This species is also a plausible intermediate to explain all three types of products after in situ generation of **1** from **3**, although the presence of diazomethane might be alternatively rationalized by synchronous 1,3-dipolar cycloreversion of **1**.

Homolytic cleavage of the N–O bond in **1** to generate diradical **15** is another first step to initiate the decay of the five-membered heterocycle. But the hydrogen shift in **15** seems to be less likely as a possible route for the formation of acetaldehyde.

We investigated the plausibility of a homolytic N–O bond cleavage by quantum chemical calculations. For an adequate quantum chemical description of the open-shell singlet state of **15**, a multi-reference method such as CASPT2 is required. In order to capture the dynamic correlation at a higher level of theory, we used CCSD(T)(F12) to compute the energies of **1** and the triplet state of **15**. CCSD(T) is adequate for these computations, since the CASSCF calculations indicate a single-reference character.

The homolytic cleavage of the N–O bond can be computed using the CCSD(T)(F12) energies and the CASPT2 singlet-triplet splitting of **15** [Eq. (1)].

$$\Delta E^{\mathrm{CCSD(T)(F12)}} = E^{\mathrm{CCSD(T)(F12)}}_{15-\mathrm{triplet}} - E^{\mathrm{CCSD(T)(F12)}}_{1-\mathrm{singlet}} + E^{\mathrm{CASPT2}}_{15-\mathrm{singlet}} - E^{\mathrm{CASPT2}}_{15-\mathrm{triplet}} \quad (1)$$

The results of the CASPT2(6,6) calculations and those following Equation (1) are collected in Table 2 for the two different conformers **15a** and **15b** (Figure 3). Since the dissociation energies of Equation (1) and CASPT2 agree very well, we conclude that the calculations provide the required accuracy to

Table 2. ZPVE- and COSMO-corrected reaction energies for the formation of **15a** and **15b** from **1** in the singlet state via homolytic cleavage of the N-O-bond, calculated with CASPT2(6,6) (def2-TZVPP basis set) and CCSD(T)(F12) (cc-pVDZ-F12 basis set).

Conformer	$\Delta E^{CASPT2}+\Delta^{solv}$ [kJ mol^{-1}]	E.q. (1) $+\Delta^{solv}$ [kJ mol^{-1}]
15a	+145.2	+155.7
15b	+151.8	+162.5

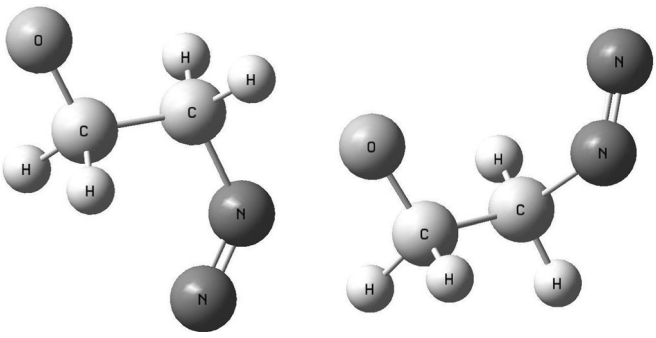


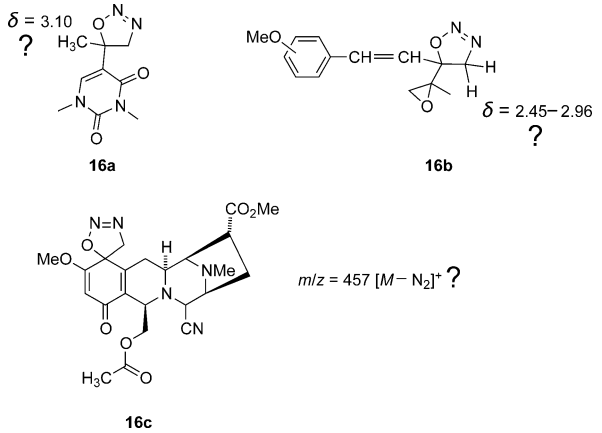
Figure 3. Geometries of the DFT-optimized conformers **15a** (left) and **15b** (right).

draw our conclusion: The dissociation energy is at least 145.2 kJ mol^{-1}, which is significantly higher than the activation barriers for a concerted formation of acetaldehyde (being in the range of 75.7–97.5 kJ mol^{-1}) or diazomethane (being in the range of 81.8–105.5 kJ mol^{-1}).[3] Therefore we can exclude a homolytic cleavage of the N–O bond from quantum chemical calculations.

The energy-minimized structures for all compounds were obtained by RI-DFT geometry optimizations with the TURBOMOLE program package[28] using the PW6B95 functional,[29] the TZVPP basis set,[30] Grimme's D3 dispersion correction,[31] and the COSMO model ($\varepsilon = 8.9$).[32] The geometry optimization of **1** was carried out as closed-shell singlet and those of compound **15a,b** as triplet. The CASPT2 calculations were performed with MOLPRO[33] and the CCSD(T)(F12) calculations with TURBOMOLE.[28,34]

The resulting single-point energies of **1**, **15a** and **15b** were corrected by the zero-point vibrational energies (ZPVE) and a solvation contribution (Δ^{solv}), both obtained from the DFT calculations. The solvation correction was computed from DFT single-point energies with and without using the COSMO model.

Several authors have claimed that they successfully synthesized single examples of 4,5-dihydro-1,2,3-oxadiazoles that can be isolated at ambient temperature.[35] Some of these reports are very old,[35a] but the structures were published also in recent papers without NMR data or other convincing spectroscopic proof.[35h] In some cases, ^{1}H NMR data are evidently not compatible with the suggested structures as shown in Scheme 8. For example, the carbon-bonded methyl group of **16a** should lead to a ^{1}H NMR signal with a significantly lower chemical shift value than $\delta = 3.10$ ppm,[35e,36] and the CH_2–N=N



Scheme 8. ^{1}H NMR[35b,e] and MS data[35d] of alleged 4,5-dihydro-1,2,3-oxadiazoles, which do not support the structure assignment of these heterocycles.

unit in the five-membered ring of **16b** should give ^{1}H NMR signals at clearly lower field than $\delta = 2.45$–2.96 ppm.[35b] When appropriate 4,5-dihydro-1,2,3-triazoles **11** are utilized as model compounds,[26] the ^{1}H NMR signals of the CH_2–N=N group in **16b** should resonate in the range of $\delta = 4.0$–4.3 ppm. The MS data of **16c** include $m/z = 457$ as the highest mass signal, which was attributed to $[M–N_2]^+$.[35d] However, it can also be interpreted as the $[M]^+$ signal of a compound with an oxirane ring instead of a 4,5-dihydro-1,2,3-oxadiazole unit. All reports on stable 4,5-dihydro-1,2,3-oxadiazoles have in common the fact that irrefutable structure proof, for example, by single-crystal X-ray diffraction, is missing. Furthermore, thermolysis followed by analysis of the succeeding products were not performed in any case, and references to other papers with allegedly isolable 4,5-dihydro-1,2,3-oxadiazoles or to previous attempts to generate elusive **1** were not cited. Thus, we have slight doubts that any heterocycle of type **1** has been directly detected or even isolated, although different substitution patterns may stabilize (or destabilize) such compounds. Structure proof by X-ray diffraction or at least analysis of the thermal decay products would dispel our doubts in the case of isolable 4,5-dihydro-1,2,3-oxadiazoles.

In summary, we have found strong evidence for the intervention of **1** in our experiments with *N*-(2-chloroethyl)-*N*-nitrosourea (**3**). In contrast to previous reports,[5] our attempts to demethylate **2** by attack of nucleophiles failed to produce **1**. In our conditions, **1** is too elusive to be detected directly, but proceeds to give oxirane, acetaldehyde, and diazomethane. Most likely, these products arise from the zwitterionic intermediate **12** (Scheme 7) by way of intramolecular displacement, 1,2-hydride shift, and fragmentation, respectively. A direct approach to **12**, starting from *N*-(2-hydroxyethyl)-*N*-nitrosourea (**14**) gave product distributions similar to those obtained with **3**. We cannot exclude that synchronous cycloreversion of **1** contributes to the formation of diazomethane. The alternative cycloreversion of **1**, leading to N_2O and ethylene, was not observed in our experiments.

In earlier reports on the decay of *N*-(2-chloroethyl)-*N*-nitrosoureas in aqueous solutions, acetaldehyde and ethylene

glycol were detected and interpreted as succeeding products of the postulated intermediate **1**.[4] Since we have been able to reveal three different pathways for the decomposition of **1** (Scheme 7), including the first proof of the 1,3-dipolar cycloreversion with formation of diazomethane, evidence of the existence of short-lived **1** is now unequivocal.

In previous quantum chemical calculations, which analyzed the decay of 4,5-dihydro-1,2,3-oxadiazoles, it has been shown that the competition between 1,2-hydride shift to give ketones and cycloreversion to produce diazo and carbonyl compounds is highly dependent on the substitution pattern of the cyclic or bicyclic substrates.[3] Generation of intermediates, similar to **12** or **15**, and formation of epoxides are not investigated in this article,[3] although the latter compounds were already suggested as secondary products of 4,5-dihydro-1,2,3-oxadiazoles, when the reaction of alkenes with N_2O to give carbonyl compounds as main products was reported for the first time in 1951.[37] In another quantum chemical study, no reaction channel connecting the 4,5-dihydro-1,2,3-oxadiazole, derived from the reaction of cyclohexene with N_2O, and cyclohexene oxide could be found.[11] In sharp contrast, the favored transformation into ethylene oxide and dinitrogen, besides the slower cycloreversion to afford formaldehyde and diazomethane, were discussed as exclusive pathways in the decomposition of **1** and described in a previous quantum chemical report.[38] However, we observed formation of acetaldehyde and ethylene oxide as major succeeding products of **1**, whereas diazomethane is generated as minor component. These results are not far from the product distribution in the industrial processes of treating cyclic olefins with N_2O, which lead mainly to ketones, while decay products of diazo compounds are detected in small amounts only (Scheme 1).[2c] We assume that epoxides, as decomposition products of 4,5-dihydro-1,2,3-oxadiazoles, might be produced also in these industrial processes, but they are possibly isomerized under the drastic reaction conditions (250–280 °C) to furnish ketones (Scheme 7).[39] However, in the case of the betain species of type **12** derived from cyclopentene via a bicyclic 4,5-dihydro-1,2,3-oxadiazole intermediate (see Scheme 1), hydride shift to give cyclopentanone is perhaps favored, and formation of cyclopentene oxide by S_Ni reaction is repressed because of the fixed *cis* configuration and stereoelectronic reasons.

Considering the central role of **1** in such important chemical transformations, the present results not only advance the understanding of the mechanism involved, but are also expected to provide a basis for the development of novel synthetic procedures for generating **1**.

Experimental Section

For experimental details and supporting spectra, please see the Supporting Information.

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Keywords: alkylation · cycloreversion · NMR spectroscopy · nucleophilic substitution · reactive intermediates

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