Generation of 4,5-Dihydro-1,2,3-oxadiazole and Study of the Decomposition Products

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Neeraj Singh
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Abstract

4,5-Dihydro-1,2,3-oxadiazoles are postulated to be key intermediates in the synthesis of ketones from alkenes on an industrial scale, alkylation of DNA in vivo, decomposition of N-nitrosoureas (potent carcinogens), and are also a subject of great interest for theoretical chemists. In this thesis, formation of the parent compound and decay into secondary products has been studied by NMR monitoring analysis. The elusive properties and the intermediacy of the parent compound, 4,5-dihydro-1,2,3-oxadiazole, in the decomposition of suitably substituted N-nitrosoureas using Tl(I) alkoxides as bases, have been confirmed by the characterisation of its decay products viz., ethylene oxide, acetaldehyde, and especially diazomethane, at very low temperatures by $^1$H NMR, $^{13}$C NMR, $^{15}$N NMR, and relevant 2D NMR methods. Moreover, it has been shown that the methylation of nucleophilic molecules by 3-methyl-4,5-dihydro-1,2,3-oxadiazolium salts, which are considered to be activated forms of $\beta$-hydroxyalkynitrosamines, does not involve 4,5-dihydro-1,2,3-oxadiazole as an intermediate, as has been reported in literature; instead, nucleophilic substitution leading to synthesis of open-chain products dominates the reaction.

Keywords: 4,5-Dihydro-1,2,3-oxadiazole, N-Nitrosourea, Tl(I) alkoxides, 1,3-Dipolar cycloreversion, $^{15}$N-labelling, Low-temperature NMR spectroscopy, Oxadiazolinium salts, Alkylation, Nucleophilic substitution, Reactive intermediates, Hydroxylamine.
Bibliografische Beschreibung

Erzeugung von 4,5-Dihydro-1,2,3-oxadiazol und Untersuchung der Zersetzungsprodukte

Abstract

4,5-Dihydro-1,2,3-oxadiazole wurden als Schlüsselintermediate in der industriellen Synthese von Ketonen aus Alkenen, der in vivo Alkylierung von DNA und der Zersetzung von N-Nitrosoharnstoffen (potente Karzinogene) postuliert. Sie sind ebenso von großem Interesse in der theoretischen Chemie. Im Rahmen dieser Arbeit wurde die Bildung der Stammverbindung und deren Zersetzung in sekundäre Produkte mittels NMR-Verfolgung studiert. Die ausgesprochene Kurzlebigkeit der Stammverbindung 4,5-Dihydro-1,2,3-oxadiazol wurde durch die Charakterisierung der Produkte bei der Zersetzung geeigneter substituierter N-Nitrosoharnstoffe mit Tl(I)-Alkoxiden bestätigt. Die Zersetzungsprodukte Ethylenoxid, Acetaldehyd und besonders Diazomethan wurden bei sehr niedrigen Temperaturen mittels $^1$H-NMR, $^{13}$C-NMR, $^{15}$N-NMR und relevanten 2D-NMR-Methoden charakterisiert.

Des Weiteren konnte gezeigt werden, dass die Methylierung nuclephiler Spezies mit 3-Methyl-4,5-dihydro-1,2,3-oxadiazoliumsalzen, welchen als aktivierte Äquivalente der β-Hydroxyalkynitrosamine verstanden werden, nicht zur Bildung von 4,5-Dihydro-1,2,3-oxadiazol als Intermediat führt, so wie dies in der Literatur berichtet wurde. Stattdessen wird die Bildung offenkettiger Produkte durch nucleophile Substitution bevorzugt.

Stichworte: 4,5-Dihydro-1,2,3-oxadiazol, N-Nitrosoharnstoff, Tl(I)-Alkoxide, 1,3-Dipolare cycloreversion, $^{15}$N-Markierung, Tieftemperatur-NMR-Spektroskopie, Oxadiazoliniumsalze, Alkylierung, nucleophile Substitution, reaktive Intermediate, Hydroxylamine.
This thesis is dedicated to my great-grandfather, great-grandmother, grandfather, grandmother, father, mother, and my sister.
List of Abbreviations

Calcd. Calculated
CENU's (2-chloroethyl)nitrosoureas
d doublet
DNA Deoxyribonucleic acid
DMF Dimethylformamide
DMSO Dimethyl sulfoxide
DMPU 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone
DEPT Distortionless Enhancement by Polarization Transfer
ESI Electrospray Ionisation
gHMBCAD Gradient-enhanced Heteronuclear Multiple Bond Correlation experiment
gHSQCAD Gradient-enhanced Heteronuclear Single Quantum Coherence experiment
gCOSY Gradient-selected Correlation Spectroscopy
HENU's (2-haloethyl)nitrosoureas
Q Hexadecyltributylphosphonium
HR-MS High-resolution Mass Spectrometry
IR Infrared spectroscopy
OMs mesyloxy
m multiplet
N₂O Nitrous oxide
NMR Nuclear Magnetic Resonance
s singlet
THF Tetrahydrofuran
TIOEt Thallium(I) ethoxide
TIPr Thallium(I) propoxide
t triplet
XRD X-ray Diffraction
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1) Introduction and aim of the research work

1.1) Source of atmospheric nitrous oxide (N$_2$O) and its impact on the present environmental conditions

Nitrous oxide was discovered\[1a\] by J. Priestley in the year 1772 and is widely known as 'laughing gas', a name given by H. Davy in the year 1799 due to its soft anaesthetic effect.\[1b\] It is also one of three compounds containing N−O bonds discovered in interstellar space.\[2\] Anthropogenic instruments viz., power plants, transport (18%), industrial chemical processes (12%), and agriculture (70%) are major contributors to the increasing concentration of stratospheric nitrous oxide. The concentration of N$_2$O rose rapidly in the post-industrial world to ~326 ppb (Figure 1) as against a constant ~280 ppb before the onset of industrialization, and continues to increase at a rate of ~0.5–0.9 ppb per annum (0.2%–0.3% annually).\[3\] This is a major cause of concern as nitrous oxide, although being a minor constituent of atmosphere, is a highly potent greenhouse gas\[4\] (300 times the deleterious effect of CO$_2$), and has an average residence time of about 120 years in the lower layers of atmosphere, primarily due to its high kinetic stability. N$_2$O gradually diffuses (Figure 2) from the troposphere to the stratosphere, where it decomposes partly through photolysis, and partly in reactions with reactive [O] and 'OH species formed upon photolysis (Scheme 1).

![Figure 1](image-url). Greenhouse gas trends.
Nitric oxide (NO), in turn, reacts with ozone to form O₂ and NO₂. The latter undergoes disproportionation to give [NO] and [O] under solar radiation, and this process occurs in a cyclical manner.⁵ Owing to the above mechanism, nitrous oxide is the most potent ozone-depleting substance (ODS), but, ironically, not much attention has been given to regulating its release into the atmosphere. Agriculture forms the major contributor⁶ to nitrous oxide concentration because of the excessive use of nitrogen-containing fertilizers (by nitrification and denitrification in the soils) and the anaerobic processes occurring in the flooded rice fields. However, little can be accomplished here due to the ever increasing demand of food supply required to feed the growing population.

On the other hand, regulation of industrial release of nitrous oxide into the atmosphere has achieved some success wherein some of the largest manufacturers of adipic acid (≈5%–8% of the total anthropogenic emission of N₂O) have concluded an agreement to supply plants with special technological cycles and to reduce the amount exhausted into the atmosphere.⁶ New catalysts and catalytic processes for decomposition of N₂O are being developed.

Herein, BASF’s methods of manufacture⁷ of ketones from alkenes using in-house waste N₂O (from adipic acid process) has achieved worldwide accolades and presents a milestone in reducing its release to the atmosphere and setting a commendable example of corporate responsibility. Such green methods are certainly the need of the hour for a sustainable future and protecting the ozone layer from further depletion, thereby, protecting life on earth as a whole.
1.2) Synthesis, structure, physical, and chemical properties of \( \text{N}_2\text{O} \)

Nitrous oxide is manufactured mainly by careful heating of solid ammonium nitrate to 200 °C.\[8\] Various phosphates may be added to get purer gas at relatively lower temperatures. Sometimes, the nitric oxide impurity is removed via chelation with ferrous sulfate.

\[
\text{NH}_4\text{NO}_3 (s) \xrightarrow{200 \degree \text{C}} \text{N}_2\text{O} + 2 \text{H}_2\text{O} \quad \Delta H = -124 \text{ kJ/mol}
\]

The commercial production of adipic acid (Scheme 2; employed in the large scale of nylon 66) and nitric acid are also a major source of nitrous oxide production.\[9\] But, largely, the nitrous oxide so produce is decomposed catalytically due to environmental concerns.

\[
\text{O} + \text{OH} + w \text{HNO}_3 \xrightarrow{} \text{HO}_2\text{C} \text{CO}_2\text{H} + x \text{N}_2\text{O} + y \text{H}_2\text{O}
\]

Scheme 2. Illustration of the industrial synthesis of adipic acid.

Other methods (as shown below) include the heating of sodium nitrite-ammonium sulfate mixture, oxidation of ammonia over manganese dioxide-bismuth oxide catalyst, etc.\[8\]

\[
2 \text{NaNO}_3 + (\text{NH}_4)_2\text{SO}_4 \xrightarrow{\Delta} \text{Na}_2\text{SO}_4 + 2 \text{N}_2\text{O} + 4 \text{H}_2\text{O}
\]

\[
2 \text{NH}_3 + 2 \text{O}_2 \xrightarrow{\text{Manganese dioxide-bismuth oxide catalyst}} \text{N}_2\text{O} + 3 \text{H}_2\text{O}
\]

Nitrous oxide is a 16-valence-electron molecule which has a \( \pi \) system of four electrons and can be represented by a zwitterionic octet resonance structure. It is considered to be a 1,3-dipole because at least one mesomer shows a separation of charge in a 1,3-relationship. It is mainly represented by the following resonance structures:

\[
\begin{align*}
\text{N}=\text{N}=\text{O}^\ominus & \quad \leftrightarrow \quad \text{N}^\oplus=\text{N}=\text{O} \quad \leftrightarrow \quad \text{N}^\ominus=\text{N}=\text{O}^\oplus \\
\text{A} & \quad \leftrightarrow \quad \text{B} & \quad \leftrightarrow \quad \text{C}
\end{align*}
\]

1,3-dipole
Nitrous oxide is a colourless, diamagnetic gas with a weak pleasant odour and sweet flavour. It is non-combustible but can act as a promoter of combustion at suitable temperature conditions. N₂O is very stable; in the absence of a catalyst at 400–500 °C, the thermal decomposition is insignificant (~0.23%).[^10] The activation energy (Eₐ) of the non-adiabatic, spin-forbidden decomposition of nitrous oxide into dinitrogen and oxygen gas is approx. 59 kcal/mol. At room temperature (21 °C) under high pressure (51 atm), nitrous oxide exists as a liquid and can be stored in steel containers.

The important physical properties of N₂O are given below (Table1).

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point</td>
<td>−90.86 °C</td>
</tr>
<tr>
<td>Boiling point</td>
<td>−88.48 °C</td>
</tr>
<tr>
<td>Critical pressure</td>
<td>71.70 atm</td>
</tr>
<tr>
<td>Critical temperature</td>
<td>36.5 °C</td>
</tr>
<tr>
<td>Critical density</td>
<td>0.45 g/cm³</td>
</tr>
<tr>
<td>Density of N₂O (liq) at boiling point</td>
<td>1.23 g/cm³</td>
</tr>
<tr>
<td>Density of N₂O (g) at 0 °C</td>
<td>1.99 mg/cm³</td>
</tr>
<tr>
<td>Enthalpy of formation (ΔfH²⁹⁸)</td>
<td>19.60 kcal/mol</td>
</tr>
<tr>
<td>Free energy of formation (ΔfG²⁹⁸)</td>
<td>24.60 kcal/mol</td>
</tr>
<tr>
<td>Entropy (S⁰)</td>
<td>52.52 cal/Kmol</td>
</tr>
<tr>
<td>Thermal capacity (C⁰_p)</td>
<td>9.19 cal/Kmol</td>
</tr>
</tbody>
</table>

**Table 1. Physical properties of N₂O.**[^8]

N₂O is a thermodynamically potent oxidant for oxo-transfer reactions (Table 1), but it is remarkably kinetically inert in the absence of a suitable activating centre (usually a transition metal); moreover, the sole by-product of oxo-transfer from N₂O, dinitrogen, is a benign, unreactive one. For these reasons, nitrous oxide is an attractive oxygen-atom source for effecting selective chemical oxidations. The low reactivity of nitrous oxide can be compensated by utilizing reaction partners with high ring strain, N-heterocyclic carbenes, frustrated-Lewis pairs and/or suitable metalorganic reagents.
1.3) Recent exemplary reports on the utilization of nitrous oxide

1.3.1) Covalent capture of \( \text{N}_2\text{O} \) by N-heterocyclic carbenes

Recently, commercially available N-heterocyclic carbenes (NHCs) viz., 1,3-dimesitylimidazole-2-ylidene (IMes), which are strong Lewis bases, have been shown to capture \( \text{N}_2\text{O} \) to give stable adducts (Scheme 3).\[^{11}\] These adducts display unique reactivity as evidenced by an alkylation reaction which results in the rupture of N–N bond. In these type of adducts, a bent \( \text{N}_2\text{O} \) group is connected through the N-atom to the carbon of the heterocycle.

![Scheme 3](image)

Scheme 3. Synthesis of NHC–\( \text{N}_2\text{O} \) adduct\[^{11a}\] and their mesomeric structures.

![Scheme 4](image)

Scheme 4. Reactions of NHC–\( \text{N}_2\text{O} \) adduct\[^{11b}\]
The bond lengths of the C-atom to the adjacent N-atoms are all approximately equal (1.36 Å). With 1.25 Å, the N−O bend length is significantly shorter. The bond angle of NNO is approximately 110°. On heating the NHC−N₂O adduct in toluene at 100 °C, dinitrogen was extruded and the oxygen enriched product was obtained (Scheme 4). The reactivity of the NHC−N₂O adduct with electrophiles like Mel was observed to give a triiodide salt (with guanidinium type cation and triiodide anion). This reaction is an interesting example of the N−N bond cleavage (Scheme 4), a rarely observed reaction pattern in N₂O chemistry.

1.3.2) Complexation of N₂O with frustrated Lewis pairs (FLPs)

Frustrated Lewis pairs (FLPs)¹² attribute their uniqueness to the high steric congestion in contributing partners which prevents the formation of classical Lewis adducts and therefore, the unquenched acidity or basicity can be exploited for further reactivity. This was utilized for reactivity to form FLP−N₂O adducts¹³ with unique structural properties (Scheme 5).

Scheme 5. Synthesis of FLP−N₂O adducts.

The N−N and N−O bonds in the N₂O fragment are 1.26 Å and 1.34 Å, respectively, and are significantly elongated in comparison to free N₂O (1.13 and 1.19). This difference is in sharp contrast to NHC−N₂O adducts wherein all the bond lengths are approximately equal. Collectively, these data indicate the bonding in these FLP−N₂O adducts is best described as P−N=N−O−B in which the 'Bu₃P and OB(C₆F₅)₃ fragments adopt a transoid disposition with respect to the N=N double bond.
1.3.3) Utilizing ring strain in reactivity with nitrous oxide

The chemistry of nitrous oxide with alkenes and/or alkynes represents a perfect example of 1,3-dipolar cycloaddition reaction wherein \( \text{N}_2\text{O} \) acts as a 1,3-dipole of diazonium betaine type, based on Huisgen's classification. Scheme 6 presents an overall view of the mechanism of such a reaction along with possible secondary products. The reaction proceeds via 1,2,3-oxadiazole intermediates which under reaction conditions can give a variety of products.\[^{[14]}\]

\[
\text{R}^1\text{R}^2 + \text{N}_2\text{O} \xrightarrow{\text{up to 350°C} \text{ up to 700 atm}} \begin{array}{c}
\text{O}^\text{N}^\text{N} \\
\text{R}^1\text{R}^2
\end{array} \xrightarrow{\text{Wolff rearrangement}} \begin{array}{c}
\text{O}^\text{C}^\text{R}^1 \\
\text{R}^2
\end{array} \xrightarrow{\text{Nu}} \begin{array}{c}
\text{O}^\text{R}^1 \\
\text{R}^2
\end{array}
\]

Scheme 6. Mechanism of 1,3-dipolar cycloaddition of \( \text{N}_2\text{O} \) with alkenes/alkynes and corresponding secondary reactions.

In the case of alkenes \( 1a \), the 1,3-dipolar cycloaddition reaction with \( \text{N}_2\text{O} \) proceeds via 4,5-dihydro-1,2,3-oxadiazole \( 2a \) which is still an intensively discussed, but still undetected intermediate and is the field of my doctoral research. Intermediate \( 2a \) can either undergo a hydride shift to give the carbonyl compound \( 5a \) or undergo Wagner–Meerwein rearrangement to yield differently substituted carbonyl compound \( 6a \). Cleavage of C–C bond of \( 2a \) can also yield carbonyl compound \( 7a \) along with diazo compound \( 8a \). Formation of cyclopropane \( 9a \) has also been suggested as a product formed from the alkene \( 1a \) and carbene originating from decay of \( 8a \).

Alkynes \( 1b \) react with \( \text{N}_2\text{O} \) via 1,2,3-oxadiazole \( 2b \), which rearranges to the ketene \( 4b \) and can be trapped by suitable nucleophiles. Intermediates of type \( 2b \) are also highly elusive molecules.
As depicted in Scheme 6, the reaction of $\text{N}_2\text{O}$ with alkenes/alkynes occurs under high temperature and pressure conditions. Recently, K. Banert et al. published$^{[14]}$ some very important results on the study of the reaction of strained alkyynes with nitrous oxide. Strained alkyynes are highly reactive molecules because of the deviation of bond angle from the normal 180° to ~163° (in case of cyclooctyne). This deformation and the consequent high reactivity has been exploited in various other important reactions such as the strain promoted alkyne-azide cycloaddition (SPAAC) reaction$^{[15]}$ developed by C. Bertozzi.

Strained alkyne 10, reacted with $\text{N}_2\text{O}$ even at $-25 \, ^\circ\text{C}$ to give the diazo carbonyl compound 11 which subsequently rearranged to the corresponding ketene 12 and other products. This is the first reported reaction at such a low temperature without the use of any metalorganic reagents and indirectly confirms the formation of the corresponding 1,2,3-oxadiazole intermediate.$^{[14]}

\[ \begin{array}{c}
\text{10} \quad \text{N}_2\text{O} \quad \text{15 bar} \quad -25 \, ^\circ\text{C} \quad 3 \text{ days} \\
\text{11} \quad \text{RT} \\
\text{12} \quad \text{13} \quad \text{14} 
\end{array} \]

\textbf{Scheme 7}. Reaction of cycloalkyne 10 with nitrous oxide.
1.4) Importance of 4,5-dihydro-1,2,3-oxadiazoles as intermediate in various fields of chemistry

4,5-Dihydro-1,2,3-oxadiazoles of type 15 are presently an unknown class of molecules. The formation of 15 can be envisioned as a consequence of 1,3-dipolar cycloaddition reaction between N₂O (1,3-dipole) and ethylene (dipolarophile). Nitrous oxide can be treated as a three atomic orbital π system containing four electrons analogous to an allyl anion, which can interact with an olefin in a six-electron transition state, energetically favoured according to Woodward–Hoffmann rules.⁴⁶ The main relevant π MOs between two fragments, the 16-electron dipole (N₂O) and ethylene are shown in Scheme 8. It is clear from the MOs of N₂O that in the triplet state, one electron is situated in the LUMO, in which antibonding interactions exist between the center and the terminal atoms, while bonding interactions exists between two terminal atoms.

The 1,2,3-oxadiazole ring system is at present mainly represented by sydnones 16 and sydnonimines⁴⁷ 17, which are isolable (Scheme 8), and extremely few compounds like 18⁴⁸ (Scheme 9).

Scheme 8. Parent compound 15 and isolable 1,2,3-oxadiazole ring systems.
4,5-Dihydro-1,2,3-oxadiazoles are postulated to be intermediates in the synthesis of ketones from alkenes under drastic conditions (high temperature and pressure, Scheme 6),[7,19,20] the decomposition of N-nitrosoureas at physiological pH,[21] the alkylation of DNA and other relevant molecules in vivo[18] by salts like 18, and are also a subject of great interest to theoretical chemists.[20,22,23] Scheme 9 depicts the possible modes of formation and subsequent products of 15.

Scheme 9. Possible modes of formation and subsequent products of 15.
1.4.1) Liquid-phase oxidation of alkenes to ketones with nearly 100% selectivity

Gas-phase oxidation of alkenes and other organic molecules by nitrous oxide was reported way back in 1951, but, owing to poor selectivity, difficult experimental conditions and modest results, not much attention was attributed to this study.\cite{24}

Recently, Panov et al. described the liquid-phase oxidation of alkenes, mainly cyclohexene and cyclopentene to cyclohexanone and cyclopentanone, respectively by N₂O with nearly 100% selectivity.\cite{19} This method received widespread attention because it presented a green, economically feasible method of synthesis of industrially relevant ketones; cyclohexanone is employed in the synthesis of nylon-66 and cyclopentanone in glutaric acid, etc. It was suggested that the reaction takes place via 1,3-dipolar cycloaddition of nitrous oxide with the cycloalkene to give dihydrooxadiazole 19/20 (highly unstable under reaction conditions) which exclusively rearranges to the corresponding ketone. The authors did not report even traces of the corresponding epoxides and excluded its formation on the basis of their observation that externally added epoxide did not rearrange to the corresponding ketone. Quantum chemical calculations analyzing the mode of decay of 4,5-dihydro-1,2,3-oxadiazoles to give ketones or diazo and carbonyl compounds has been attributed to substitution pattern of the cyclic or bicyclic substrates.\cite{20} Another theoretical study\cite{23} performed on 19 suggests the exclusive formation of corresponding ketone and also the possibility to detect 19 at low temperatures ($\Delta H = -7.7$ kcal/mol); however, 19 and 20 are unknown molecules.

![Scheme 10. Liquid-phase oxidation of cyclic alkenes by nitrous oxide.](image)

This method of oxidation by N₂O was further developed by BASF Ludwigshafen and is employed in the synthesis of twelve-membered ring ketones (30,000 tonne scale).\cite{7}
Cyclododecanone is synthesized from cyclododecatene in only two steps and with the use of only one catalyst utilized for reduction of the double bond (Scheme 11). Previously, the same synthesis was achieved in four steps and three catalysts were needed. Cyclododecanone is utilized in the synthesis of nylon-12.

Scheme 11. BASF’s synthesis of cyclododecanone utilizing N₂O.

The industrial method depicted in Scheme 11 also proceeds via the postulated dihydrooxadiazole which extrudes dinitrogen to yield the ketone (via 1,2-hydride shift). Similarly, the oxidation of a cyclododecene (cis/trans 34 : 66) by nitrous oxide has been postulated to proceed via dihydrooxadiazole intermediates (21 and 22; not observed experimentally) and 1,3-dipolar cycloaddition step has been postulated to be the rate-determining step (Scheme 12). Activation barrier was found to be lower for trans isomer ($\Delta \Delta H^\ddagger \approx 12$ kJ/mol).[25]

Scheme 12. BASF’s process of cyclododecene oxidation by N₂O.
1.4.2) Decomposition of N-nitrosoureas under physiological conditions

N-Nitrosoureas occupy a central role in the field of medicine as they are considered to be highly mutagenic and/or carcinogenic molecules.\cite{21a,b} Simple N-nitrosoureas, viz. N-methyl-N-nitrosourea, have been found to be one of the principal cancer causing agents found in cigarette smoke. However, more complex analogues, especially, (2-chloroethyl)nitrosoureas (CENU), 1,3-bis(2-chloroethyl)-1-nitrosurea (BCNU), 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), chlorozotocin, and others have higher anticancer activity as compared to their teratogenicity/mutagenicity and are employed in the treatment of certain neoplasma.\cite{21b}

\[ \text{Scheme 13. Proposed decomposition products of } N\text{-nitrosoureas at physiological pH via pathways A, B, and C.} \]

It has been reported that these compounds decompose readily under physiological conditions to produce species that have been found to alkylate and cross-link DNA both \textit{in vivo} and \textit{in vitro}.\cite{21f,g}
The nature and origin of some of the products have been suggested in few reports and outlined in Scheme 13. The decomposition of \(N\)-nitrosoureas has been proposed to occur possibly by three distinct pathways (A, B and C).\(^{[21b,e]}\) Pathway A leads to the elimination of hydrogen chloride and subsequent cyclization to yield \(2-(\text{alkylimino})-N\)-nitrosooxazolidine 23 which can decompose further to acetaldehyde. Removal of isocyanate by ring cleavage can lead to diazohydroxide 24 and simultaneous loss of dinitrogen occurs to yield acetaldehyde (one of the products observed experimentally). Evidence has been discussed wherein 24 was synthesized, characterized and its subsequent decomposition to acetaldehyde was observed, however, the mechanism proposed is different than the one represented in Scheme 13.

Generation of diazohydroxide 25 (highly susceptible to acid catalyzed hydrolysis) via pathway B to generate the 2-chloroethyl cation (or its kinetic equivalent) which can further react with suitable nucleophiles to give 2-chloroethanol and/or 1,2-dichloroethane, or eliminate a proton to give chloroethene. In certain \(N\)-nitrosoureas, experimental evidence for pathway B has been observed in that 25 or 2-chloroethyl cation, both alkylate and form interstrand cross-links in DNA and between DNA and proteins.

Pathway C has been suggested to proceed via the formation of \(N\)-acyloxadiazolinium species 26 which via base catalyzed decomposition (by formation of tetrahedral intermediate and loss of proton) leads to transient 15. The formation of ethylene glycol, observed experimentally in the decomposition of BCNU by Brundrett et al.\(^{[21c]}\) has been hypothesized to proceed via 15 which leads to diazohydroxide 27 which ultimately loses dinitrogen and hydroxide in the presence of water.

In addition, \textit{ab initio} (Hartree-Fock) calculations, in one of the scenarios, performed to predict the plausible intermediates leading to the observed products of decomposition of HENU's ((2-haloethyl)nitrosoureas)) have focussed mainly on the geometry of the (Z) and (E)-2-haloethanediazohydroxide (25) to rationalize the formation and implication of 15 as an intermediate.\(^{[22b]}\) Argument has been presented in favour of Z isomers owing to the favorable conformation of the transition state leading to 15.
1.4.3) Alkylation of DNA and other suitable molecules by 3-methyl-1,2,3-oxadiazolinium tosylate

β-Hydroxyalkynitrosamines, derived from widely available commercial alkanolamines, are common environmental contaminants exhibiting considerably high carcinogenicity.[18a] These molecules are different from the common dialkynitrosamines, viz. N,N-dimethyl-N-nitrosamine, in that the carcinogenicity expressed cannot be explained by the usual enzymatic α-hydroxylation mechanism explained in Scheme 14 because they are not a substrate for the cytochrome P-450 enzymes.

![Scheme 14. Mechanism of DNA methylation in case of 28.](image)

In particular, mechanism of cancer causing activity of N-methyl-N-nitroso-2-hydroxyethylamine 30 has received considerable attention due to its potent hepatocarcinogenicity in female F344 rats.[18a,b] It has been found that compounds like 30 preclude biochemical activation prior to acting as a carcinogen. Three different pathways[18c] have been suggested for the biochemical activation: (a) conversion of β-nitrosamino alcohol into more reactive aldehyde by alcohol dehydrogenase, (b) enzymatic sulfation of the hydroxyl group to generate 33 via 31, (c) chain-shortening reactions to generate methyl-substituted nitrosamines which are substrates for P-450 enzymes.

Pathway 'b' leading to the formation of 33 is a promising one since it involves the generation of 3-methyl-1,2,3-oxadiazolinium ion which then possibly methylates or hydroxyethylates DNA. As mentioned in Scheme 9, compound 18 which also includes the same cation was actually used in various studies to investigate the possible methylation and/or alkylation in laboratory conditions due to better solubility in organic solvents and ease of handling. The formation of 18 from 32 (Scheme 15) proceeds via the anchimeric assistance of the N-nitroso oxygen leading to an Sn2 reaction at the carbon attached to the nucleofuge tosylate.
Scheme 15. Proposition to explain formation of 3-methyl-4,5-dihydro-1,2,3-oxadiazolinium cation and subsequent alkylation.

It has been reported that the reaction of 18 with guanine and guanosine proceeded with the formation of the corresponding methylated derivatives in good yields.\cite{18a} Similarly, the reaction of 3,4-dichlorothiophenol with 18 gave the corresponding methyl thioether in >90% yield.\cite{18a} Relatively minor yield (13%) of N-methylmorpholine was reported in the reaction between 18 and morpholine.\cite{18h} All these results were explained by the demethylation of the 3-methyl-1,2,3-oxadiazolinium cation by the corresponding nucleophiles, thereby, generating 15 (Scheme 16). However, nothing has been mentioned about the properties of 15 and/or subsequent primary decomposition products.

Scheme 16. Demethylation of 18 and most favourable mode of fragmentation as per theoretical calculations.
Quantum chemical calculations\textsuperscript{[22a]} have also suggested the attack of nucleophiles on the methyl group of 18 as a favourable reaction since the methyl carbon is one of the most electropositive one. The most favourable mode of decomposition of 15 on the basis of sequential stretching of NO, NC, or OC bonds has been stated to be the 1,3-dipolar cycloversion (Scheme 16) generating diazomethane and formaldehyde, although, these products have never been observed experimentally.
1.4.4) Introduction to thallium(I) alkoxides

Thallium(I) alkoxides are basic compounds which are known since 1800. These compounds can be synthesized from TIOEt (commercially available) by Bradley’s method.\[26a\] The special property of these alkoxides, especially, TIOEt and TIOPr is that they are soluble in apolar organic solvents\[26\] (even at low temperatures). These compounds are generally moisture sensitive and therefore should be handled under inert gas conditions.

\[
\begin{align*}
\text{TIOEt} & + \text{ROH} \xrightarrow{\text{under } N_2} \text{TIOR} + \text{EtOH} \\
R &= \text{n-C}_x\text{H}_y \\
\text{n-C}_x\text{H}_y \\
\text{n-C}_x\text{H}_y \\
\text{n-C}_x\text{H}_y
\end{align*}
\]

Scheme 17. Bradley's method for the syntheses of Ti(I) alkoxides.

1.4.5) Special case of QN$_3$

Hexadecyltributylphosphonium azide (QN$_3$) is an ionic compound highly useful in the synthesis of unusual azides where classical methods have failed.\[27\] Owing to its high lipophilicity, it is soluble in very nonpolar organic solvents like cyclohexane and cyclopentane even at low temperatures. The low melting point of this substance warrants its usage as a (supercooled) melt and allows for extremely rapid nucleophilic substitution reactions. It can be synthesized from commercially available hexadecyltributylphosphonium bromide (QBr) by exchange reaction reaction with sodium azide or from QOMs (Scheme17).

\[
\begin{align*}
\text{QBr} & \xrightarrow{\text{NaBr}} \text{QN}_3 \\
\text{MeOMs} & \xrightarrow{\text{N}_{3}} \text{QN}_3 \\
\text{OMs=Mesylate} & \xrightarrow{\text{NaOMs}} \text{QN}_3
\end{align*}
\]

**Aim of the research work**

The aim of my research work includes the generation of 4,5-dihydro-1,2,3-oxadiazole 15 to study the nature of its true secondary products (Scheme 9). In spite of the immense importance of 15 and analogous molecules in various fields of chemistry including industrial, medicinal, and theoretical, the true nature of 15 and its decomposition products have still not been reported.

The intermediacy of 15 in base-catalyzed decomposition of suitably substituted N-nitrosoureas has been suggested, but, since almost all the studies have been done under physiological conditions, the true nature of secondary products and the mechanism of decomposition of 15 is still not fully understood. It, therefore, becomes imperative to present clear evidence for the generation of 15 in the reactions with different bases and to establish the mechanism of decomposition of 15 and formation of true secondary products.

Similarly, the demethylation of 18, thereby generating 15 has also been proposed with various suitable nucleophiles in order to study the observed site of attack of the nucleophile and the resulting products. However, conflicting reports have been published questioning the methylating capability of 18.\[^{18d}\] Since, these reactions help to establish whether 18 like compounds are actually the biochemically activated forms of β-hydroxyalkylnitrosamines, the elucidation of the interaction mechanism (demethylation or some other) with suitable nucleophiles will help to understand the chemistry of these interesting compounds and also to comment on the important question of possible intermediacy of 15.

Moreover, the industrial method employing nitrous oxide for the green synthesis of ketones has also been suggested to include the formation of 15 like compounds (19, 20, 21, and 22), however, these are unknown molecules and methods to generate these intermediates under milder conditions would be helpful to establish the formation of these compounds in these important processes.
2. Results and discussion

2.1 Synthesis of \textit{N}-(2-chloroethyl)-\textit{N}-nitrosourea (34) and study of its reaction with various bases by NMR spectroscopy

\textit{N}-(2-Chloroethyl)-\textit{N}-nitrosourea (34) was synthesized by a known procedure\cite{21h} from 2-chloroethylamine hydrochloride by reaction with KOCN and subsequent nitrososation of \textit{N}-(2-chloroethyl)urea by NaNO\textsubscript{2}/H\textsubscript{2}SO\textsubscript{4}. Before the reactions of 34 with suitable bases are discussed, it is essential to understand the structural peculiarities of CENUs, the difference in the conformation adopted by CENUs in nonpolar aprotic solvents and aqueous solutions, and the mechanism of base induced decomposition of \textit{N}-nitrosoureas.

Compounds like 34 have a peculiar structure because they can adopt various conformations owing to restricted rotation about any of the three bonds, \textit{N}\textsubscript{1}−\textit{N}\textsubscript{2}, \textit{N}\textsubscript{2}−\textit{C}, and \textit{C}−\textit{N}\textsubscript{3} (Scheme 19). Hindered rotation about \textit{N}\textsubscript{1}−\textit{N}\textsubscript{2} can give rise to rotamers which is quite common in \textit{N}-nitroso compounds. Rotational barrier about the \textit{C}−\textit{N}\textsubscript{3} has been proposed to be much more than in common amides and related compounds possibly owing to greater dipolar resonance contributions and intramolecular hydrogen bonding (Scheme 19).\cite{21d} Due to this, the NH resonances in \textsuperscript{1}H NMR are separated by approx. δ = 1.30 ppm and appear as broad peaks because of quadrupolar effect of \textsuperscript{14}N.

![Scheme 19. Mechanism of hindered rotation about C−N\textsuperscript{3} bond.](image-url)
It has been reported in nonpolar aprotic solvents, that compounds like 34 adopt a conformation wherein the nitroso group is aligned syn to the haloethyl moiety, the nitroso nitrogen lone pair anti to it, and this has been corroborated by single crystal XRD data as well as by NMR spectroscopic measurements.\cite{21d} Assessment of the correct conformation in CENUs is also supplemented by the $^{2}J(^{15}\text{NO},^{13}\text{CO}) = 5.0–3.66$ Hz in accordance with 'W' conformation of this moiety and is in close agreement to the expected trans value by reference to model compounds. In a related molecule, viz. MeCCNU, XRD data suggests the bonding distance between the NH proton and nitroso group to be 2.28 Å, which is well below the maximum allowed value for bonding to occur (3.20 Å). This evidence has been presented for weak intramolecular hydrogen bonding between the NH proton and the nitrogen lone pair of the nitroso group, and this information is believed to be one of the reasons for the CENUs to adopt a single conformation in nonpolar solvents.

Scheme 20. Observed rotamers of 34 in nonpolar solvents and aqueous solution.
On the other hand, the decomposition of \( N \)-nitrosoureas in aqueous solution proceeds via the formation of a tetrahedral intermediate arising from the hydration of the carbonyl group, and the secondary products so obtained are highly dependent on the \( pH \) of the reaction medium; the rate of the reaction being dependent on the nature and concentration of the buffer so used.\(^{[21d]}\)

Scheme 21 outlines the intent behind the utilization of various bases for the study of the decomposition of suitable \( N \)-nitrosoureas like \( 34 \) under nonpolar aprotic conditions. The deprotonation of the amide proton by base leads to the formation of isocyanic acid\(^{[21i]}\) (HNCO) and the syn diazotate fragment which is perfectly aligned for intramolecular \( S_N2 \) substitution at the carbon bonded to the nucleofuge and therefore directly results in the formation of \( 15 \). The subsequent decomposition products possible can be accounted from \( 15 \). Ethylene oxide formation results from the extrusion of dinitrogen and subsequent \( S_Ni \) (ring closure) reaction. Loss of dinitrogen and simultaneous 1,2-H shift can lead to the acetaldehyde. Formation of diazomethane and formaldehyde can be presented as an example of 1,3-dipolar cycloreversion reaction.

**Scheme 21.** Mechanism of formation of \( 15 \) and the subsequent secondary products.
Since the studies conducted on the decomposition of suitably substituted HENU's under physiological conditions only implicated 15 as an intermediate to rationalize the observed secondary products, viz., acetaldehyde and ethylene glycol,\textsuperscript{21c} it is only logical to devise methods to generate 15 under low temperature conditions with suitable bases to circumvent the probable thermal instability of the dihydrooxadiazole 15.
2.1.1 Study of the reaction of $N$-(2-chloroethyl)-$N$-nitrosourea (34) with thallium(I) alkoxides

Thallium(I) alkoxides are versatile bases\textsuperscript{[26]} which have seldom found effective utilization in the field of organic synthesis. Generally, inorganic bases containing sodium, potassium, lithium, etc. are used in organic transformations owing to their ready availability and wide applicability. But, reactions where NMR spectroscopic monitoring is required at subzero temperatures, for example, in characterization of highly unstable reaction intermediates, these general sodium/potassium/lithium bases are of limited use as reagents because of their low solubility in organic solvents.

Thallium(I) alkoxides, however are soluble in a range of organic solvents such as diethyl ether, benzene, toluene, chloroform and dichloromethane. Thallium cation although analogous to alkali metal cations, displays considerable covalent character when bonded to oxygen and/or nitrogen atoms, which are in turn bonded to alkyl groups.\textsuperscript{[26d]} The state of aggregation in these alkoxides has been found to be tetrameric in solutions based on cryoscopic or ebullioscopic relative molecular mass determinations. X-ray data for thallium methoxide (TIOMe) suggests the presence of thallium atoms occupying the corners of a regular tetrahedron.\textsuperscript{[26a,b]} The covalent character of these alkoxides is probably responsible for their solubility in organic solvents.

The synthesis of thallium(I) ($E$)-methanediazotate\textsuperscript{[26d]} as reported by Keefer et al. is an interesting example whose structure has been elucidated by XRD technique and is very stable as against the potassium analogue which is extremely moisture-sensitive and requires tedious techniques for re-crystallization. This report throws light on the stabilisation provided by thallium ion to such a delicate diazotate moiety which is totally unprecedented in the sodium/potassium analogues.

These qualities of thallium(I) alkoxides were adequate for utilization of these bases in reaction with 34 and other $N$-nitrosoareas at low temperatures to study the generation of 15 and subsequent decomposition to the secondary products (Scheme 21).
2.1.1.1 Reaction of \( N-(2\text{-chloroethyl})-N\text{-nitrosourea} \) (34) with thallium(I) ethoxide

Thallium(I) ethoxide (TlOEt) is commercially available as a dense liquid (\( d = 3.522 \text{ g/ml at 25 }^\circ\text{C} \)). It exists also as a tetramer in solution as confirmed by \(^{203}\text{Tl}\) and \(^{205}\text{Tl}\) NMR data.\(^{[26b]}\) It was first used in experiments with 34 in the temperature range −40 °C to −20 °C to generate 15. The idea was to clarify whether 15 can be identified by continuous monitoring with NMR spectroscopy. TlOEt (1.0 eq) was added to a solution of 34 in \( \text{CD}_2\text{Cl}_2 \) maintained at −40 °C, and the reaction mixture was monitored by NMR spectroscopy up to −20 °C. Immediately, in \(^1\text{H} \) NMR spectrum, ethylene oxide was identified as a singlet at \( \delta = 2.66 \) ppm, acetaldehyde in traces, and diazomethane as a singlet at \( \delta = 3.33 \) ppm in traces along with strong signals of 1-ethoxyethyl carbamate (38).

![Scheme 22](image-url)
Formaldehyde which should also be formed along with diazomethane in small amounts was not observed which was as expected because it is a highly electrophilic aldehyde and may have reacted with TIOEt to give a plethora of products in miniscule amounts.

The formation of 1-ethoxyethyl carbamate (38) can be explained by two plausible mechanistic pathways. First, the isocyanic acid so formed undergoes nucleophilic addition with TIOEt to give urethane 35 which undergoes nucleophilic substitution reaction with the thallium-hemiacetal 36, which in turn, is formed by nucleophilic addition of TIOEt with acetaldehyde, to give carbamate 38 (Scheme 22). The formation of 38 from urethane 35 and thallium-hemiacetal 36 involves the tetrahedral intermediate 37 which ultimately splits off ethoxide to afford the carbamate product.

Alternatively, the formation of carbamate 38 can also be rationalized as a nucleophilic addition reaction between thallium-hemiacetal 36 and isocyanic acid wherein the HOMO of 36 interacts with π* of the carbonyl group of isocyanic acid (Scheme 23).

Scheme 23. Alternative mechanism for the formation of 1-ethoxyethyl carbamate (38).

The identification of diazomethane in traces as a secondary product of 15 is unprecedented and can be rationalized by 1,3-dipolar cycloreversion of 15. Since this mode of decomposition of 15 has been proposed to be the most favourable one based on quantum chemical calculations, the detection of diazomethane is of paramount significance to assert the intermediacy of 15 in base induced decomposition of suitably substituted N-nitrosoureas.

The formation of CH₂N₂ + [HCHO] from 15 can be interpreted as a 1,3-dipolar cycloreversion producing the octet-stabilized propargyl-allenyl type diazomethane and formaldehyde with a C=O bond.
This type of cycloreversion, in general, can be induced thermally, photochemically or by electron impact. Orbital symmetry, in case of thermal cycloreversion from the ground state dictates that these processes are allowed as suprafacial reactions with respect to both the fragments involving an aromatic (Hückel) transition state. Thus, the formation of diazomethane and formaldehyde from 15 can be regarded as a $[\sigma_2s + \sigma_2s + \omega_2s]$-concerted reaction.

The transition state geometry in these reactions mainly depends on the nature of the 1,3-dipole fragment. *Ab initio* MO calculations conducted on allyl-type 1,3-dipoles propose a parallel-plane transitions state, however, in case of propargyl-allenyl type of 1,3-dipoles (for e.g., CH$_2$N$_2$), calculations show a one-plane transition state to be the most likely one (Scheme 24).[28]

**Scheme 24.** General mechanism of 1,3-dipolar cycloreversions and possible analogy with formation or cleavage of dihydrooxadiazole 15.
No signals of the dihydrooxadiazole 15 (presumably an AA‘BB’ system) were, however, observed in the entire temperature range (−40 °C to −20 °C).

Since 15 was still elusive, it was only logical to study the reaction of 34 with TIOEt at even lower temperatures by NMR spectroscopy. Therefore, 34 was reacted with TIOEt (1.1 eq) in CD₂Cl₂ at −90 °C and monitored by NMR spectroscopy. The idea was that at such lower temperatures, the decomposition of 15 could be slowed down and its characterisation might be possible.

![Figure 3](image)

**Figure 3.**¹H NMR spectrum of the reaction between 34 and TIOEt at −90 °C in CD₂Cl₂.

As can be seen in Figure 3, even at −90 °C ethylene oxide, acetaldehyde and diazomethane can be identified clearly as the secondary products of 15 along with greater amounts of unreacted 34. Acetaldehyde can be seen in lesser amounts at such a lower temperature but, on warming to −20 °C, it was almost totally converted to 38.
Identity of products was also confirmed by $^1$H, $^1$H gCOSY spectrum at $-80$ °C.

The fact, that 15 could still not be detected and only the decomposition products were observed, hints towards the inherent instability of 15 probably due to the weak N−O bond and interaction of lone pairs of the NNO part in 15. The clear signal of diazomethane at $-90$ °C provides support to the decomposition via 1,3-dipolar cycloreversion of 15.

Furthermore, to ensure that acetaldehyde was not directly resulting from TIOEt by transfer and loss of hydride as in Meerwein–Ponndorf–Verley (MPV) reduction (Scheme 25), a different thallium alkoxide, viz., thallium propoxide (TlOPr) was also employed in the monitoring of reaction with 34 by NMR spectroscopy.

![Scheme 25](image.png)

**Scheme 25.** General mechanism of MPV reduction using Aluminum alkoxides.
2.1.1.2 Reaction of \( N-(2\text{-chloroethyl})-N\text{-nitrosourea} (34) \) with thallium(I) propoxide

Thallium(I) propoxide, TlOPr, was synthesized from commercially available TIOEt by a known procedure involving an exchange reaction in \( n\text{-propanol} \).\(^{[26b]}\) Unlike TIOEt, it is a white crystalline solid. TlOPr, like TIOEt is a moisture-sensitive compound and should be stored under nitrogen atmosphere. It is also soluble in organic solvents like diethyl ether, benzene, toluene, dichloromethane, and chloroform, making it a highly useful base to be employed in NMR monitoring experiments at lower temperatures.

![Scheme 26. Reaction of 34 with TlOPr and observed products.](image)

TlOPr (1.1 eq) was reacted with 34 in CD\(_2\)Cl\(_2\) at \(-60 \, ^\circ\text{C}\), and the reaction was monitored by NMR spectroscopy up to \(-20 \, ^\circ\text{C}\). Even at \(-60 \, ^\circ\text{C}\), ethylene oxide, acetaldehyde, diazomethane, and 1-propoxyethyl carbamate (39) (trace) could be identified along with unreacted \( N\text{-nitrosourea} (34) \). The mechanism of formation of the observed products is similar to that discussed in previous section and can be understood as detailed in Scheme 22, 23, and 26. In this case, however, the aldehyde ethanal was observed in much greater yields as acetaldehyde in the reaction of 34 with
TIOEt wherein ethanal was observed in traces as almost all of it was converted to carbamate 38.

This result proved that acetaldehyde did not result from TIOEt via a Meerwein–Ponndorf–Verley (MPV) reaction as discussed in the previous section, and was an actual decomposition product of 15. In this case also, no signals of the corresponding dihydrooxadiazole 15 were observed.

The products obtained in the reaction of 34 with TIOEt and TIOPr are summarized in Table 1 for convenience.

**Table 1.** Yield[^a] of products obtained from 34 and thallium(I) alkoxides.

<table>
<thead>
<tr>
<th>Base</th>
<th>Temperature (°C)</th>
<th>CH₃CHO</th>
<th>Ethylene Oxide</th>
<th>Diazomethane</th>
<th>Carbamate 38 or 39</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIOEt</td>
<td>−20 °C</td>
<td>trace</td>
<td>15%</td>
<td>Trace</td>
<td>67%</td>
</tr>
<tr>
<td>TIOPr</td>
<td>−20 °C</td>
<td>32%</td>
<td>28%</td>
<td>3%</td>
<td>trace</td>
</tr>
</tbody>
</table>

[^a]: Yields were measured by ¹H NMR spectroscopy using an internal standard.

The most striking difference encountered in the reaction of 34 with TIOPr when compared to that with TIOEt was the higher yield of diazomethane (3% yield) as against traces observed with TIOEt. This result was very peculiar and therefore, it became necessary to test the stability of diazomethane in the presence of both of these bases.
2.1.1.3 Stability of diazomethane in the presence of TIOEt and TIOPr

Stability of diazomethane in the presence of TIOEt:

Diazomethane was synthesized by using a general procedure utilizing \(N\)-methyl-\(N\)-nitrosourea\(^{[30a]}\) and KOH/H\(_2\)O/CDC\(_3\)\(_3\).\(^{[30b]}\) 2.0 equivalents of TIOEt were added to the CH\(_2\)N\(_2\) solution in CDC\(_3\) maintained at \(-10^\circ\)C, and after 15 min, \(^1\)H NMR indicated 92% reduction in the concentration (with respect to the solvent) of diazomethane as against negligible reduction observed in the NMR tube containing pure diazomethane solution. A small amount of occlusion was visible in the NMR tube containing TIOEt which could not be identified owing to its insolvability.

Stability of diazomethane in the presence of TIOPr:

Similarly, in line with the above experiment, TIOPr (1.1 eq) showed a 17% decrease in the concentration of diazomethane at \(-10^\circ\)C after 20 min with respect to solvent in \(^1\)H NMR.

The much greater reduction in the concentration of diazomethane in the presence of TIOEt as compared to TIOPr is in accordance with the results of the experiment of \(N\)-nitrosourea 34 with these bases, wherein, the reaction of 34 with TIOEt gave only traces of diazomethane, and on the other hand with TIOPr, approximately 3% yield of diazomethane was observed.

Since the yield of diazomethane was very small and its identity being confirmed only by \(^1\)H NMR and \(^1\)H,\(^1\)H gCOSY, it was necessary to clarify whether the signal at \(\delta = 3.32\) ppm in \(^1\)H NMR belonged to diazomethane. \(^{13}\)C NMR was of no help, since the extremely low concentration of diazomethane coupled with the very slow relaxation of diazo carbon, rendered this NMR method inadequate. To dispel any doubts about the identity of diazomethane, the \(^{15}\)N analogue of 34 was synthesized and its reaction with thallium alkoxides was monitored by NMR spectroscopy, mainly by \(^{15}\)N NMR spectroscopy.
2.1.2 Synthesis of the $^{15}$N analogue of 34 and monitoring of its reaction with thallium(I) alkoxides

$^{15}$N labelled analogue 40 of N-(2-chloroethyl)-N-nitrosourea 34 was synthesized analogously to the general procedure$^{[21h]}$ by the nitrosation of N-(2-chloroethyl) urea with Na$^{15}$NO$_2$/H$_2$SO$_4$ in 24% yield as a cream coloured solid.

\[ \text{Cl}N\text{H}_2\text{NH}_2 + \text{Na}^{15}\text{NO}_2/\text{H}_2\text{SO}_4 \xrightarrow{\text{Ice-bath, 30 min}} \text{Cl}N^{15}\text{NO}\text{NH}_2 \]  

\[ \text{N-}(2\text{-chloroethyl})\text{urea} \quad 40 \]

\[ \text{Cl}N\text{H}_2\text{NH}_2^{15}\text{NO} \xrightarrow{\text{TlOR, } -80 \degree \text{C}} \text{N}^2\text{N}^{15}\text{O}^{15}\text{N} \]

\[ 15a \]

\[ \text{CH}_2N^{15}\text{N} + \text{N}^2\text{N} \]

\[ (\text{by } ^{15}\text{N NMR spectroscopy}) \quad + \quad \text{other products of } 15 \]

Scheme 27. Synthesis of $^{15}$N labelled 40 and its reaction with TIOR

The monitoring of the reaction of 40 with TIOR mainly by $^{15}$N NMR spectroscopy was undertaken to, besides confirming the formation of diazomethane, also determine whether the formation of ethylene and nitrous oxide from 15 was occurring by 1,3-dipolar cycloversion. Since no signal corresponding to ethylene was observed in the corresponding $^1$H NMR as discussed in sections 2.1.1.1 and 2.1.1.2, the possibility of detecting nitrous oxide was bleak, but to exclude this mode of decomposition of 15, this study was necessary. With the help of $^{15}$N NMR spectroscopy at very low temperatures, the identification of N$_2$O might be possible.
Firstly, TIOEt was employed to monitor the reaction of 40 at very low temperatures by $^{15}$N NMR, $^1$H NMR and relevant 2D NMR techniques. $^{15}$N labelled 40 was reacted with TIOEt (1.1 eq) in CD$_2$Cl$_2$ at −80 °C and the reaction was monitored by $^{15}$N NMR spectroscopy. Immediately, in the $^{15}$N NMR spectrum, a singlet at $\delta = -69.74$ ppm$^{[31]}$ corresponding to $^{15}$N≡N along with $^{15}$NO signal of unreacted 40 at $\delta = 184.33$ ppm could be clearly observed (Figure 4). The fact that even dinitrogen gas was detected at −80 °C clearly points towards the inherent instability of 15/15a and rationalization given in the sections 2.1.1.1 and 2.1.1.2 for the products so observed is completely ratified. Since, diazomethane was only observed in traces in the reaction of 34 with TIOEt, no corresponding $^{15}$N NMR signal of diazomethane was observed in this experiment also.

![Figure 4. $^{15}$N NMR spectrum measured at −80 °C after treating 40 with TIOEt.](image-url)
From −80 °C to −50 °C, a continuous increase in the intensity of \(^{15}\text{N}=\text{N}\) and a consequent decrease in the \(^{15}\text{NO}\) signal of 40 was observed. No signal corresponding to \(^{15}\text{N}\)=\text{NO}\) (at around \(\delta = -229.60\) ppm; measured in DMSO-d\(_6\))\(^{[31]}\) was observed; thereby, eliminating the possibility of 1,3-dipolar cycloreversion of 15 to ethylene and nitrous oxide. Dihydrooxadiazole 15 can be considered to be a product of 1,3-dipolar cycloaddition reaction between nitrous oxide (1,3-dipole) and ethylene (dipolarophile), but, as observed, the 1,3-dipolar cycloreversion reaction does not lead to the reacting partners, a general outcome of these cycloaddition/cycloreversion mechanisms.

Similarly, TiOPr was utilized in reaction with 40 and the reaction was monitored by NMR spectroscopy from −80 °C to −10 °C.

**Figure 5.** \(^{15}\text{N}\) NMR spectrum measured at −80 °C after treating 40 with TiOPr.
The idea behind this reaction was to confirm the identity of diazomethane (CH$_2$N$^{15}$N in this case). $^{15}$N labelled 40 was reacted with TIOPr (1.1 eq) in CD$_2$Cl$_2$ at −80 °C and the reaction was monitored by $^{15}$N NMR spectroscopy within the temperature range −80 °C to −10 °C. In this case, also, we observed in the $^{15}$N NMR spectrum at −80 °C, signals of $^{15}$N≡N and $^{15}$NO signal of unreacted 40 along with a clearly visible signal of CH$_2$N$^{15}$N at $\delta = 14.17$ ppm and the corresponding doublet with $\delta = 3.34$ ppm and $^3J(^{15}$N,$^1$H) = 1.1 Hz in the $^1$H NMR spectrum.[21e,31,32] 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$_2$N$^{15}$N for comparison from $^{15}$NO labelled $N$-methyl-$N$-nitrosourea (synthesized analogously to the well-known procedure of synthesis of diazomethane) and KOH in H$_2$O/CD$_2$Cl$_2$.[30]

As was observed in the case of the reaction of 40 with TIOEt, here also, there was an increase in the intensity of $^{15}$N≡N and a consequent decrease in the $^{15}$NO signal of 40 in the $^{15}$N NMR spectrum as the temperature was increased. No $^{15}$N signal corresponding to nitrous oxide in the entire temperature range was observed in this case also, thus, eliminating the possibility of cycloreversion of 15 to ethylene as a mode of decomposition.

The synthesis of CH$_2$N$^{15}$N was also realized by the reaction of $^{15}$NO labelled $N$-methyl-$N$-nitrosourea with TIOPr in CD$_2$Cl$_2$. Along with CH$_2$N$^{15}$N, surprisingly, we also observed very clear signals of thallium(I) (Z)-methanediazotate (41) (Scheme 28); a highly elusive diazotate which could not be characterized till date. Thallium(I) (E)-methanediazotate has been characterized[26d] by Keefer et al. by NMR spectroscopy and XRD, but, they were unable to characterize the (Z) isomer 41 citing its high reactivity towards moisture.

Scheme 28. Synthesis of thallium(I) (Z)-methanediazotate
Compound 41 was stable only for 2 h at −60 °C. This compound exhibited a well-defined doublet at $\delta = 3.17$ ppm and $^3J(^{15}\text{N},^1\text{H}) = 4.0$ Hz in $^1\text{H}$ NMR spectrum. In $^{15}\text{N}$ NMR spectrum, a signal at $\delta = 104.38$ ppm can be assigned to $^{15}\text{NO}$ in 41. In the $^{15}\text{N},^1\text{H}$ long-range (gHMBCAD) 2D NMR experiment, only one correlation peak was observed.

Since the NMR spectrum of 41 is totally different from the corresponding (E)-isomer, which exhibits a singlet at $\delta = 3.43$ ppm ($^1\text{H}$ NMR measured in CD$_2$Cl$_2$), and the fact that it is completely converted to diazomethane at room temperature (with respect to the solvent), corresponds only to the structure of elusive 41.

The experiments described in sections 2.1.1 and 2.1.2 clearly establish the instability of dihydrooxadiazole 15, and also its mode of decomposition into the secondary products so observed. In the next section, the formation of 15 from 34 has been described with various bases in order to test the generality of the reaction and also the effect of these bases on the nature of secondary products.
2.1.3 Study of the reaction between \( N-(2\text{-chloroethyl})-N\text{-nitrosourea} \) (34) and other bases

2.1.3.1 Reaction of \( N-(2\text{-chloroethyl})-N\text{-nitrosourea} \) (34) with KOH and aq. KOH

The first conventional base utilized to study the base-catalyzed decomposition of 34 was KOH. Finely ground solid KOH (3.0 eq) was reacted with 34 in \( \text{CD}_2\text{Cl}_2 \) at 0 °C, and the conversion was monitored by NMR spectroscopy. This was a heterogeneous reaction mixture since KOH is insoluble in \( \text{CD}_2\text{Cl}_2 \). At 0 °C, signals of secondary products of 15, viz., ethylene oxide and acetaldehyde (Scheme 22) could be seen in the \(^1\text{H} \) NMR spectrum, however, the reaction was very slow as indicated by the presence of unreacted 34. No signals corresponding to 15 were observed.

The formation of the observed products can be understood by the abstraction of amide proton by hydroxide and then the same mechanism being followed as outlined in Scheme 21.

On warming to room temperature, 34 was totally consumed and the signals of ethylene oxide (9% yield) and acetaldehyde (6% yield) grew in intensity. No diazomethane or formaldehyde was observed in this reaction.

Subsequently, aq. KOH was utilized next as a suitable base for monitoring the reaction with 34 by NMR spectroscopy. This reaction was inspired by the well known synthesis of diazomethane from \( N\text{-methyl-}N\text{-nitrosourea} \) wherein 40% aqueous KOH solution is utilized in a biphasic reaction medium at lower temperature. 3.0 equivalents of aq. KOH were added to a solution of 34 in \( \text{CD}_2\text{Cl}_2 \) at −20 °C and the reaction was monitored by NMR spectroscopy at the same temperature. The secondary products (Scheme 21), viz., ethylene oxide (17% yield), acetaldehyde (15% yield) along with new signals of \textit{trans}-2-butenal (4% yield) (Scheme 29) could be identified in the \(^1\text{H} \) NMR spectrum.\[^{33a}\]

No signals corresponding to 15 were obtained even in this case.

The formation of \textit{trans}-2-butenal or crotonaldehyde can be understood by KOH induced aldol condensation of acetaldehyde and the signals in the \(^1\text{H} \) NMR spectrum were compared with the literature available data for complete identification.
Scheme 29. Reaction of 34 with aq. KOH, observed secondary products. Yields were measured by $^1$H NMR spectroscopy using an internal standard.
2.1.3.2 Reaction of \(N\)-(2-chloroethyl)-\(N\)-nitrosourea (34) with amines as bases

Diisopropylamine (DIPA) was used as the first secondary amine to study the decomposition of 34 owing to its weakly basic nature and non-metallic properties. In contrast to KOH, DIPA is very soluble in organic solvents and therefore, it was utilized with the idea that this reaction could be monitored by NMR spectroscopy at even lower temperatures with a possibility to detect 15 and that the weakly basic properties coupled with slight steric hindrance would deter unwanted side reactions.

Diisopropylamine (2.0 eq) was added to a solution of 34 in \(\text{CD}_2\text{Cl}_2\) at 0 °C and the reaction was monitored by NMR spectroscopy. At 0 °C, however, no reaction was observed and therefore, the reaction mixture was warmed up to room temperature. At room temperature, ethylene oxide (4% yield) and acetaldehyde (3% yield) could be easily identified as secondary products of 15 in \(^1\text{H}\) NMR spectrum with no signals of elusive 15 being observed.

In this case, the abstraction of amide proton is achieved by the neutral diisopropylamine and then the usual mechanism is followed (Scheme 21). The nucleofuge chloride is captured by the protonated diisopropylammonium cation to give the corresponding hydrochloride salt.

Subsequently, 2,2,6,6-tetramethylpiperidine (TEMP), a hindered organic base which is slightly less basic than diisopropylamine, was utilized in the reaction with 34 with the view that the hindered nature would impede unwanted reactions and because of its good solubility in organic solvents, monitoring by NMR spectroscopy would be easier.

2.0 equivalents of TEMP were added to a solution of 34 in \(\text{CD}_2\text{Cl}_2\) at 0 °C and the reaction was monitored by NMR spectroscopy. At 0 °C, the reaction was minimal and the reaction mixture was warmed up to room temperature for completion. At room temperature, the same secondary products as seen with DIPA, viz., ethylene oxide (3% yield), acetaldehyde (4% yield) and diazomethane (in traces) were observed in the \(^1\text{H}\) NMR spectrum (Scheme 30), thereby confirming the intermediacy of 15 in this reaction.
Scheme 30. Reaction of 34 with TEMP and observed secondary products. Yields were measured by $^1$H NMR spectroscopy using an internal standard.

As has been described in this section, in all cases, the observed secondary products of 15 are ethylene oxide and acetaldehyde with the exception of the reaction of 34 with aqueous KOH wherein crotonaldehyde was also observed as a secondary product of the already formed acetaldehyde and the reaction of 34 with TEMP wherein traces of diazomethane were observed. Yields of the products in sections 2.1.1 to 2.1.4 are represented in tabular form (Table 2) for convenience.

Table 2. Yield[a] of the products formed from 34 and suitable bases in CD$_2$Cl$_2$.

<table>
<thead>
<tr>
<th>Base</th>
<th>Temperature (°C)</th>
<th>CH$_3$CHO</th>
<th>Ethylene oxide</th>
<th>Diazomethane</th>
</tr>
</thead>
<tbody>
<tr>
<td>KOH</td>
<td>r.t.</td>
<td>6%</td>
<td>9%</td>
<td>-</td>
</tr>
<tr>
<td>Aq. KOH</td>
<td>$-20^\circ$C</td>
<td>15%</td>
<td>17%</td>
<td>-</td>
</tr>
<tr>
<td>DIPA</td>
<td>r.t.</td>
<td>3%</td>
<td>4%</td>
<td>-</td>
</tr>
<tr>
<td>TEMP</td>
<td>r.t.</td>
<td>4%</td>
<td>3%</td>
<td>traces</td>
</tr>
</tbody>
</table>

[a] Yields were measured by $^1$H NMR spectroscopy using solvent as internal standard.

Similarly, sodium methoxide (NaOMe) was also used to study the decomposition of 34 at low temperatures. N-nitrosourea 34 was dissolved in THF-$d_8$, cooled to $-40^\circ$C, and treated with NaOMe (1.1 eq) in 0.1 mL CD$_3$OD. Immediately, ethylene oxide, acetaldehyde, and hemiacetal 42[$^{33b}$] could be identified as the secondary products, but,
the reaction was not complete at this temperature. Therefore, the reaction mixture was warmed to 0 °C, and subsequently to room temperature, but the reaction remained incomplete. However, the yields of the products so obtained can be written based on consumed 34 as represented in Scheme 31.

\[
34 \xrightarrow{\text{NaOMe/CD}_2\text{OD}} \underset{-40 \degree \text{C to } 0 \degree \text{C}}{\text{THF-}d_6} \xrightarrow{\triangle} \text{CH}_3\text{CHO} + \text{MeOH} + \text{H}_2\text{C}-\text{OH} \quad 16\% \quad 4\% \quad 25\%
\]

**Scheme 31.** Ratio of products obtained in the reaction of NaOMe with 34. Yields are based on consumed 34.

The objective of utilizing different bases, including amines and alkali metal based, was to study the effect of the base on the primary decomposition products of 15. However, identical decomposition products were observed as with thallium(I) alkoxides within the limits of the individual experimental conditions.
2.1.4 Synthesis of \( N\)-(2-tosyloxyethyl)-\( N\)-nitrosoourea (44) and its reaction with TIOPr

\( N\)-(2-tosyloxyethyl)-\( N\)-nitrosoourea (44) was synthesized from the literature known \( N\)-(2-hydroxyethyl)-\( N\)-nitrosoourea (43)\(^{[34]}\) by general tosylation procedure (Scheme 32) utilizing TsCl/py. Tosyloxy group (OTs) is considered to be a very good leaving group in \( S_N2 \) reaction, and as the mechanism of decomposition of suitably substituted \( N\)-nitrosooureas having good leaving groups, involves an intramolecular \( S_N2 \) attack of the diazotate-oxygen (Scheme 21), this seemed to be a good choice for studying the reaction with TIOPr at low temperature.

\[ \begin{align*}
\text{TsCl/py} & \quad \text{−20 °C} \\
\text{HO} & \quad \text{TsO} \\
43 & \quad 44 \quad 50\%
\end{align*} \]

Scheme 32. Synthesis of \( N\)-(2-tosyloxyethyl)-\( N\)-nitrosoourea 44.

\( N\)-nitrosoourea 44 was reacted with TIOPr (1.1 eq) in THF-d\(_8\) at −40 °C and the reaction was monitored by \(^1\)H NMR spectroscopy. Ethylene oxide and acetaldehyde can be identified as products, but the reaction did not reach completion even at room temperature. Diazomethane, if formed, could not be identified because of overlapping signals in the required range. There could be two reasons for incomplete reaction: a) relatively low solubility of 44 as compared to 34; b) although, \(^1\)H NMR of 44 indicated the formation of a single rotamer, but, concrete information about the type of conformation cannot be said with certainty.

\[ \begin{align*}
\text{TsO} & \quad \text{NO} \quad \text{NH}_2 \\
\text{44} & \quad \text{TIOPr} \quad \text{THF-d}_8 \quad \text{−40 °C to RT} \\
& \quad \text{O} \quad + \quad \text{CH}_3\text{CHO} \\
\end{align*} \]

Scheme 33. Ratio of products obtained in the reaction of 44 with TIOPr.
2.1.5 Synthesis of N-(2-hydroxyethyl)-N-nitroso urea (43) and its reaction with TlOPr

The study of the reaction of N-(2-hydroxyethyl)-N-nitroso urea (43) with TlOPr was envisioned to understand its mechanism of decomposition under basic conditions.

![Scheme 34](image)

**Scheme 34.** Mechanism of product formation obtained in the reaction of 43 with TlOPr.

43 was reacted with TlOPr (1.1 eq) in CD$_2$Cl$_2$ at -20 °C and the reaction was monitored by $^1$H NMR spectroscopy. Because 43 has limited solubility in dichloromethane, the reaction did not reach completion, nevertheless, ethylene oxide, acetaldehyde, and diazomethane could be identified as depicted in Scheme 34.

This reaction proceeds with abstraction of amide proton by TlOPr, producing thallium-diazotate 45/46, which on protonation give rise 47. Loss of water yields betain 48, which can either give the observed products by itself or cyclize to dihydrooxadiazole 15 and then decompose to the observed products (Scheme 34).

A previous study$^{[35]}$ of base catalyzed decomposition (under aqueous buffer) of 43; however found only acetaldehyde, and ethylene glycol as decomposition products.
since the conditions of the experiment would not be conclusive for the stability of diazomethane.

This outcome of this reaction entails three possibilities:

a) It might be possible that 15, when formed in the reaction of thallium(I) alkoxides with 34 undergoes ring opening to betain 48 and then decomposes to the observed decay products. This mode of rearrangement can be possible through thallium-assisted catalysis. Thallium-cation can bond to oxygen-atom in 15, and thereby, weaken the N–O bond and accelerate heterolytic cleavage. However, it is highly likely that the cycloreversion of 15 to diazomethane is a non-synchronous normal process owing to the inherent weakness in the N–O bond, and thallium-cation has no role to play.

b) The cyclization of betain 48 to dihydrooxadiazole 15 is also a theoretical possibility with a very low energy barrier (unpublished results of Prof. J. Friedrich) and then the observed products can be accounted as per Scheme 21.

c) The possibility that both dihydrooxadiazole 15 and betain 48 decompose to the observed products by their own mechanisms and that there is no link between these two entities is also real.
2.1.6 Exploring the possibility of a diradical intermediate in the decomposition of dihydrooxadiazole 15.

Another plausible, but highly unlikely mode of decomposition of dihydrooxadiazole 15 involves the homolytic cleavage of the N−O bond in 15. However, the formation of acetaldehyde as one of the decomposition products of 15 via H-shift is less likely to occur from the diradical 49.

Scheme 35. Homolytic cleavage of 15 to give diradical 49.

In order to investigate the plausibility of a homolytic cleavage of 15, high level quantum chemicals were performed by B. Fiedler and J. Friedrich at TU Chemnitz. For an adequate quantum chemical description of the open-shell singlet state of 49, a multi-reference method such as CASPT2 is required. In order to capture the dynamic correlation at a higher level of theory, CCSD(T)(F12) was used to compute the energies of 15 and the triplet state of 49. CCSD(T) is adequate for these computations, since 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:

\[
\Delta E^{CCSD(T)(F12)} = E^{CCSD(T)(F12)}_{15\text{-triplet}} - E^{CCSD(T)(F12)}_{1\text{-singlet}} + \\
E^{CASPT2}_{15\text{-singlet}} - E^{CASPT2}_{15\text{-triplet}}
\]

(1)

The results of the CASPT2(6,6) calculations and those following equation (1) are collected in Table 3 for the two different conformers 49a and 49b. Since the dissociation energies of equation (1) and CASPT2 agree very well, these calculations provide the required accuracy to draw the conclusion: The dissociation energy is at least 145.2 kJ/mol, which is significantly higher than the activation barriers resulting
from other quantum chemical calculations for a concerted formation of acetaldehyde (being in the range of 75.7–97.5 kJ/mol) or diazomethane (being in the range of 81.8–105.5 kJ/mol).[20] These quantum chemical calculations provide enough evidence to exclude a homolytic cleavage of 15 to give 49.

Table 3. ZPVE- and COSMO-corrected reaction energies for the formation of 49a and 49b from 15 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).

<table>
<thead>
<tr>
<th>Conformer</th>
<th>$\Delta E^{\text{CASPT2}} + \Delta^{\text{solv}}$ [kJ/mol]</th>
<th>Eqn.1 + $\Delta^{\text{sof}}$ [kJ/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>49a</td>
<td>+ 145.2</td>
<td>+ 155.7</td>
</tr>
<tr>
<td>49b</td>
<td>+ 151.8</td>
<td>+ 162.5</td>
</tr>
</tbody>
</table>

Figure 6. Geometries of DFT-optimized conformers 49a (left) and 49b (right).

The energy-minimized structures of all compounds were obtained by RI-DFT geometry optimizations with the TURBOMOLE program package,[36] using the PW6B95 functional,[37] the TZVPP basis set,[38] Grimme's D3 dispersion correction,[39] and the COSMO model ($\epsilon = 8.9$).[40] The geometry optimization of 15 was carried out as closed-shell singlet and those of biradical 49 as triplet. The CASPT2 calculations were performed with MOLPRO[41] and the CCSD(T)(F12) calculations with TURBOMOLE.[36,42]
The resulting single point energies of 15, 49a, and 49b were corrected by the zero point vibrational energies (ZPVE) and a solvation contribution ($\Delta^{\text{solv}}$), both obtained from the DFT calculations. The solvation correction was computed from DFT single-point energies with and without using the COSMO model.

**Note:** The quantum chemical calculations mentioned in this entire section were carried out by Prof. Joachim Friedrich and Mr. Benjamin Fiedler of the Theoretical Chemistry of TU Chemnitz. These data have been mentioned here as they provide a part of the complete picture for the mode of decomposition of the dihydrooxadiazole 15.
2.1.7 Synthesis of 3-methyl-4,5-dihydro-1,2,3-oxadiazolium tosylate (18) and the study of the reaction with suitable nucleophiles

Different suitable nucleophiles were reacted with the oxadiazolinium salt 18 in order to study the mechanism of the reaction, and whether salt 18 functions as a methylating agent, thereby, generating dihydrooxadiazole 15 as mentioned in Section 1.4.3.

2.1.7.1 Synthesis of 3-methyl-4,5-dihydro-1,2,3-oxadiazolium tosylate (18), determination of its structure, and possible sites for nucleophilic attack

Compound 18 was synthesized through the literature known method.[18c,i] The structure for 18, as known in literature, was assigned only on the basis of $^1$H NMR and $^{13}$C NMR data, which for such compounds with an intriguing structure is not sufficient. This is similar to other oxadiazole compounds[43] wherein XRD data were imperative for unambiguous structure elucidation. Therefore, to be sure of the structure and chemistry of 18, its structure was assigned by single crystal XRD.[44] X-ray quality crystals were grown from a mixture of CH$_2$Cl$_2$/Et$_2$O kept −20 °C for a period of 21 days.

![Figure 7. ORTEP representation (50% probability level) of the molecular structure of 18 with atom numbering scheme; hydrogen atoms and further co-crystallized species (H$_3$O$^+$, TsO$^-$) are omitted for clarity. XRD analysis performed by M. Korb and H. Lang of the inorganic chemistry of TU Chemnitz.](image-url)
The presence of positive charge on N1 atom and the presence of N=N double bond was verified first, by a short N1–N2 bond distance of 1.238(3) Å, and furthermore, by the flat geometry of the heterocyclic core. The C17 atom (methyl group) is shifted out of plane by 0.065(4) Å, thereby, concluding the presence of a $sp^2$ hybridised N1 atom.

Oxadiazolinium salt 18 can considered to be an approximate model compound for the biologically activated form of N-(2-hydroxyethyl)-N-nitrosomethylamine$^{[18c]}$ (33), a potent hepatocarcinogen. Compound 33 is considered to be responsible for genetic alteration caused by DNA methylation/hydroxyalkylation, thereby resulting in the phenotypic expression, cancer. Since, oxadiazolinium salt 18 differs from 33 only in the nature of counter-anion, the mechanism of its action should also closely mimic that of 33.

Scheme 36. Possible sites of nucleophilic attack on 18 and the resulting type of products.

Compound 18 was chosen as suitable candidate for generating dihydrooxadiazole 15 based on some reports in literature, wherein, the methylating nature of 15 was prominent. Since, demethylation of 18 should directly lead to 15; this method could be the most promising to discuss about the chemical nature and the decomposition products of 15.

Mechanistically, there can be three possible sites for nucleophilic attack on 18 (Scheme 35). Reaction at site "a" will directly lead to dihydrooxadiazole 15 (the desired product) and subsequently to its secondary products (Scheme 21). Reaction at site "b" would
lead to open chain rotamers of type B. Furthermore, reaction at site "c" should lead to compounds of type C.

Quantum chemical calculations[22a] performed on 18 at the 6–31G* basis set level reveal that both the sites, "a" and "b", are susceptible to nucleophilic attack because of the high electropositive charge density on these carbon atoms. On the other hand, calculations show that site "c" is a poorer site for nucleophilic attack. These calculations also predict that carbon 4 might be a softer site (HSAB principle) relative to carbon 6 (Me group).

Furthermore, ab initio level calculations reveal that for dihydrooxadiazole 15 so formed from attack at site "a", the most energetically favorable path of its decomposition should be the formation of diazomethane and formaldehyde based on the inherent weakness of the N–O bond (predicted on the basis of heats of formation).

Therefore, in order to exploit the possible demethylating ability of 18 to generate 15, firstly, literature known examples wherein methylated products were obtained in good to excellent yields from 18 were explored, and furthermore, special nucleophiles were used in reaction with the salt 18.
2.1.7.2 Attemptes to reproduce the literature-reported methylating ability of oxadiazolinium tosylate 18

It was reported in literature, that the reaction of 18 with 3,4-dichlorothiophenol in dichloromethane produced a 90% yield of the corresponding methylated product 50.\textsuperscript{[18a]}

\begin{center}
\includegraphics[width=\textwidth]{scheme37.png}
\end{center}

\textbf{Scheme 37.} Supposed examples exhibiting methylating ability of 18 as described in few reports.

The reaction of 18 with 3,4-dichlorothiophenol (1.0 eq/ 2.0 eq) was now performed (repeated) in chloroform at room temperature, under reflux, etc. but in none of the cases, compound 50 was found even in traces, instead, a complex mixture was obtained in each case. The use of 3,4-dichlorothiophenol, as a trapping agent for alkylating intermediates like 18, has been questioned in another report.\textsuperscript{[18d]} In their study with \textit{N},\textit{N}-dimethyl-\textit{N}-nitrosamine, they asserted that methylated thioether 50, was produced as an artifact of the analytical procedure. In \textit{\textsuperscript{1}H} NMR spectra, there was no signal at $\delta = 2.47$ ppm for methyl protons, and in \textit{\textsuperscript{13}C} NMR spectra, no signal was observed at $\delta = 15.78$ ppm for methyl carbon of 50.

Similarly, reports on methylation of morpholine by 18 to give \textit{N}-methylmorpholine (13% yield)\textsuperscript{[18h]} were found to be non-reproducible under various reaction conditions, and no signals corresponding to the methyl protons of product 51 were found at $\delta = 2.25$ ppm in \textit{\textsuperscript{1}H} NMR spectrum, and likewise no signal at $\delta = 46.43$ ppm in \textit{\textsuperscript{13}C} NMR spectrum.

Because of uncertain reports in literature, hexadecyltributylphosphonium (Q) based nucleophiles were used next, which are especially useful in monitoring of difficult
nucleophilic substitution reactions by NMR spectroscopy even at very low temperatures\textsuperscript{[27]} owing to their excellent solubility in organic solvents. Other suitable nucleophiles were also utilized to study the displacement reaction under a high number of different conditions.
2.1.7.3 Study of the reaction between oxadiazolinium tosylate 18 and QN₃ or tetramethylguanidinium azide (TMGA)

Hexadecyltributylphosphonium azide (QN₃) (2.0 eq) was added to a solution of 18 in CDCl₃ at −45 °C and the reaction was monitored by ¹H NMR spectroscopy. Immediately, we could observe the azide-containing product 52 (which can exist as two rotamers), and methyl azide[45] along with unreacted 18 (Scheme 38). The reaction was completed after 40 min. The formation of 52 (61% yield) can be interpreted as a result of attack of the needle-like azide nucleophile at carbon 5 of 18 and consequent ring opening. This result was expected because C-5 is one of the most electropositive atoms in 18, as predicted by ab initio calculation. The observation of methyl azide (17% yield) in this reaction was an encouraging sign, as it meant that a S_N2 reaction was also occurring at the methyl carbon (C6) to give the methyl azide and consequently, dihydrooxadiazole 15. However, none of the decomposition products of 15 or signals corresponding to 15 were observed. This formation of methyl azide can only be interpreted as a product of the instability of 52 in the presence of QN₃.

Scheme 38. Reaction of oxadiazolinium tosylate 18 with QN₃.

After complete consumption of 18, the reaction mixture was maintained at −20 °C for another 24 h, and ¹H NMR spectrum was measured. Surprisingly, it was found that the yield of methyl azide had increased to 23%.
This observed increase in the yield of methyl azide seems to confirm the interpretation that in the presence of QN₃, the azide 52 is not stable and slowly give methyl azide.

To be sure of our interpretation, in another experiment of 18 with QN₃, after complete reaction, all the volatiles including methyl azide were removed and the residue was again treated with QN₃ (1.0 eq). Again, methyl azide could be observed clearly in 5% yield. Methyl azide was confirmed by comparison of the NMR data in literature. These results of observed methyl azide should be considered as a FATA MORGANA, however, it is crystal clear that azidomethane is not formed by attack at the methyl group of 18.

Similarly, 18 was also treated with TMGA (2.0 eq) at −45 °C, and the reaction was monitored by NMR spectroscopy. As previously discussed with QN₃, same products, viz., 52 (77% yield) and methyl azide (15% yield) were observed after 1 h. These results indicate that the size and nature of the cation had little role to play.

**Scheme 39.** Reaction of oxadiazolinium tosylate 18 with tetramethylguanidinium azide (TMGA).

Furthermore, in the next section, many different nucleophiles such as bromide, iodide, thiocyanate, etc. were used in reactions with 18 to broaden this approach of attempted demethylation.
2.1.7.4 Study of the reaction between oxadiazolinium tosylate 18 and various suitable nucleophiles

2.1.7.4.1 Reaction with QI, QBr, and QSCN

First, hexadecyltributylphosphonium iodide (QI) was used in the reaction with 18. QI can be synthesized from QOMs (hexadecyltributylphosphonium mesylate) by simple exchange reaction with NaI in a mixture of Et₂O/water. The idea behind the reaction with QI was that the large size and polarisable nature of iodide would promote Sₙ₂ reaction at the N-methyl group of 18. QI (2.0 eq) was added to a solution of 18 in CDCl₃ at −45 °C and the reaction was monitored by NMR spectroscopy up to room temperature. After 30 min at room temperature, the iodo-substituted rotamers 53a and 53b could be identified with no signal of CH₃I at δ = 2.16 ppm in the ¹H NMR spectrum. Similarly, no signal at δ = −23.60 ppm was observed for methyl iodide in the corresponding ¹³C NMR spectrum.

Scheme 40. Reaction of oxadiazolinium tosylate 18 with various nucleophiles and origin of formation of rotamers.
As opposed to the reaction of 18 with QN₃, separate rotamers were observed in this case. Since no methyl iodide was observed, even in traces, no attack of the iodide at the N-methyl group of 18 had occurred in this case also.

Moreover, QBr and QSCN were used to study the reaction with 18 at low temperatures. QBr and QSCN were synthesized analogously to the synthesis of QI by exchange reaction with NaBr and NH₄SCN, respectively. No signal at δ = 2.68 ppm in ¹H NMR analysis for methyl bromide (CH₃Br) was observed. Similarly, no signal at δ = 2.60 ppm in ¹H NMR detection for methyl thiocyanate (CH₃SCN) was observed. Concise information about the reactions of 18 with QI, QBr, and QSCN are presented in Table 4.

Table 4. Yields[a] of the rotational isomers (rotamers) formed in the reaction of 18 with QI, QBr, and QSCN.

<table>
<thead>
<tr>
<th>Nucleophilic Agent</th>
<th>Temperature (°C)</th>
<th>Time (in min)</th>
<th>Rotamers 53/54/55</th>
</tr>
</thead>
<tbody>
<tr>
<td>QI</td>
<td>RT</td>
<td>30</td>
<td>83%</td>
</tr>
<tr>
<td>QBr</td>
<td>RT</td>
<td>45</td>
<td>87%</td>
</tr>
<tr>
<td>QSCN</td>
<td>RT</td>
<td>45</td>
<td>93%</td>
</tr>
</tbody>
</table>

[a] Yields were measured by ¹H NMR spectroscopy using an internal standard and combined yields are reported for both major and minor rotamers.

2.1.7.4.2 Thermolysis of 18

Thermolysis of oxadiazolinium salt 18 was performed at 170 °C, and the volatiles were condensed under high vacuum (10⁻³ mbar) over CDCl₃. Along with many other different products (however, no methyl tosylate), acetaldehyde (one of the decomposition products of 15; Scheme 21) was obtained in 15% yield. This result can be interpreted by invoking the formation of dihydrooxadiazole 15 under high temperatures. Ethylene oxide; however, was not detected, as it might have isomerized to acetaldehyde under the reaction conditions.
2.1.7.4.3 Reaction with other nucleophiles

Reaction of oxadiazolinium tosylate 18 with various other nucleophilic/suitable reagents under heterogeneous/homogeneous phase was also studied; however, as represented in Scheme 41, no reactions occurred.

Scheme 41. Different nucleophilic reagents used in reaction with salt 18.

As described in the entire section 2.1.7, using different types of nucleophiles under a high number of different reaction conditions, the methylaing ability of oxadiazolinium salt 18 has been clearly shown to not involve 15 as an intermediate, and in cases, for e.g. in vivo methylation of DNA or other suitable nucleophiles, methylation, if observed, may be occurring by some other mechanism without involving intermediacy of 15.
2.1.7.5 Synthesis of 3,5,5-triimethyl-4,5-dihydrop-1,2,3-oxadiazolium mesylate (58) and the study of its reaction with suitable nucleophiles

Compound 58 was synthesized with the view that the presence of geminal dimethyl groups at C-5 would discourage $S_N^2$ reaction there, and displacement reaction at $N$-methyl group might be promoted. The synthesis of mesylate 58, by a general mesylation method\textsuperscript{[46]}, 58 is an interesting reaction since mesylation of tertiary alcohols in the presence of base generally leads to an elimination reaction; however, in the case of 58, no elimination reaction was observed and the formation of open chain mesylate 57 was achieved in appreciable yield. Cyclization of 57 to 58 was accomplished by refluxing a solution of 57 in a non-nucleophilic solvent (CH$_2$Cl$_2$), and the neighbouring group participation of nitroso group is therefore, clearly evident (Scheme 42). Compound 56 was synthesized via a reported procedure\textsuperscript{[47]}.

![Scheme 42. Synthesis of mesylate 58 (Ms = methanesulfonyl).](image)

The expected products from the reaction of mesylate 58 with suitable nucleophiles, wherein displacement reaction occurs at the $N$-methyl group, resulting in the possible substituted dihydrooxadiazole 59, are 2,2-dimethyloxirane via $S_N^i$ reaction, butan-2-one via 1,2-methyl shift, diazomethane and acetone via 1,3-dipolar cycloversion reaction (Scheme 43). These secondary products are suggested in an analogous manner to the decomposition products of dihydrooxadiazole 15.
To check whether demethylation of 58 with nucleophiles is a feasible way to generate 59, it was reacted with a variety of suitable nucleophiles such as QN₃, TMGA, QI, etc., but no reaction was observed in any of the cases. Success was achieved in discouraging S_N2 reaction at C-5; however, no other reaction was observed at all.

This result can be interpreted as an evidence that in compounds like 18 and 58, S_N2 reaction at the N-methyl group does not occur, and therefore these compounds should not be considered as methylating agents involving S_N2 mechanism, and certainly do not involve 4,5-dihydro-1,2,3-oxadiazole 15 or 15 like molecules as intermediates as is clear from the nature of products obtained in the entire section 2.1.7.
2.1.8 Misrepresented examples of compounds allegedly including a 4,5-dihydro-1,2,3-oxadiazole ring system

Several authors have claimed the successful isolation of 4,5-dihydro-1,2,3-oxadiazoles even at ambient temperatures.\[48\] Some of the reports are very old and are not worth mentioning due to the absence of reliable analytical methods in those times. However, few reports in the recent literature are worth mentioning. These are discussed here point wise.

a) First such case deals with the work of Botta et al. wherein the authors have discussed the formation of dihydrooxadiazole $61^{[48a]}$ which was synthesized by a reaction of 1,3-dimethyl-5-formyluracil (60) in methanol with a large excess of ethereal solution of diazomethane (Scheme 44). When the reaction was repeated under a variety of conditions, a complex mixture was found with no signals corresponding to that of published 61 in the $^1$H NMR and $^{13}$C NMR spectra. Even the $^1$H NMR data of compound 61 are absolutely incompatible with its structure. For e.g., the carbon-bonded methyl group has been claimed to resonate at $\delta = 3.10$ ppm in the $^1$H NMR spectrum, which should clearly be observed at a significantly lower chemical shift value.

\[\text{Scheme 44. Alleged dihydrooxadiazoles with incompatible NMR data and irreproducible procedure.}\]
Ironically, as shown in Scheme 44, the same authors reported the synthesis of 1,3,4-oxadiazole 62\textsuperscript{[48b]} via the same reaction which yielded 61, and they did not even cite their own previous publication, which is quite remarkable.

b) Second case also involves two separate examples of 1,2,3-oxadiazole derivative 63\textsuperscript{[48c]} and 64\textsuperscript{[48d]} which also appear to be incompatible with the published analytical data. For 63, two protons of the CH₂−N=N unit have been reported to give a signal at δ = 2.45–2.96 ppm in the \textsuperscript{1}H NMR spectrum, which clearly should appear at a much lower chemical shift value.

\begin{align*}
\text{Scheme 45. Alleged molecules containing 4,5-dihydro-1,2,3-oxadiazole unit.}
\end{align*}

Similarly, compound 64 shows the highest mass signal at \textit{m/z} = 457, which was attributed to (M−N₂\textsuperscript{+}). However, this can also be interpreted as a signal of the oxirane instead of the dihydrooxadiazole unit.
c) Furthermore, compound \textsuperscript{67}\textsuperscript{[48e]} was claimed to be synthesized as a minor component in a reaction of benzaldehyde, tert-butyl isocyanide, sulfur, and diazophosphine \textsuperscript{65} (Scheme 46). This experiment, when repeated, gave only the major compound \textsuperscript{66} with no signals corresponding to \textsuperscript{67} (Figure 8). The interesting point in this paper was that the authors had overlooked a clear signal in \textsuperscript{13}C NMR and did not account for it while assigning the structure for \textsuperscript{67}.

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme46.png}
\caption{Published procedure for the synthesis of \textsuperscript{67}; however experimentally not observed.}
\end{figure}
\end{center}

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{Figure8.png}
\caption{\textsuperscript{1}H NMR of the reaction mixture (Scheme 46) with no signals corresponding to \textsuperscript{67}.}
\end{figure}
\end{center}
2.1.9 Synthesis of suitable O-(aminocycloalkyl)hydroxylamines and study of the reaction with various oxidizing agents

As explained in Section 1.4.1, the importance of 4,5-dihydro-1,2,3-oxadiazole type intermediates in the industrial synthesis (by BASF Ludwigshafen) of cyclopentanone and cyclododecanone via the reaction of the corresponding alkenes and nitrous oxide is clearly evident.\cite{7,25} Dihydrooxadiazole intermediates, viz., 20 and 21/22 have been studied by quantum chemical calculations and especially, in the case of 20, various modes of decomposition and their intrinsic importance have been commented upon (Scheme 47). It was also mentioned in some theoretical reports (evaluated for gas phase) that compounds like 20 should be stable even at room temperature.\cite{25}

![Diagram of chemical reactions](attachment:image.png)

**Scheme 47.** Theoretical calculations at CCSD(T)TZVdP predicting the stability of 20 and its various possible modes of decomposition.

Dihydrooxadiazole 20 is formed by the 1,3-dipolar cycloaddition reaction of nitrous oxide with cyclopentene. This intermediate can undergo retro-[2+3] cycloaddition to give the diazoaldehyde 68, which may extrude dinitrogen gas to afford the carbene 69, which in turn can yield a variety of products as mentioned in Scheme 47.

Similar decomposition products might also be possible for 21/22. The generation of dihydrooxadiazoles 20 and 21/22 was attempted via a different route, involving the
synthesis of suitable O-(aminoalkyl)hydroxylamines and the study of their reaction with various relevant oxidizing agents.

2.1.9.1 Synthesis of O-(cis-2-aminocyclopentyl)hydroxylamine (76) and study of the reaction with oxidizing agents

Compound 76 was claimed to be synthesised in good yields in a patent,\textsuperscript{[49]} however, the method was found to be irreproducible. Therefore, a new multi-step synthesis as outlined in Scheme 48 was developed. The cis arrangement of the substituents in 76 was necessary as the final step was a heterocyclic ring formation which would only be possible when both the substituents lie on the same side of the parent cyclopentane ring.

Scheme 48. Multi-step synthesis of compound 76. DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone.
As shown in Scheme 48, compound 76 was synthesized via a multi-step synthesis from 2-bromocyclopentanone. 2-azidocyclopentanone was synthesized via azidation reaction\(^ {50} \) in methanol. Subsequent reduction\(^ {51} \) with sodium borohydride gave a mixture of alcohols 70 and 71. The identity of the stereoisomers 70 and 71 was confirmed by comparison with literature available data\(^ {52} \). Electrophilic amination utilizing chloramine\(^ {53} \) and/or di-tert-butyl oxaziridine/KH\(^ {54} \) gave the corresponding hydroxylamines 72 and 73. Staudinger reduction\(^ {55} \) was employed to synthesize salts 74 and 75, which were further converted to the corresponding amines 76 and 77 using 30% aq. NaOH solution. Compounds 76 and 77 could not be separated, and therefore, were used as such in further reaction because the amount of the undesired trans-isomer 77 was low.

The mixture of compound 76/77 was utilized in a series of reaction with many different oxidizing agents (Scheme 49) with the view that ring closure might be affected. This mechanism is similar to that of the formation of tetramethyl tetrazene from dimethyl hydrazine using oxidizing agents such as activated MnO\(_2\), HgO, etc. However, unfortunately, this methodology was not successful because mostly a complex mixture with very broad signals in \(^1\)H NMR spectra were observed, and nothing conclusive could be inferred.

Scheme 49. Unsuccessful attempts to initiate intramolecular cyclization in the presence of various oxidizing agents.

The secondary products as depicted in Scheme 47, were also not found in these reactions.
2.1.9.2 Synthesis of O-(2-aminocyclododecyl)hydroxylamine (80) and similar compounds, and study of the reaction with oxidizing agents

The importance of intermediates 21/22 in the industrial synthesis of cyclododecanone utilizing nitrous oxide (Section 1.4.1) stems from the fact that these intermediates are unknown molecules and their role in this reaction is only based on the logic of chemical synthesis. As mentioned in the previous section, compound 80 was synthesized to study its reaction with suitable oxidizing agents. In this case, however, the stereochemistry of the substituents in 80 was not important, since such a large ring generally allows for a large number of interchange among conformations because of small energy barriers. The synthesis of 80 was achieved through a three-step synthesis, involving azidolysis\(^{[52,56]}\) of epoxide 78, electrophilic amination\(^{[54]}\) of the corresponding hydroxy group in 78 to give 79, and finally Staudinger reduction\(^{[55]}\) to give the desired compound 80 (Scheme 50).

![Scheme 50. Synthesis of O-(2-aminocyclododecyl)hydroxylamine 80.](image)

As depicted in Scheme 49, same oxidizing agents were used to explore the possibility of a ring closure reaction to 21 type intermediate; however, due to the formation of a complex mixture with broad peaks in \(^1\)H NMR spectra, nothing conclusive could be drawn from these reactions.
Similarly, few compounds like 81, and 82 (via analogous methods)\textsuperscript{52,57} were also synthesized to achieve 80-like starting material, viz., 83 for studying its reactivity with oxidizing agents. However, this entire sequence could not be completed because electrophilic amination was not possible.

\begin{center}
\textbf{Scheme 51. Attempted synthesis of compound 83.}
\end{center}
3.0 Summary

To summarize the objective of this research work, the generation of 4,5-dihydro-1,2,3-oxadiazole 15 and the characterisation of the true decomposition products (Scheme 52) has been achieved in the elegantly designed and conducted experiments involving the base catalyzed decomposition of \textit{N}-(2-chloroethyl)-\textit{N}-nitrosourea 34/40 monitored by NMR spectroscopy at very low temperatures. Unequivocal evidence of the intermediacy of 15 and proof of the short-lived properties of this very elusive species has been confirmed.

\[
\text{ON} \quad \text{N} \quad \text{Cl} \\
\text{Cl} \quad \text{N} \quad \text{H} \\
\text{34} \quad \text{Base (B)} \\
\text{Low Temperature} \\
to \text{RT}
\]

\[
\begin{align*}
\text{CH}_3\text{CHO} & \quad + \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{H} \\
\text{15} & \quad \text{Carbamate} \\
& \quad \text{trans-2-butenal}
\end{align*}
\]

\[
\begin{align*}
\text{Directly from} & \quad \text{From acetaldehyde} \\
\text{B = TiOEt} & \quad \text{track} \quad 15\% \quad \text{trace} \quad 67\% \quad – \\
\text{TiOPr} & \quad 32\% \quad 28\% \quad 3\% \quad \text{trace} \quad – \\
\text{KOH} & \quad 6\% \quad 9\% \quad – \quad – \quad – \\
\text{Aq. KOH} & \quad 15\% \quad 17\% \quad – \quad – \quad 4\% \\
\text{DIPA} & \quad 3\% \quad 4\% \quad – \quad – \quad – \\
\text{TEMP} & \quad 4\% \quad 3\% \quad \text{trace} \quad – \quad –
\end{align*}
\]

\textbf{Scheme 52.} Different decomposition products arising from dihydrooxadiazole 15 and acetaldehyde (a secondary product of 15) in the base-induced decomposition of \textit{N}-nitrosourea 34.
Although 15 is too unstable to be directly detected, the results in this work show that it undergoes ring contraction (SNi) leading to ethylene oxide, 1,2-hydride shift to form acetaldehyde, and 1,3-dipolar cycloreversion to produce diazomethane, whereas formation of ethylene and N₂O is not observed, hence, ruled out. The formation of diazomethane has been supported by ¹⁵N NMR investigations on the ¹⁵N labelled substrate 40. In the reaction of 40 with TlOPr at −80 °C, the detection of nitrogen gas (¹⁵N≡N), diazomethane (CH₂N¹⁵N), and unreacted 40 confirms the highly unstable nature of the intermediate 15 and leaves no doubt on the authenticity of the secondary products so obtained. In earlier reports on the decay of N-(2-chloroethyl)-N-nitrosourea 34 in aqueous solutions, acetaldehyde and ethylene glycol were detected and interpreted as succeeding products of the postulated intermediate 15.

Scheme 53. Cleavage reactions of the intermediates 48 and 85 generated from the precursors 15, 84, and 43.

The decay of short-lived heterocycle 15 can be compared with the well-known chemistry of 4,5-dihydro-1,2,3-triazoles of type 84 (Scheme 53).[58] In the case of 15, as found in this work, the decomposition is dominated by cleavage of the very weak N–O bond followed by the loss of dinitrogen and ring closure to form a three-membered ring (SNi). Alternatively, 1,2-hydride shift leads to a carbonyl compound, or carbon-carbon 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 84. 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. However, formation of imines with less carbon atoms and diazo compounds via cleavage of the carbon-carbon bond is also known in the case of special heterocycles of type \(84\).\[^{[59]}\] But, there are also differences in the succeeding reactions of \(15\) and the known chemistry of \(84\), that included 1,3-dipolar cyclorevision to produce azides \(RN_3\) and alkenes. An analogous transformation, generation of nitrous oxide and ethylene, is, however, not found in the case of dihydrooxadiazone \(15\). On the other hand, more than thousand examples of stable 4,5-dihydro-1,2,3-triazoles are reported in literature, and even heterocyclic compounds \(84\) without substitution at C-4 and C-5 have been isolated at room temperature.\[^{[61]}\] This clearly points towards the elusive properties of \(15\) which prevent its direct detection even at very low temperatures; possibly because of the very weak N–O bond.

Support is also extended to the heterolytic cleavage of the N–O bond in \(15\) because the possibility of a diradical intermediate \(49\) has been excluded on the basis of quantum chemical calculations performed by B. Fiedler and J. Friedrich. In these calculations, the homolytic cleavage of the N–O bond in \(15\) requires at least 145.2 kJ/mol, 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) or diazomethane (being in the range 81.8–105.5 kJ/mol on the basis of previous quantum chemical calculations).\[^{[20]}\]

The products of the reaction of \(43\) with TiOPr are similar to those obtained from \(34\) and TiOPr. The intermediate in case of \(43\), is the betain \(48\) which can also be considered plausible for the observation of the secondary products of \(15\) (Scheme 53). But, it can also be highly plausible that the betain \(48\) cyclizes to \(15\) under reaction conditions to produce the observed products, especially, the formation of diazomethane can be rationalized by synchronous 1,3-dipolar cyclorevision of \(15\).

Moreover, the results of the experiments of \(18\) with different suitable nucleophiles under various reaction conditions, clearly give substitution reaction at C-5 of \(18\) and no attack of the nucleophiles was found at C-4 or the methyl group. The observation of \(CH_3N_3\) can be considered to be occurring because of the instability of the azido-substituted NO-rotamers in the presence of QN\(_3\) and certainly not because of the attack
of the azide nucleophile at the methyl group of 18 because none of the secondary products of 15 were observed.

\[
\begin{align*}
\text{O}^+ & \quad \text{N}\text{O}^- \\
18 & \quad + \quad \text{QNu} \\
\text{CDCl}_3 & \quad \text{low temperature} \\
\text{H}_3\text{C}^- & \quad \text{N}^+ \quad \text{Nu} \\
+ & \quad \text{H}_3\text{C}^- \quad \text{N}^+ \quad \text{Nu} \\
+ & \quad \text{CH}_3\text{Nu}
\end{align*}
\]

Mixture of rotamers

\[
\begin{array}{ccc}
\text{Nu} = \text{N}_3^- & \text{(TMGA)} & \text{61\%}^{*}, \text{(77\%)}^{*} & \text{17\%} \text{ (15\%)} \\
\text{I} & \text{83\%} & \text{–} \\
\text{Br} & \text{87\%} & \text{–} \\
\text{SCN} & \text{93\%} & \text{–} \\
\end{array}
\]

\* = Single rotamer observed

No substitution reaction occurred with the above nucleophiles.

Scheme 54. Products of $S_n2$ reaction of oxadiazolinium salts 18 and 58 with suitable nucleophiles.

This fact is also corroborated by the experiments conducted with the oxadiazolinium salt 58, wherein the geminal dimethyl groups completely block the possibility of any kind of substitution reaction at C-5 as observed experimentally. These results clearly exclude the intermediacy of 15 in a possible demethylation of 18 or 18-like compounds as was previously published in literature. Because compounds like 18 have been
invoked as plausible intermediates in the *in vivo* activation of β-hydroxyalkyl-nitrosamines which are potent carcinogens, it can now be safely said that demethylation of 18-like molecules is not found and does not involve the generation of dihydrooxadiazole 15.

![Scheme 55. Unsuccessful attempts of ring closure with hydroxylamines 76 and 80.](image)

On the other hand, synthesis of *O*-[(2-aminocycloalkyl)hydroxylamines, viz., 76 and 80 has been realised through multi-step syntheses; however, their utility to produce dihydrooxadiazoles 20 and 21/22 via ring closure by treatment with oxidizing agents is not experimentally viable.
4.0 Outlook

Analogous to the base-induced decomposition of N-nitrosoureas mentioned in section 2.1, the reaction of literature unknown compounds of type 86 and 87 (Scheme 56) with suitable bases can also lead to the generation of dihydrooxadiazole 19 and 20. The success of this reaction can be understood from the decomposition products as mentioned in Scheme 47. Two factors would however dominate the outcome of such a reaction:

a) The correct rotamer should be present in the apolar solvent, wherein the lone pair at the nitroso nitrogen should be *syn* to the amide group, and

b) The temperature at which the reaction proceeds, because low temperatures are essential to characterize (if possible directly!) dihydrooxadiazoles 19/20 which should be also comparable in stability to 15.

Scheme 56. Possible new types of N-nitrosoureas 86 and 87.
4.1 Synthesis of Isothiazole-3(2H)-thiones as a side project

During the course of this doctoral work, we came across the report of Alizadeh and Hosseinpour[62] on the synthesis of 2H,6H-1,5-dithiocines 90 by treatment of isonitriles 88 with diesters or diketone 89 in the presence of elemental sulfur via the mechanism shown in Scheme 57. We had some doubts about the structure of the heterocycles 90 because the $^{13}$C NMR signals of the thioimidate carbons (S−C=N) were found at $\delta = 183−190$ ppm, and such low field signals are not compatible with this group.[63] The substructures of thioamides (S=C−N) are more plausible to interpret the observed signals.

Scheme 57. Claimed and now revised structures of the products resulting from the reactions of 88 with 89 in the presence of elemental sulfur.
When we repeated the reactions of 88 with 89 in the presence of elemental sulfur, identical substances were isolated. Whereas Alizadeh and Hosseinpour obtained 90a–g as yellow powders, we obtained more or less colored crystals after repeated chromatography and recrystallization. Our substances showed significantly different melting points than those reported for 90a–g.

Our work proved that the real structures of the products of the reactions of 88 with 89 are isothiazole-3(2H)-thiones 93, and not 2H,6H-1,5-dithiocines 90 as claimed by the authors, on the basis of $^{13}$C NMR data interpretation, elementary analyses, HRMS data, and ultimately by single-crystal diffraction analysis.

Our work has already been published.$^{[63]}$
5.0 Experimental part

5.1 Instrumentation and techniques

Melting Points were determined on a BOETIUS apparatus from PENTAKON DRESDEN company, and are uncorrected.

IR spectra were measured on a FT-IR Spectrometer IFS 28 from BRUKER or on Nicolet iS5 from THERMO FISCHER SCIENTIFIC. Spectra were measured in suitable organic solvents and are reported in cm$^{-1}$ in decreasing order of wavenumber ($\tilde{\nu}$).

NMR spectra were measured on a UNITY INOVA 400 FT spectrometer from VARIAN. $^1$H NMR spectra were measured at 400 MHz, $^{13}$C NMR at 100 MHz, and $^{15}$N NMR at 40.5 MHz. NMR signals were referenced to TMS ($\delta = 0$) or solvent signals and recalculated relative to TMS. $^{15}$N NMR were referenced to external MeNO$_2$ ($\delta = 0$). DEPT 135, and 2D NMR methods such as gCOSY, gHSQCAD, and gHMBCAD were used when necessary. Multiplicities of the signals are reported using the standard notations: $s =$ singlet, $d =$ doublet, $t =$ triplet, $q =$ quartet, $m =$ multiplet, br. $s =$ broad singlet, etc.

Mass spectra were obtained from micrOTOF QII spectrometer from BRUKER utilizing Electrospray-Ionisation technique (ESI).

X-Ray diffraction data were obtained in cooperation with Professor Heinrich Lang (Inorganic Chemistry) by Dipl.-Chem. M. Korb using Gemini S diffractometer from OXFORD DIFFRACTION company. Structures were solved by direct methods with SHELXTL-NT V5.1 program package and plotted with ORTEP-3.

Quantitative elementary analyses were performed on a Vario Micro Tube from ELEMENTAR ANALYSENSYSTEME GMBH HANAU.

Thin layer chromatography was performed using Macherey-Nagel Polygram SIL G/UV$_{254}$ foils.

Flash chromatography was performed with Silica gel 60 M (Particle-size 0.04–0.063 mm) as the stationary phase from the company Macherey-Nagel.
**Note 1:** $N$-nitrosoureas are potent mutagens/carcinogens, and therefore, should be handled with utmost precaution ensuring no contact with bare skin, and unutilized $N$-nitrosoureas, before disposal, should be converted to corresponding amines by treatment with aq. NaHCO$_3$ solution for a period of 24–36 h.

**Note 2:** Thallium(I) alkoxides (like metallic Thallium) are extremely toxic chemicals which manifest their toxicity slowly, and, therefore should be handled very carefully. Unreacted thallium(I) alkoxides can be precipitated as thallium(I) chlorides by treatment with potassium chloride (KCl) and disposed off suitably.
5.2 Synthesis of \textit{N}-(2-chloroethyl)-\textit{N}-nitrosourea (34)

![Structure of Compound 34]

Compound 34 was synthesized via a literature known procedure.\cite{21h}

To a solution of conc. sulfuric acid (1.5 g) and distilled water (10 mL) cooled in an ice bath was added \textit{N}-(2-chloroethyl)urea\cite{21h} (2.46 g, 20 mmol). Then, a cold solution of NaNO\textsubscript{2} (1.40 g, 20 mmol, 1.0 eq) in distilled water (3 mL) was added drop wise with stirring over a period of 15 min, during which precipitation of a pale yellow-colored solid occurred. The reaction mixture was filtered over a Buchner funnel, the solid so obtained was washed well with distilled water (20 mL), and dried under high vacuum at room temperature to give 34 (0.85 g, 27%).

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 3.49\) (t, 2H, \(J = 6.8\) Hz, ClCH\textsubscript{2}), 4.16 (t, 2H, \(J = 6.8\) Hz, CH\textsubscript{2}NNO), 5.62 (br. s, 1H, NH), 6.86 (br. s, 1H, NH).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta = 38.83\) (t, ClCH\textsubscript{2}), 39.77 (t, CH\textsubscript{2}NNO), 153.94 (s, CO).

The assignment was done on the basis of \textsuperscript{13}C, \textsuperscript{1}H correlation.

5.2.1 Reaction of \textit{N}-(2-chloroethyl)-\textit{N}-nitrosourea (34) with TIOEt within the temperature range of −40 °C to −20 °C

To a vigorously stirred solution of \textit{N}-nitrosourea 34 (37.88 mg, 0.25 mmol), in CD\textsubscript{2}Cl\textsubscript{2} (0.76 mL) was added TIOEt (62.36 mg, 0.25 mmol, 1.0 eq). Immediately, the reaction mixture was transferred using a cold pipette (cooled by dipping into liquid nitrogen) into a pre-cooled NMR tube maintained at −40 °C, and NMR spectra were measured from −40 °C to −20 °C. As observed by NMR spectroscopy, the reaction is completed at −20 °C. The products so obtained are ethylene oxide (15%), acetaldehyde (trace), and carbamate 38 (67%) as under:
For ethylene oxide:

$^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta = 2.66$ (s).

$^{13}$C NMR (100 MHz, CD$_2$Cl$_2$): $\delta = 41.06$ (t, CH$_2$).

For 1-ethoxyethyl carbamate:

Spectral data for 1-ethoxyethyl carbamate (38):

$^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta = 1.15$ (t, 3H, $^3$J = 7.0 Hz, CH$_3$CH$_2$), 1.30 (d, 3H, $^3$J = 4.8 Hz, CHCH$_3$), 3.34 (dq, 1H, $^2$J = 8.4 Hz, $^3$J = 4.8 Hz, OCH$_2$H), 3.63 (dq, 1H, $^2$J = 8.4 Hz, $^3$J = 4.8 Hz, OCH$_2$H), 5.83 (q, 1H, $^3$J = 4.8 Hz, CH$_3$CH). NH signals were not observed.

$^{13}$C NMR (100 MHz, CD$_2$Cl$_2$): $\delta = 15.77$ (q, CH$_2$CH$_3$), 27.16 (q, CHCH$_3$), 62.13 (t, CH$_2$), 98.50 (d, CH), 178.73 (s, CO, observed only after overnight measurement). Assignment of signals accomplished with $^{13}$C,$^1$H gHSQCAD.

Carbamate 38 could not be isolated after evaporation of volatiles due to probable polymerisation to an insoluble black residue.

5.2.2 Monitoring of the reaction between N-nitrosourea (34) and TIOEt at −90 °C

As mentioned in Section 5.2.1, similar reaction using N-nitrosourea 34 (25 mg, 0.165 mmol) and TIOEt (45.27 mg, 0.181 mmol, 1.1 eq) in CD$_2$Cl$_2$ (0.8 mL) was performed at −90 °C and monitored by NMR spectroscopy in order to study the elusive properties of dihydrooxadiazole 15 and its decomposition products.
5.2.3 Reaction of $N$-(2-chloroethyl)-$N$-nitrosourea (34) with TlOPr within the temperature range of $-60 \, ^\circ\text{C}$ to $-20 \, ^\circ\text{C}$

To a vigorously stirred solution of $N$-nitrosourea 34 (10 mg, 0.065 mmol), in CD$_2$Cl$_2$ (0.76 mL) maintained at $-60 \, ^\circ\text{C}$ was added TlOPr (19.12 mg, 0.072 mmol, 1.1 eq, synthesized via a known method). Immediately, the reaction mixture was transferred using a cold pipette (cooled by dipping into liquid nitrogen) into a pre-cooled NMR tube maintained at $-60 \, ^\circ\text{C}$, and NMR spectra were measured from $-60 \, ^\circ\text{C}$ to $-20 \, ^\circ\text{C}$. As observed by NMR spectroscopy, the reaction is completed at $-20 \, ^\circ\text{C}$, and the yields (NMR yield) of the products here are calculated at $-20 \, ^\circ\text{C}$. The products so obtained are ethylene oxide (28%), acetaldehyde (32%), diazomethane (3%), and carbamate 39 (trace) as under:

For ethylene oxide:

$^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta = 2.64$ (s).

$^{13}$C NMR (100 MHz, CD$_2$Cl$_2$): $\delta = 41.0$ (t, CH$_2$).

For acetaldehyde:

$^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta = 2.16$ (d, 3H, $^3$J = 2.8 Hz, CH$_3$), 9.72 (q, 1H, $^3$J = 2.8 Hz, CHO).

$^{13}$C NMR (100 MHz, CD$_2$Cl$_2$): $\delta = 31.16$ (q, CH$_3$), 200.33 (CHO).

For diazomethane:

$^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta = 3.32$ (s).

$^{13}$C NMR (100 MHz, CD$_2$Cl$_2$): The signal for diazo carbon could not be obtained because of the very low concentration of diazomethane formed and also owing to the slow relaxation time of the C=N$_2$ carbon.
5.2.4 Stability of diazomethane in the presence of TlOEt

Diazomethane was synthesized from N-methyl-N-nitrosourea utilizing a known procedure in KOH/H$_2$O/CDCl$_3$.\textsuperscript{[30]} N-methyl-N-nitrosourea (51 mg, 0.05 mmol) was dissolved in CDCl$_3$ and cooled to $-10$ °C. To this solution was added TlOEt (26.34 mg, 0.1 mmol, 2.0 eq) and the reaction mixture was stirred for 15 min, and then decanted to give the clear yellow diazomethane/CDCl$_3$ solution. Two separate NMR tubes maintained at $-10$ °C were filled with equal amounts of the clear yellow CH$_2$N$_2$/CDCl$_3$ solution and $^1$H NMR spectra were measured. Subsequently, to one of the NMR tubes, was added TlOEt (2.0 eq) and again $^1$H NMR spectra were measured for both the NMR tubes after 15 min at $-10$ °C. 92% decrease in the concentration of diazomethane was observed in the NMR tube containing TlOEt, while negligible decrease in the concentration of diazomethane was observed in the one with pure diazomethane solution (without added TlOEt).

For CH$_2$N$_2$:

$^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta = 3.37$ (s).

5.2.5 Stability of diazomethane in the presence of TlOPr

The same procedure as mentioned above was also used for studying the stability of diazomethane in the presence of TlOPr (1.1 eq). After a period of 20 min at $-10$ °C, 17% reduction in the concentration of diazomethane was observed in the NMR tube containing TlOPr.
5.2.6 Synthesis of $^{15}$N labelled $N$-nitrosourea 40

$N$-nitrosourea 40 was synthesized analogous to the synthesis of 34.$^{[30a]}$

To a solution of conc. sulfuric acid (1.5 g) and distilled water (10 mL) cooled in an ice bath was added $N$-(2-chloroethyl)urea (2.46 g, 20 mmol). Then, a cold solution of Na$^{15}$NO$_2$ (1.54 g, 22 mmol, 1.1 eq) in distilled water (3 mL) was added drop wise with stirring over a period of 15 min, during which precipitation of a pale yellow colour solid occurred. The reaction mixture was filtered over a Buchner funnel, the cream-coloured solid so obtained was washed well with distilled water (20 mL), and dried under high vacuum at room temperature to give the $^{15}$N labelled 34 (0.73 g, 24%).

$^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta = 3.52$ (t, 2H, $J = 6.8$ Hz, ClCH$_2$), 4.15 (t, 2H, $J = 6.8$ Hz, CH$_2$N$^{15}$NO), 5.70 (br. s, 1H, NH), 6.89 (br. s, 1H, NH).

$^{13}$C NMR (100 MHz, CD$_2$Cl$_2$): $\delta = 39.56$ (t, ClCH$_2$), 40.16 (t, CH$_2$N$^{15}$NO, $^2J(^{15}$N, $^{13}$C) = 0.8 Hz), 154.27 (s, CO, $^2J(^{15}$N, $^{13}$C) = 3.7 Hz).

$^{15}$N NMR (40.5 MHz, CD$_2$Cl$_2$): $\delta = 184.52$ ($^{15}$NO).

5.2.7 Monitoring of the reaction between $N$-nitrosourea 40 and TIOEt from −80 °C to −50 °C

The reaction between $^{15}$N labelled $N$-nitrosourea 40 (15 mg, 0.09 mmol) and TIOEt (24.70 mg, 0.099 mmol, 1.1 eq) in CD$_2$Cl$_2$ (0.8 mL) was monitored by $^{15}$N NMR spectroscopy from −80 °C to −50 °C. The $^{15}$N NMR spectrum of the reaction mixture at −80 °C is as under:

$^{15}$N NMR (40.5 MHz, CD$_2$Cl$_2$): $\delta = -69.74$ ($^{15}$N≡N), 184.33 ($^{15}$NO from 40).
5.2.8 Monitoring of the reaction between $N$-nitrosourea 40 and TIOPr from −80 °C to −10 °C

The reaction between $^{15}$N labelled $N$-nitrosourea 40 (15 mg, 0.09 mmol) and TIOPr (26.08 mg, 0.099 mmol, 1.1 eq) in CD$_2$Cl$_2$ (0.8 mL) was monitored by $^{15}$N NMR spectroscopy from −80 °C to −10 °C. The $^{15}$N NMR spectrum of the reaction mixture at −80 °C is as under:

$^{15}$N NMR (40.5 MHz, CD$_2$Cl$_2$): $\delta = -69.74$ (15N≡N), 14.17 (CH$_2$N$^{15}$N), 184.33 (15NO from unreacted 40).

For CH$_2$N$^{15}$N:

$^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta = 3.34$ (d, $^3J(15N,^1H) = 1.1$ Hz).

The identity of CH$_2$N$^{15}$N was further confirmed by $^{15}$N,$^1$H long-range (gHMBCAD) 2D NMR spectroscopy.

The reaction was monitored up to −10 °C wherein the gradual decrease in the concentration of 40 with a consequent increase in the concentration of $^{15}$N≡N signal in the $^{15}$N NMR spectra is clearly evident.

5.2.9 Synthesis of CH$_2$N$^{15}$N and thallium(I) (Z)-methanediazotate (41) from $^{15}$N labelled $N$-methyl-$N$-nitrosourea

$^{15}$N labelled $N$-methyl-$N$-nitrosourea was synthesized analogous$^{[30a]}$ to a literature known procedure.

$^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta = 3.15$ (d, 3H, $^3J(15N,^1H) = 0.8$ Hz, CH$_3$), 5.68 (br. s, 1H, NH), 6.90 (br. s, 1H, NH).

$^{13}$C NMR (100 MHz, CD$_2$Cl$_2$): $\delta = 26.50$ (q, CH$_3$, $^2J(15N,^{13}C) = 0.9$ Hz), 154.53 (s, CO).

$^{15}$N NMR (40.5 MHz, CD$_2$Cl$_2$): $\delta = 182.56$ (15NO).
To a mixture of $^{15}$N labelled N-methyl-N-nitrosourea (10 mg) in CD$_2$Cl$_2$ (0.76 mL) maintained at −60 °C, was added TIOPr (1.1 eq) and the reaction mixture was stirred at this temperature for 1 h. Subsequently, the reaction mixture was transferred to a pre-cooled NMR tube maintained at −60 °C and NMR spectra were recorded. The reaction was completed in an additional 30 min, as observed by NMR spectroscopy. NMR yields of CH$_2$N$^{15}$N, and diazotate 41 are 31% and 14%, respectively.

For CH$_2$N$^{15}$N:

$^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta = 3.34$ (d, $^3$J($^{15}$N,$^1$H) = 1.2 Hz).

$^{13}$C NMR (100 MHz, CD$_2$Cl$_2$): $\delta = 23.49$ (t, CH$_2$, $^1$J($^{13}$C,$^{14}$N) = 14.9 Hz).

$^{15}$N NMR (40.5 MHz, CD$_2$Cl$_2$): $\delta = 14.57$ (CH$_2$N$^{15}$N).

Assignment for diazomethane was further confirmed by $^{15}$N,$^1$H long-range (gHMBCAD) 2D NMR spectroscopy.

For thallium(I) (Z)-methanediazotate (41):

[Diagram]

$^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta = 3.17$ (d, $^3$J($^{15}$N,$^1$H) = 4.0 Hz).

$^{15}$N NMR (40.5 MHz, CD$_2$Cl$_2$): $\delta = 104.46$ ($^{15}$NOTl).

The structure of 41 was further confirmed by $^{15}$N,$^1$H long-range (gHMBCAD) 2D NMR spectroscopy. On warming to −10 °C, 41 was totally converted to CH$_2$N$^{15}$N.
5.3 Reaction of \(N\)-nitrosourea 34 with various bases

5.3.1 Study of the reaction between \(N\)-nitrosourea 34 and KOH (s)

To a solution of 34 (20 mg, 0.132 mmol) in \(\text{CD}_2\text{Cl}_2\) (0.76 mL) maintained at 0 °C was added solid KOH (22.2 mg, 0.39 mmol, 3.0 eq). The reaction mixture was stirred at this temperature for 30 min, and then the contents were transferred to a pre-cooled NMR tube maintained at 0 °C. As observed by NMR spectroscopy, the reaction was completed on warming to room temperature. Ethylene oxide (9%) and acetaldehyde (6%) can be identified as products from the NMR spectra. The yields reported are NMR yields. NMR data were identical to that mentioned in Sections 5.2.1 and 5.2.3.

5.3.2 Study of the reaction between \(N\)-nitrosourea 34 and aq. KOH

To a solution of 34 (20 mg, 0.132 mmol) in \(\text{CD}_2\text{Cl}_2\) (0.76 mL) maintained at −20 °C was added a solution of KOH (22.2 mg, 0.39 mmol, 3.0 eq) in water (0.2 mL). The reaction mixture was stirred at this temperature for 10 min, and then the contents were transferred to a pre-cooled NMR tube maintained at −20 °C. The reaction was completed within 10 min at this temperature. As observed by NMR spectroscopy, ethylene oxide (17%), acetaldehyde (15%), and trans-2-butenal (crotonaldehyde) (4%) can be identified as products. The yields reported are NMR yields. NMR data of ethylene oxide and acetaldehyde were identical to that mentioned in Sections 5.2.1 and 5.2.3.

\(^1\text{H} \text{NMR (400 MHz, } \text{CD}_2\text{Cl}_2\): } \delta = 2.0 \text{ (dd, 3H, } J^3 = 7.2 \text{ Hz, } J^4 = 1.6 \text{ Hz, CH}_3\), 6.08 (ddq, 1H, \( J^3 = 15.2 \text{ Hz, } J^3 = 8.0 \text{ Hz, } J^4 = 1.6 \text{ Hz, CHCHO})\), 6.88 (dq, 1H, \( J^3 = 15.2 \text{ Hz, } J^3 = 7.2 \text{ Hz, CH}_3\text{CH})\), 9.44 (d, 1H, \( J^3 = 8.0 \text{ Hz, CHO})\).

Signals are identical to the literature available data.\(^{[33]}\)
5.3.3 Study of the reaction between \textit{N}-nitrosourea 34 and diisopropylamine (DIPA)

To a solution of \textit{34} (20 mg, 0.132 mmol) in CD$_2$Cl$_2$ maintained at 0 °C was added DIPA (26.71 mg, 0.26 mmol, 2.0 eq). The reaction mixture was stirred at this temperature for 15 min, and then the contents were transferred to a pre-cooled NMR tube maintained at 0 °C. The reaction was, however, completed on warming to room temperature, as observed by NMR spectroscopy. Ethylene oxide (4%) and acetaldehyde (3%) can be identified as products. Yields reported here are NMR yields. NMR data were identical to that mentioned in Sections 5.2.1 and 5.2.3.

5.3.4 Study of the reaction between \textit{N}-nitrosourea 34 and 2,2,6,6-tetramethylpiperidine (TEMP)

To a solution of \textit{34} (20 mg, 0.132 mmol) in CD$_2$Cl$_2$ maintained at 0 °C was added DIPA (36.72 mg, 0.26 mmol, 2.0 eq). The reaction mixture was stirred at this temperature for 15 min, and then the contents were transferred to a pre-cooled NMR tube maintained at 0 °C. The reaction was, however, completed on warming to room temperature, as observed by NMR spectroscopy. Ethylene oxide (3%) and acetaldehyde (4%) can be identified as products. Yields reported here are NMR yields. NMR data were identical to that mentioned in Sections 5.2.1 and 5.2.3.

5.3.5 Study of the reaction between \textit{N}-nitrosourea 34 and sodium methoxide

To a solution of \textit{34} (20 mg, 0.132 mmol) in THF-d$_8$ (0.76 mL) maintained at −40 °C was added a solution of sodium methoxide (7.84 mg, 0.145 mmol, 1.1 eq) in CD$_3$OD (0.1 mL). The reaction mixture was stirred at this temperature for 30 min, and then the contents were transferred to a pre-cooled NMR tube maintained at −40 °C. As observed by NMR spectroscopy, the reaction was incomplete even at room temperature; however, acetaldehyde, ethylene oxide, and 1-methoxyethanol \textit{42} can be clearly identified in yields of 4%, 16%, and 25%, respectively (calcd. at −40 °C).
For ethylene oxide:

\[ ^1H \text{ NMR (400 MHz, THF-d}_8\text{): } \delta = 2.53 \text{ (s).} \]

For acetaldehyde:

\[ ^1H \text{ NMR (400 MHz, THF-d}_8\text{): } \delta = 2.06 \text{ (d, 3H, } ^3J = 2.8 \text{ Hz, CH}_3\text{), 9.63 \text{ (q, 1H, } ^3J = 2.8 \text{ Hz, CHO).} \]

For 1-methoxyethanol (42):

\[ ^1H \text{ NMR (400 MHz, THF-d}_8\text{): } \delta = 1.16 \text{ (d, 3H, } ^3J = 5.2 \text{ Hz, CH}_3\text{CH), 3.23 \text{ (s, 3H, OCH}_3\text{), 4.53 \text{ (q, } ^3J = 5.2 \text{ Hz, CH}_3\text{CH), OH cannot be assigned with certainty. Data is in good agreement with the published report.}^{[33b]} \]

A good \(^{13}\text{C NMR spectrum could not be obtained.} \]

5.4 Synthesis of \(N\)-(2-tosyloxyethyl)-\(N\)-nitrosourea (44)

The precursor \(N\)-(2-hydroxyethyl)-\(N\)-nitrosourea (43) was synthesized using a literature known method.\(^{[34]}\) To a solution of this precursor (0.5 g, 3.75 mmol) in dry pyridine (4 mL) at 0 °C, was added TsCl (1.43 g, 7.5 mmol, 2.0 eq), and the reaction mixture was stirred at this temperature for 1 h and subsequently for 22 h at −20 °C. Thereafter, the reaction mixture was poured into ice (16 g) and 1 M HCl (34 mL), and was extracted with dichloromethane (50 mL). The organic phase was evaporated to dryness, and diethylether (50 mL) was added. The diethyl ether solution was filtered, washed with
water, and dried over MgSO$_4$ for 4 h. After evaporation of the solvent in vacuo, 44 was obtained as a white solid (0.64 g, 50%).

**mp:** 67–68 °C

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 2.42$ (s, 3H, CH$_3$C$_6$H$_4$), 4.02 (m, 2H, TsOCH$_2$), 4.07 (m, 2H, TsOCH$_2$CH$_2$), 5.70 (br. s, 1H, NH), 6.80 (br. s, 1H, NH), 7.32 (d, 2H, $J = 8.4$ Hz, Ar), 7.71 (d, 2H, $J = 8.4$ Hz, Ar).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 21.65$ (q, CH$_3$), 37.30 (t, CH$_2$NNO), 65.09 (t, OCH$_2$), 127.88 (Ar), 129.91 (Ar), 132.39 (Ar), 145.15 (Ar), 153.83 (s, CO).

Assignment was done by gCOSY and gHSQCAD data.

**HR-MS (ESI):** $m/z$ calcd. for C$_9$H$_{14}$NO$_3$S [M − CN$_2$O$_2$ + H]$^+$ 216.0694; found: 216.0797; $m/z$ calcd. for C$_9$H$_{14}$NO$_3$SNa [M − CN$_2$O$_2$ + H + Na]$^+$ 239.0592; found: 239.0446.

### 5.4.1 Study of the reaction between $N$-(2-tosyloxyethyl)-$N$-nitrosourea (44) and TIOPr

$N$-nitrosourea 44 (20 mg, 0.07 mmol) was taken in THF-d$_8$ (0.76 mL), and to this mixture was added TIOPr (20.30 mg, 0.077 mmol, 1.1 eq) at −40 °C. The reaction mixture was stirred for 10 min, and then transferred to a pre-cooled NMR tube maintained at −40 °C. This reaction was not complete even at room temperature; however, at −40 °C, ethylene oxide and acetaldehyde can be identified in a ratio of 4.70 : 1.00.

For **ethylene oxide**:

$^1$H NMR (400 MHz, THF-d$_8$): $\delta = 2.54$ (s).

For **acetaldehyde**:

$^1$H NMR (400 MHz, THF-d$_8$): $\delta = 2.08$ (d, 3H, $^3J = 2.8$ Hz, CH$_3$), 9.63 (q, 1H, $^3J = 2.8$ Hz, CHO).
5.5 Study of the reaction between \( N\)-(2-hydroxyethyl)-\( N\)-nitrosourea (43) and TlOPr

TlOPr (43.47 mg, 0.165 mmol, 1.1 eq) was added to a suspension of \( N\)-nitrosourea 43 (20 mg, 0.15 mmol) in CD\(_2\)Cl\(_2\) (1.0 mL) maintained at \(-20\) °C. The reaction mixture was stirred at this temperature for 75 min. Subsequently, the reaction mixture was transferred into a pre-cooled NMR tube maintained at \(-20\) °C, and the reaction was monitored by NMR spectroscopy. Ethylene oxide (19%), acetaldehyde (7%), and diazomethane (4%) can be identified as products. The yields reported are NMR yields and based on consumed 43 (~7.0 mg). The amount of consumed 43 was calculated by weighting the amount of insoluble solid left in the round-bottom flask.

For ethylene oxide:

\(^1\text{H} \text{NMR (400 MHz, CD}_2\text{Cl}_2\): } \delta = 2.63 \text{ (s).}

For acetaldehyde:

\(^1\text{H} \text{NMR (400 MHz, CD}_2\text{Cl}_2\): } \delta = 2.15 \text{ (d, 3H, } ^3J = 2.8 \text{ Hz, CH}_3), 9.72 \text{ (q, 1H, } ^3J = 2.8 \text{ Hz, CHO).}

For diazomethane:

\(^1\text{H} \text{NMR (400 MHz, CD}_2\text{Cl}_2\): } \delta = 3.32 \text{ (s).}
5.6 Synthesis of 3-methyl-4,5-dihydro-1,2,3-oxadiazolium tosylate (18)

Oxadiazolinium salt 18 was synthesized via a literature known procedure and the NMR data were compared.[18c,i]

$^1\text{H NMR (400 MHz, DMSO-}d_6\text{)}$: $\delta = 2.28$ (s, 3H, CH$_3$C$_6$H$_4$), 4.20 (s, 3H, NCH$_3$), 4.84 (t, 2H, $J = 12.0$ Hz, CH$_2$), 5.28 (t, 2H, $J = 12.0$ Hz, CH$_2$), 7.11 (d, 2H, $J = 8.0$ Hz, Ar), 7.47 (d, 2H, $J = 8.0$ Hz, Ar).

$^{13}\text{C NMR (100 MHz, DMSO-}d_6\text{)}$: $\delta = 20.77$ (q, CH$_3$C$_6$H$_4$), 41.65 (q, NCH$_3$), 60.16 (t, CH$_2$), 77.86 (t, CH$_2$), 125.46 (d, 2 x CH, Ar), 128.04 (d, 2 x CH, Ar), 137.57 (s, Ar), 145.77 (s, Ar).

X-ray quality crystals of 18 were obtained from CH$_2$Cl$_2$/Et$_2$O mixture kept at $-20$ °C for 21 days. The crystals were not stable at room temperature as they turned into a viscous liquid within a matter of minutes.

5.6.1 Synthesis of $N$-(2-azidoethyl)-$N$-methylnitrous amide (52) and methyl azide

i) From QN$_3$: To a solution of 18 (15 mg, 0.06 mmol) in CDCl$_3$ (0.76 mL) maintained at $-45$ °C, was added QN$_3$[27] (56.37 mg, 0.12 mmol, 2.0 eq), and the reaction mixture was transferred into a pre-cooled NMR tube maintained at $-45$ °C. The reaction was monitored up to room temperature; however, the reaction was completed after 40 min at $-45$ °C. Products obtained at $-45$ °C via $^1\text{H NMR}$ spectrum are azido compound 52.
(61%) and methyl azide (17%). The yields reported here are NMR yields. Compound 52 was purified by careful recondensation of the reaction mixture at $3 \times 10^{-3}$ while maintaining the temperature of the reaction mixture between −60 °C and −40 °C. Methyl azide (CH$_3$N$_3$) which also recondensed along with 52 was removed by bubbling dry nitrogen gas into the condensate. Attempted removal of the solvent in vacuo, however, lead to partial decomposition of 52.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 3.40$ (t, 2H, $J = 5.6$ Hz, CH$_2$N$_3$), 3.62 (t, 2H, $J = 5.6$ Hz, CH$_2$CH$_2$N$_3$), 3.75 (s, 3H, CH$_3$). Assignment was supported by $^{13}$C,$^1$H gCOSY.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 40.50$ (q, CH$_3$), 44.25 (CH$_2$), 46.84 (CH$_2$).

IR (CDCl$_3$): $\tilde{\nu} = 2133$ (s), 2103 (s), 1466 (m), 1034 (s) cm$^{-1}$.

HR-MS (ESI): $m/z$ calcd. for C$_3$H$_8$N$_5$O [M + H]$^+$ 130.0729; found: 130.0725.

For methyl azide (CH$_3$N$_3$):

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 2.97$ (s).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 37.45$ (q, CH$_3$, observed after recondensation of the reaction mixture).

Similar reaction of 18 (20 mg, 0.077 mmol) with QN$_3$ (72.34 mg, 0.154 mmol, 2.0 eq) was repeated, and after the removal of initially formed methyl azide, QN$_3$ (1.0 eq) was added and again the formation of methyl azide occurred in small amounts (5%).

ii) From tetramethylguanidinium azide (TMGA): To a solution of 18 (20 mg, 0.077 mmol) in CDCl$_3$ (0.76 mL) maintained at −45 °C, was added TMGA (19.00 mg, 0.12 mmol, 2.0 eq), and the reaction mixture was transferred into a pre-cooled NMR tube maintained at −45 °C. The reaction was monitored up to room temperature; however, the reaction was completed after 1 h at −45 °C. Products obtained at −45 °C via $^1$H NMR spectrum are azido compound 52 (77%) and methyl azide (15%). The yields reported here are NMR yields.
For azido compound 52:

\[ ^1H\text{ NMR (400 MHz, CDCl}_3\text{): } \delta = 3.38 \text{ (t, 2H, J = 5.6 Hz, CH}_2\text{N}_3\text{), 3.63 (t, 2H, J = 5.6 Hz, CH}_2\text{CH}_2\text{N}_3\text{), 3.77 (s, 3H, CH}_3\text{).} \]

\[ ^{13}C\text{ NMR (100 MHz, CDCl}_3\text{): } \delta = 40.91 \text{ (q, CH}_3\text{), 44.57 (CH}_2\text{), 46.96 (CH}_2\text{).} \]

5.6.2 Synthesis of \( N\)-(2-iodoethyl)-\( N\)-methylnitrous amide rotamers (53a and 53b)

QI was synthesized from QOMs by an analogous method.\[^{27}\] To a solution of 18 (15 mg, 0.06 mmol) in CDCl\(_3\) (0.76 mL) maintained at \(-45^\circ C\), was added QI (66.56 mg, 0.12 mmol, 2.0 eq), and the reaction mixture was transferred into a pre-cooled NMR tube maintained at \(-45^\circ C\). The reaction was monitored up to room temperature. Products determined at room temperature after 30 min are the mixture of iodo-substituted rotamers 53a and 53b in a combined yield of 83% (NMR Yield). A distinction between the rotational isomers 53a and 53b cannot be made on the basis of NMR spectroscopy; however, they are formed in a ratio of 1.67 : 1.0.

For major rotamer:

\[ ^1H\text{ NMR (400 MHz, CDCl}_3\text{): } \delta = 3.03 \text{ (t, 2H, J = 7.2 Hz, CH}_2\text{I), 3.70 (s, 3H, CH}_3\text{), 3.80 (t, 2H, J = 7.2 Hz, CH}_2\text{CH}_2\text{I).} \]

\[ ^{13}C\text{ NMR (100 MHz, CDCl}_3\text{): } \delta = -4.06 \text{ (t, CH}_2\text{I), 47.18 (q, CH}_3\text{), 53.25 (t, CH}_2\text{CH}_2\text{I).} \]
For minor rotamer:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 2.92$ (s, 3H, CH$_3$), 3.32 (t, 2H, $J = 6.8$ Hz, CH$_2$I), 4.40 (t, 2H, $J = 6.8$ Hz, CH$_2$CH$_2$I).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 0.47$ (t, CH$_2$I), 39.27 (q, CH$_3$), 54.92 (t, CH$_2$CH$_2$I).

5.6.3 Synthesis of $N$-(2-bromoethyl)-$N$-methylnitrous amide rotamers (54a and 54b)

To a solution of oxadiazolinium salt 18 (20 mg, 0.077 mmol) in CDCl$_3$ maintained at $-30 \, ^\circ$C, was added QBr (78.18 mg, 0.154 mmol, 2.0 eq), and the reaction mixture was warmed up to room temperature and stirred for 45 min. The contents were then transferred into an NMR tube and studied by NMR spectroscopy. The bromo-substituted rotamers 54a, and 54b were formed in a combined yield of 87% (NMR yield). A distinction between the rotational isomers 54a and 54b cannot be made on the basis of NMR spectroscopy; however, they are formed in a ratio of 4.11 : 1.0.

For major rotamer:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 3.35$ (t, 2H, $J = 6.4$ Hz, CH$_2$Br), 3.80 (s, 3H, CH$_3$), 3.88 (t, 2H, $J = 6.4$ Hz, CH$_2$CH$_2$Br).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 25.68$ (t, CH$_2$Br), 40.21 (q, CH$_3$), 46.92 (t, CH$_2$CH$_2$Br).
For minor rotamer:

\[ ^1H \text{ NMR (400 MHz, CDCl}_3): \delta = 3.02 \text{ (s, 3H, CH}_3\text{), 3.59 \text{ (t, 2H, } J = 6.4 \text{ Hz, CH}_2\text{Br), 4.49 (t, 2H, } J = 6.4 \text{ Hz, CH}_2\text{CH}_2\text{Br).} \]

\[ ^{13}\text{C NMR signals could not be obtained owing to low concentration.} \]

5.6.4 Synthesis of \( N \)-methyl-\( N \)-(2-thiocyanatoethyl)nitrous amide rotamers (55a and 55b)

QSCN was synthesized from QOMs by an analogous reaction.[27] To a solution of oxadiazolinium salt 18 (20 mg, 0.077 mmol) in CDCl\(_3\) maintained at \(-30^\circ\text{C}\), was added QSCN (74.81 mg, 0.154 mmol, 2.0 eq), and the reaction mixture was warmed up to room temperature and stirred for 45 min. The contents were then transferred into an NMR tube and studied by NMR spectroscopy. The thiocyanato-substituted rotamers 55a, and 55b were formed in a combined yield of 93% (NMR yield). A distinction between the rotational isomers 55a, and 55b cannot be made on the basis of NMR spectroscopy; however, they are formed in a ratio of 2.05 : 1.0.

For major rotamer:

\[ ^1H \text{ NMR (400 MHz, CDCl}_3): \delta = 3.07 \text{ (t, 2H, } J = 6.8 \text{ Hz, CH}_2\text{SCN), 3.85 \text{ (s, 3H, CH}_3\text{), 3.89 \text{ (t, 2H, } J = 6.8 \text{ Hz, CH}_2\text{CH}_2\text{SCN).} \]

\[ ^{13}\text{C NMR (100 MHz, CDCl}_3): \delta = 32.09 \text{ (t, CH}_2\text{SCN), 40.18 \text{ (q, CH}_3\text{), 44.80 \text{ (t, CH}_2\text{CH}_2\text{SCN), 111.97 \text{ (s, SCN).} \]
For **minor rotamer**:

\[^1\text{H \text{NMR (400 MHz, CDCl}_3\text{):} \delta = 3.05 \text{ (s, 3H, CH}_3\text{), 3.37 \text{ (t, 2H, } J = 6.4 \text{ Hz, CH}_2\text{SCN), 4.54 \text{ (t, 2H, } J = 6.4 \text{ Hz, CH}_2\text{CH}_2\text{SCN).}}

\[^{13}\text{C \text{NMR signals could not be obtained because of low concentration.}}

**5.6.5 Thermolysis of oxadiazolinium tosylate 18**

Thermolysis of oxadiazolinium tosylate 18 (80 mg, 0.31 mmol) was performed by heating the neat compound under vacuum (10^{-3} \text{ mbar}) at high temperature (170 °C), and the volatiles were recondensed into CDCl\textsubscript{3} (0.76 mL) cooled by liquid N\textsubscript{2} over a period of 2 h. Acetaldehyde can be identified as one of the products formed in 15\% yield (NMR yield). The NMR data of acetaldehyde agrees with that reported in Section 5.2.3.
5.7 Synthesis of 3,5,5-trimethyl-4,5-dihydro-1,2,3-oxadiazolium mesylate (58)

Synthesis of mesylate 58 involves the synthesis of open-chain mesylate 57 from a known compound 2-methyl-1-[methyl(nitroso)amino]-2-propanol (56).

5.7.1 Synthesis of 2-methyl-1-[methyl(nitroso)amino]propan-2-yl methanesulfonate (57)

To a solution of 2-methyl-1-[methyl(nitroso)amino]-2-propanol (56) \[^{[47]}\] (26.4 mg, 0.2 mmol) in dry dichloromethane (1 mL) at 0 °C was added triethylamine (0.04 mL, 30.24 mg, 0.30 mmol, 1.5 eq), methanesulfonyl chloride (0.023 mL, 34.25 mg, 0.30 mmol, 1.5 eq), and the reaction mixture was stirred for 30 min. Subsequently, dichloromethane (5 mL) was added, and the reaction mixture was washed with cold 10% HCl (5 mL), saturated aq. NaHCO$_3$ (5 mL), and brine (5 mL). The organic phase was dried over Na$_2$SO$_4$ and solvent evaporated in vacuo to give 57 as a yellow oil (72%). This compound was pure enough and was used as such in the next step.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.66 (s, 6H, $2 \times$ CH$_3$), 3.00 (s, 3H, NCH$_3$), 3.16 (s, 3H, OSO$_2$CH$_3$), 4.41 (s, 2H, CH$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 25.21 (q, $2 \times$ CH$_3$), 34.07 (q, NCH$_3$), 40.84 (q, OSO$_2$CH$_3$), 62.39 (t, CH$_2$), 91.31 (s, C(CH$_3$)$_2$).

This compound 57 was found as a single rotamer, and it is highly probable that the NO oxygen atom is placed anti-periplanar to the OMs group since cyclization to mesylate 58 occurred readily as detailed in the next step.
5.7.2 Synthesis of mesylate 58 from open-chain mesylate 57

A solution of compound 57 (31 mg, 0.15 mmol) in dichloromethane (2 mL) was refluxed for 1 h. Subsequently, the solvent was removed in vacuo to give oxadiazolinium mesylate 58 as a yellow oil in quantitative yield.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.83$ (s, 6H, 2 $\times$ CH$_3$), 2.66 (s, ca. 3H, OSO$_2$CH$_3$), 4.42 (s, 3H, NCH$_3$), 5.06 (s, 2H, CH$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 26.44$ (q, 2 $\times$ CH$_3$), 39.72 (q, OSO$_2$CH$_3$), 43.33 (q, NCH$_3$), 67.57 (t, CH$_2$), 102.0 (s, C(CH$_3$)$_2$).

The structure was also supported by $^{13}$C,$^1$H gHSQCAD.

HR-MS (ESI): $m/z$ calcd. for C$_6$H$_{16}$N$_2$O$_4$S [M + 2H]$^+$ 212.0831; found: 212.1024.
5.8 Synthesis of O-(cis-2-aminocyclopentyl)hydroxylamine (76)

Compound 76 was synthesized in a multi-step synthesis from 2-bromocyclopentanone along with small amounts of the trans-isomer 77.

5.8.1 Synthesis of cis-2-azidocyclopentan-1-ol (70) and trans-2-azidocyclopentan-1-ol (71)

Compounds 70 and 71 are literature known compounds and have been synthesized here by an analogous method. Under an atmosphere of nitrogen, was placed 2-azidocyclopentanone (3.41 g, 27.25 mmol) in anhydrous MeOH (30 mL), and cooled to 0 °C. To this solution was added NaBH₄ (1.55 g, 40.88 mmol, 1.5 eq) portionwise, and the suspension was stirred for 1 h at 0 °C. Subsequently, the reaction mixture was poured into saturated brine solution (30 mL), and the water phase was extracted with diethyl ether (3 × 50 mL). The organic phase was dried over anhydrous MgSO₄ and evaporated in vacuo to yield a mixture of azidocyclopentanols 70 and 71 in a combined yield of 82 % (2.85 g). The product was an 80 : 20 mixture of 70 and 71 based on ¹H NMR data.

The data for stereochemical information was confirmed by literature known data and also by comparison of compound 71 (¹H NMR) signals obtained by the azidolysis of cyclopentene oxide in another experiment.
5.8.2 Synthesis of \(O\text{-}(\text{cis}-2\text{-azidocyclopentyl})\text{hydroxylamine (72) and } O\text{-}(\text{trans}-2\text{-azidocyclopentyl})\text{hydroxylamine (73)}\)

Electrophilic amination\(^{[53,54]}\) of the mixture of stereoisomers 70 and 71 obtained in Section 5.8.1 was accomplished via two different methods:

i) **Electrophilic amination by chloramine:** A mixture of aq. NaOCl solution (38.74 mL, ca. 19 M) and diethylether (149 mL) was cooled to 0 °C. Subsequently, 42 mL of 25% aq. ammonia solution was added cautiously (due to gas evolution). After complete addition, the organic phase was separated and dried over anhydrous CaCl\(_2\) for 1 h at −50 °C. By this method, around 2.02 g of chloramine is obtained as a solution in diethylether.

Under an atmosphere of nitrogen and strictly anhydrous conditions was placed NaH (0.35 g, 14.58 mmol, 1.1 eq) in anhydrous THF (15 mL). Subsequently, the mixture of 70 and 71 (1.0 g, 7.86 mmol) along with 18-crown-6 (0.21 g, 0.1 eq) was added to the sodium hydride suspension. This reaction mixture was stirred for 1 h at room temperature. Subsequently, chloramine in diethylether (2.02 g, 39.32 mmol, 5.0 eq), synthesized as above, was added dropwise and the stirring was continued overnight at room temperature. The reaction was stopped by the addition of 1 mL of ethanol, and 30 mL of distilled water was added to dissolve the precipitate which had formed. The organic phase was washed with distilled water (2 × 25 mL), and the water phase was extracted with diethylether (2 × 30 mL). The combined organic phase was dried over anhydrous MgSO\(_4\), and the solvent was evaporated \textit{in vacuo}. The residue was purified by column chromatography over silica gel using \(n\)-hexane : Et\(_2\)O (1:1) to give a mixture of 72 and 73 as a clear oil (80 mg, 8%), with 73 being the minor component (almost traces). The ratio of these stereoisomers cannot be determined owing to overlapping of the signals in \(^1\text{H} \text{NMR}.\) This method, however, suffered from extremely bad yields.
ii) **Electrophilic amination by 3,3-di-tert-butylloxaziridine**: 3,3-di-tert-butylloxaziridine was synthesized by a known method.\[54]\n
Under an atmosphere of argon, was placed KH (38 mg, 0.96 mmol, 30% suspension in mineral oil). To the KH suspension in mineral oil was added excess dry pentane, and the liquid part was pipetted out very carefully. After washing, potassium hydride was dried carefully by applying vacuum for 15 min. To dry KH was added dry DMPU (0.9 mL), 18-crown-6 (25 mg, 0.1 eq) and the resulting suspension was stirred. Subsequently, to this suspension was added the mixture of stereoisomers (70 and 71, 112 mg, 0.79 mmol) in 0.9 mL of dry DMPU, dropwise. Immediately, gas evolution was observed, and this reaction mixture was stirred for 1 h at room temperature. In another flask, was placed 3,3-di-tert-butylloxaziridine (357 mg, 1.58 mmol) in 0.9 mL dry DMPU and this solution was cooled to and maintained at −40 °C. Then, the alkoxide mixture was added to the oxaziridine solution dropwise, while maintaining the temperature at −40 °C. After the addition was complete, the reaction mixture was warmed up to room temperature, and stirred for 2 h. The reaction mixture was then diluted with 30 mL of 1 M HCl and washed with dichloromethane (3 x 30 mL). The aqueous layer was made alkaline with 1 M NaOH until pH = 12 (approx.), and was extracted with diethylether (3 x 30 mL). The combined extracts were dried over MgSO₄ and concentrated in vacuo. The residue was recondensed at 55 °C and under high vacuum (9 x 10⁻³ mbar) to obtain the mixture of stereoisomers 72 and 73 in a combined yield of 55%. Less than 10% of the trans-isomer 73 can be accounted for via the $^1$H NMR spectrum.

For **O-(cis-2-azidocyclopentyl)hydroxylamine (72)**:

![Structure of O-(cis-2-azidocyclopentyl)hydroxylamine (72)](image)

$^1$H NMR (400 MHz, CDCl₃): $\delta = 1.46$–$1.96$ (m, 6H, 3 x CH₂), 3.91 (dt, 1H, $^3J = 8.4$ Hz, 4.8 Hz, CHN₃), 4.08 (dt, 1H, $^3J = 8.4$ Hz, 6.4 Hz, CHONH₂), 6.07 (br. s, 2H, ONH₂).

$^{13}$C NMR (100 MHz, CDCl₃): $\delta = 19.49$ (t, CH₂), 27.21 (t, CH₂), 27.97 (t, CH₂), 63.04 (d, CHN₃), 86.30 (d, CHONH₂).
For \textit{O-(trans-2-azidocyclopentyl)hydroxylamine (73)}:

\[
\begin{align*}
\text{ONH}_2 & \\
\text{73} & \\
\text{N}_3
\end{align*}
\]

The signals in $^1$H NMR, more or less, merged with those of compound 72.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 21.64$ (t, CH$_2$), 29.15 (t, CH$_2$), 29.62 (t, CH$_2$), 65.45 (d, CHN$_3$), 89.25 (d, CHONH$_2$).

Combined analytical data for 72 and 73:

IR (CCl$_4$): $\tilde{\nu} = 3320$ (m), 2949 (m), 2097 (s).

HR-MS (ESI): $m/z$ calcd. for C$_5$H$_{11}$N$_4$O [M + H]$^+$ 143.0933; found: 143.0932: $m/z$ calcd. for C$_5$H$_{11}$N$_4$ONa [M + Na]$^+$ 165.0754; found: 165.0747.

\subsection*{5.8.3 Synthesis of hydroxylamine salts; 74 and 75 from the mixture of 72 and 73}

We used a general method for the Staudinger reduction.\textsuperscript{[55]} To a solution of the mixture of 72 and 73 (389 mg, 2.73 mmol) in dry MeOH (28 mL) was added PPh$_3$ (1.07 g, 4.10 mmol, 1.5 eq), and the reaction mixture was refluxed for 75 min. After the reaction mixture had cooled down to room temperature, the solvent was removed in vacuo. The residue was dissolved in a minimum amount of toluene, and few drops of conc. HCl was added until no more precipitation occurred. Subsequent filtration and washing with diethyl ether yielded a mixture of stereoisomers 74 and 75 in a ratio of 6.27 : 1 in a combined yield of 67% (213 mg).
For **O-(cis-2-aminocyclopentyl)hydroxylamine hydrochloride (74):**

\[
\begin{align*}
\text{ONH}_2 &- \text{nHCl} \\
74 & \text{n=1 or 2}
\end{align*}
\]

\(^1\)H NMR (400 MHz, \(\text{D}_2\text{O}\)): \(\delta = 1.71-2.15\) (m, 6H, 3 \(\times\) CH\(_2\)), 3.76 (dt, 1H, \(3^J = 8.8\) Hz, 4.8 Hz, CHNH\(_2\)), 4.72 (dt, 1H, \(3^J = 6.2\) Hz, 4.8 Hz, CHONH\(_2\)). Peaks for NH\(_2\), and ONH\(_2\) protons not observed.

\(^{13}\)C NMR (400 MHz, \(\text{D}_2\text{O}\)): \(\delta = 19.55\) (t, CH\(_2\)), 26.70 (t, CH\(_2\)), 28.00 (t, CH\(_2\)), 52.88 (d, CHNH\(_2\)), 84.50 (d, CHONH\(_2\)).

For **O-(trans-2-aminocyclopentyl)hydroxylamine hydrochloride (75):**

\[
\begin{align*}
\text{ONH}_2 &- \text{nHCl} \\
75 & \text{n=1 or 2}
\end{align*}
\]

\(^1\)H NMR (400 MHz, \(\text{D}_2\text{O}\)): \(\delta = 1.66-2.20\) (m, 6H, 3 \(\times\) CH\(_2\)), 3.64 (dt, 1H, \(3^J = 8.4\) Hz, 4.8 Hz, CHNH\(_2\)), 4.67 (dt, 1H, \(3^J = 6.8\) Hz, 4.8 Hz, CHONH\(_2\)).

\(^{13}\)C NMR (400 MHz, \(\text{D}_2\text{O}\)): \(\delta = 20.92\) (t, CH\(_2\)), 28.18 (t, CH\(_2\)), 29.02 (t, CH\(^2\)), 55.39 (d, CHNH\(_2\)), 88.03 (d, CHONH\(_2\)).

Combined IR and HR-MS (ESI) data for 76, and 77:

IR (KBr): \(\tilde{\nu} = 3118\) (m), 2979 (m), 2945 (m).

HR-MS (ESI): \(m/z\) calcd. for \(\text{C}_5\text{H}_{13}\text{N}_2\text{O}[M - \text{nHCl} + \text{H}, \text{n} = 1\ or\ 2]^{+}\ 117.1028\); found: 117.1022.
5.8.4 Synthesis of hydroxylamines 76 and 77

Hydroxylamines 76 and 77 were generated by treating a solution of salts 75 and 77 in water with excess of 30% aq. NaOH solution and extraction by diethyl ether. 76 and 77 were obtained in a ration of 6 : 1.

For \(O\)-\(cis\)-2-aminocyclopentyl)hydroxylamine (76):

\[
{\text{ONH}_2}
\]
\[
\begin{array}{c}
{\text{NH}_2} \\
76
\end{array}
\]

\(^1\text{H NMR (400 MHz, CDCl}_3\):} \quad \delta = 1.22–1.83 (m, 6H, 3 x CH\_2), 3.2 (m, 1H, CHNH\_2), 3.86 (m, 1H, CHONH\_2), 4.94 (br. s, 2H, NH\_2), 5.38 (br. s, 2H, ONH\_2).

For \(O\)-\(trans\)-2-aminocyclopentyl)hydroxylamine (77):

\[
{\text{ONH}_2}
\]
\[
\begin{array}{c}
{\text{NH}_2} \\
77
\end{array}
\]

\(^1\text{H NMR (400 MHz, CDCl}_3\):} \quad \delta = 1.22–2.06 (m, 6H, 3 x CH\_2), \text{signal for CHNH}_2 \text{ overlapped by 76}, 3.73 (m, 1H, CHONH\_2), \text{exchangeable proton signals (NH\_2, and ONH\_2) overlapped by the signals of 76}.}
5.9 Synthesis of O-(2-aminocyclododecyl)hydroxylamine (80) and (4E,8E)-12-azidocyclododeca-4,8-dienol (82)

Hydroxylamine 80 was synthesized by a multi-step synthesis involving the synthesis of β-azidoalcohol 78, azidohydroxylamine 79, and finally 80.

5.9.1 Synthesis of 2-azido-1-cyclododecanol (78)

A cis/trans mixture of cyclododecene oxide (182 mg, 1.0 mmol), was dissolved in a 10 : 1 mixture of DMF-H$_2$O (11 mL). To this solution was added NH$_4$Cl (53 mg, 1.0 mmol, 1.0 eq) and NaN$_3$ (98 mg, 1.51 mmol, 1.51 eq), and the reaction mixture was refluxed for 3 h. After cooling to room temperature, the reaction mixture was filtered and extracted with diethyl ether. The organic phase was washed with brine, dried over MgSO$_4$, and solvents evaporated in vacuo. Purification was accomplished by flash chromatography on silica gel (8 Et$_2$O : 2 EtOAc), resulting in a white solid as a mixture of diastereoisomers (151 mg, 67%); however, the second diastereoisomer was formed in almost traces.

For 2-azido-1-cyclododecanol (78):

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.32–1.82 (m, 20H, 10 $\times$ CH$_2$), 1.94 (br. s, 1H, OH), 3.51 (dt, 1H, $^3$J = 7.6 Hz, 5.2 Hz, CHN$_3$), 3.70 (dt, 1H, $^3$J = 7.6 Hz, 4.8 Hz, CHOH).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 20.72 (t, CH$_2$), 21.00 (t, CH$_2$), 23.04 (t, CH$_2$), 23.07 (t, CH$_2$), 23.40 (t, CH$_2$), 23.63 (t, CH$_2$), 23.69 (t, CH$_2$), 23.81 (t, CH$_2$), 27.34 (t, CH$_2$), 30.07 (t, CH$_2$), 64.65 (d, CHN$_3$), 70.30 (d, CHOH).

Compound 78 is a literature-known compound,$^{[56b]}$ but, was synthesized by a known procedure for other β-azidoalcohols.$^{[52]}$
5.9.2 Synthesis of $O$-(2-azidocyclododecyl)hydroxylamine (79)

A general method was used.\[^{[54]}\] Under an atmosphere of argon, was placed KH (47 mg, 1.2 mmol, 30% suspension in mineral oil). To the KH suspension in mineral oil was added excess dry pentane, and the liquid part was pipetted out very carefully. After washing, potassium hydride was dried carefully by applying vacuum for 15 min. To dry KH was added dry DMPU (1.1 mL), 18-crown-6 (110 mg) and the resulting suspension was stirred. Subsequently, to this suspension was added 78 (110 mg, 0.98 mmol) in 1.1 mL of dry DMPU, dropwise. Immediately, gas evolution was observed, and this reaction mixture was stirred for 2 h at room temperature. In another flask, was placed 3,3-di-tert-butyloxaziridine (440 mg, 1.96 mmol) in 1.1 mL dry DMPU and this solution was cooled to and maintained at $-40^\circ$C. Then, the alkoxide mixture was added to the oxaziridine solution dropwise, while maintaining the temperature at $-40^\circ$C. After the addition was complete, the reaction mixture was stirred at $-40^\circ$C for 1 h, and subsequently, warmed up to room temperature, and stirred for 2 h. The reaction mixture was then diluted with 30 mL of 1 M HCl and washed with dichloromethane ($3 \times 30$ mL). The aqueous layer was made alkaline with 1 M NaOH until pH = 12 (approx.), and was extracted with diethyl ether ($3 \times 30$ mL). The combined extracts were dried over MgSO$_4$ and concentrated \textit{in vacuo} to give 79 as a transparent oil (370 mg, 35%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.31$−1.80 (m, 20H, 10 × CH$_2$), 3.51 (ddd, 1H $^3J = 6.0$ Hz, 4.8 Hz, 4.4 Hz, CHN$_3$), 3.70 (dt, 1H, $^3J = 8.4$ Hz, 4.8 Hz, CHONH$_2$), 5.41 (br. s, 2H, ONH$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 20.50$ (t, CH$_2$), 21.40 (t, CH$_2$), 22.91 (t, CH$_2$), 22.93 (t, CH$_2$), 23.69 (t, CH$_2$), 23.78 (t, 2 × CH$_2$), 24.21 (t, CH$_2$), 26.42 (t, CH$_2$), 27.79 (t, CH$_2$), 61.99 (d, CHN$_3$), 83.78 (d, CHONH$_2$). Compound 78 was used as such in the next step.
5.9.3 Synthesis of \(O\)-(2-aminocyclododecyl)hydroxylamine (80) from compound 79

A general method was used.\[^{[55]}\] To a solution of compound 79 (240 mg, 1.0 mmol) in dry MeOH (10 mL), was added PPh\(_3\) (394 mg, 1.5 mmol, 1.5 eq), and the reaction mixture was refluxed for 2.5 h, and finally cooled to room temperature. The solvent was removed in vacuo and the residue was purified by flash chromatography over silica gel (6 CHCl\(_3\) : 2 \text{n}-hexane : 2 MeOH) to give hydroxylamine 80 as a transparent oil (150 mg, 70%, crude yield). However, compound 80 could not be purified completely. Analogous method used.\[^{[55]}\]

\(^1\text{H NMR (400 MHz, CDCl}_3\): } \delta = 1.10–1.84 (m, 20H, 10 \text{CH}_2), 1.33 (\text{br. s, 2H, NH}_2), 2.86 (m, 1H, CHNH2), 3.43 (m, 1H, CHONH2), 5.32 (\text{br. s, 2H, ONH}_2).

\(^{13}\text{C NMR (100 MHz, CDCl}_3\): } \delta = 20.17 (t, CH\text{2}), 21.87 (t, CH\text{2}), 23.06 (t, CH\text{2}), 23.11 (t, CH\text{2}), 23.31 (t, CH\text{2}), 23.69 (t, CH\text{2}), 24.18 (t, CH\text{2}), 24.70 (t, CH\text{2}), 25.97 (t, CH\text{2}), 30.92 (t, CH\text{2}), 50.07 (d, CHNH2), 86.14 (d, CHONH2).

HR-MS (ESI): \text{m/z calcd. for C}_{12}\text{H}_{26}\text{N}_2\text{ONa [M + Na]}^+ 237.1943; found: 237.1937.
Compound 82 was synthesized from the epoxide 81 which in turn was synthesized from the commercially available triene, viz., \((1E,5E,9Z)-1,5,9\)-cyclododecatriene.

5.9.4 Synthesis of \((4E,8E)-13\)-oxabicyclo[10.1.0]trideca-4,8-diene (81)

\[(1E,5E,9Z)-1,5,9\)-cyclododecatriene (194 mg, 1.2 mmol) was dissolved in \((\text{CF}_3)_2\text{CHOH}\) (1 mL), and to this solution was added \(\text{H}_2\text{O}_2\) (68 mg, 2.0 mmol, 1.67 eq, 35% stock solution). This reaction mixture was heated at 70 °C for 20 h. After cooling to room temperature, the reaction mixture was washed with brine. The organic phase was evaporated in vacuo which yielded a mixture of 80 along with another isomer in small amounts, and a combined yield of 87% (187 mg).

Compound 81 is a literature-known molecule;\(^{[57b]}\) however, it was now synthesized by another general method to prepare epoxides.\(^{[56a]}\)

\(^1\text{H NMR (400 MHz, CDCl}_3\): \(\delta = 1.04−1.22\) (m, 2H, CH\(_2\)), 2.01−2.23 (m, 10H, 5 \(x\) CH\(_2\)), 2.49 (dt, \(^3J = 8.8\) Hz, 2.4 Hz, CHO), 2.72 (dt, \(^3J = 10.4\) Hz, 2.4 Hz, CHO), 5.18−5.38 (m, 4H, \(-\text{CH=CH}−\)).

\(^{13}\text{C NMR (100 MHz, CDCl}_3\): \(\delta = 23.50\) (t, CH\(_2\)), 26.82 (t, CH\(_2\)), 28.29 (t, CH\(_2\)), 30.01 (t, CH\(_2\)), 31.90 (t, CH\(_2\)), 31.94 (t, CH\(_2\)), 58.91 (d, CHO), 59.61 (d, CHO), 128.89 (d, \(-\text{CH=CH}−\)), 129.85 (d, \(-\text{CH=CH}−\)), 130.90 (d, \(-\text{CH=CH}−\)), 130.14 (d, \(-\text{CH=CH}−\)).
5.9.5 Synthesis of \((4E,8E)-12\)-azidocyclododeca-4,8-dienol (82) from 81

A general method was used.\(^{[52]}\) Compound 81 (179 mg, 1.0 mmol) was dissolved in a 10 : 1 mixture of DMF-\(\text{H}_2\text{O}\) (11 mL). To this was added \(\text{NH}_4\text{Cl}\) (53 mg, 1.0 mmol, 1.0 eq), \(\text{NaN}_3\) (98 mg, 1.51 mmol, 1.51 eq), and the reaction mixture was refluxed for 16 h. After cooling, filtration, extraction with \(\text{Et}_2\text{O}\) (3 \(\times\) 10 mL), the organic phase was washed with brine, dried over \(\text{MgSO}_4\), and the solvent was evaporated \textit{in vacuo}. Compound 82 was obtained as a clear, transparent oil in 64% yield (143 mg) along with minor amounts of another diastereomer.

\(\textsuperscript{1}H\text{ NMR (400 MHz, CDCl}_3\):} \(\delta = 1.46–2.12 \text{ (m, 12H, 6} \times \text{CH}_2\), 3.60 \text{ (m, 1H, CHN}_3\), 3.85 \text{ (m, 1H, CHOH), 5.34–5.50 (m, 4H, –CH=CH–).}

\(\textsuperscript{13}C\text{ NMR (100 MHz, CDCl}_3\):} \(\delta = 22.10 \text{ (t, CH}_2\), 26.50 \text{ (t, CH}_2\), 27.89 \text{ (t, CH}_2\), 27.97 \text{ (t, CH}_2\), 30.91 \text{ (t, CH}_2\), 31.63 \text{ (t, CH}_2\), 64.36 \text{ (d, CHN}_3\), 72.41 \text{ (d, CHOH), 129.43 (d, –CH=CH–), 129.62 (d, –CH=CH–), 131.33 (d, –CH=CH–), 131.86 (d, –CH=CH–).}

\text{HR-MS (ESI):} \text{ m/z not observed.}
References


[25] Inputs from BASF, Ludwigshafen.


[34] W. Lijinsky, M. D. Reuber, Cancer Res. 1983, 43, 214–221.


$^1$H NMR (CDCl$_3$)
Reaction of TIOEt with 34
$^1$H NMR (CD$_2$Cl$_2$)
$\sim$20 °C

![NMR spectrum of compounds](image-url)

**Chemical Structure**

![Structural formula of compound 38](image-url)

**Assignments**

- **EtOH**: Peaks at δ 1.19, 1.17, 1.15, 1.13 ppm
- **Compounds**: Peaks at δ 5.32, 5.20 ppm
Reaction of TIOEt with 34
$^{13}$C NMR (CD$_2$Cl$_2$)
$-20$ °C

![Chemical Structure]

δ (ppm):
- 98.470
- 62.133
- 54.381
- 54.340
- 53.568
- 53.398
- 41.058
- 27.158
- 15.769

EtOH
Reaction of TIOEt with 34 \(^{13}\)C NMR CD\(_2\)Cl\(_2\) overnight measurement
Reaction of TIOEt with 34
$^1$H NMR (CD$_2$Cl$_2$)
$-90 \, ^\circ\text{C}$
Reaction of TIOEt with 34
$^1$H NMR (CD$_2$Cl$_2$)
−80 °C
Reaction of TIOEt with 34
\(^1\)H NMR (CD\(_2\)Cl\(_2\))
−80 °C
gCOSY
Reaction of TIOPr with 34
$^1$H NMR (CD$_2$Cl$_2$)
~60 °C
Reaction of TIOPr with 34
$^1$H NMR (CD$_2$Cl$_2$)
$-20 \, ^\circ$C
Reaction of TIOPr with 34
$^{13}$C NMR (CD$_2$Cl$_2$)
room temperature
Pure diazomethane solution
$^1$H NMR CDCl$_3$
$-10 \, ^\circ\text{C}$
Pure diazomethane solution
$^1$H NMR CDCl$_3$
After 15 min at −10 °C
Pure diazomethane solution
$^1$H NMR CDCl$_3$
$-10 \, ^\circ\text{C}$
Diazomethane solution + TIOEt (2.0 eq)
$^1$H NMR CDCl$_3$
After 15 min at $-10 \, ^\circ$C
Pure diazomethane solution
$^1$H NMR CDCl$_3$
$-10 \, ^{\circ}\text{C}$
Diazomethane solution plus TIPr (1.1 eq)

$^1$H NMR CDCl$_3$

After 15 min at ~10 °C
$^{15}\text{N NMR (CD}_2\text{Cl}_2)$
Reaction of TIOEt with 40
$^{15}$N NMR (CD$_2$Cl$_2$)
$\sim$50 °C

$^{15}$N=N=CH$_2$
(traces)

$^{15}$N=N

40

184.329

15.059

70.053

$\delta$ (ppm)

400 350 300 250 200 150 100 50 0 -50 -100 -150 -200 -250 -300 -350 -400
Reaction of TIOEt with 40
$^1$H NMR (CD$_2$Cl$_2$)
$-50 \, ^\circ$C
Reaction of TIOPr with 40
$^{15}$N NMR (CD$_2$Cl$_2$)
$-80$ °C
Reaction of TIOPr with 40
$^1$H NMR (CD$_2$Cl$_2$)
-80 °C
Reaction of TIOPr with 40 \(^{15}\text{N}_2\text{H}_2\) gHMBCAD (CD\(_2\)Cl\(_2\))

\(-80\, ^\circ\text{C}\)
Reaction of TIOPr with 40
$^{15}\text{N}$ NMR (CD$_2$Cl$_2$)
$-60 \degree \text{C}$
Reaction of TIOPr with 40 $^{15}$N NMR (CD$_2$Cl$_2$) 
$-40 ^\circ$C
Reaction of TiOPr with 40
$^1$H NMR (CD$_2$Cl$_2$)
$-40 \, ^\circ\text{C}$

$^{15}$N\text{H} = N\text{H} = \text{CH}_2$

CH$_3$CHO

PrOH

PrOH

$\delta$ (ppm)
Reaction of TIOPr with 40 $^{15}\text{N, H gHMBCAD (CD}_2\text{Cl}_2)$

$-40 \, ^\circ\text{C}$
Reaction of TIOPr with 40
$^{15}$N NMR (CD$_2$Cl$_2$)
$-10 \, ^\circ$C
$^1$H NMR ($CD_2Cl_2$)

$^{15}$N labeled $\alpha$-methyl-$\alpha$-nitrosourea
$^{13}\text{C NMR (CD}_2\text{Cl}_2)$

$^{15}\text{N labeled } N\text{-methyl-N-nitrosourea}$
$^{15}\text{N NMR (CD}_2\text{Cl}_2)$

$^{15}\text{N labeled } N\text{-methyl-}N\text{-nitrosourea}$

\[ \text{Diagram of the molecule with } ^{15}\text{N labeled } N\text{-methyl-}N\text{-nitrosourea} \]

\[ \delta \text{ (ppm)} \]

400 350 300 250 200 150 100 50 0 -50 -100 -150 -200 -250 -300 -350 -400
Reaction of $N$-methyl-$N$-nitrosourea with TIOPr at -60 °C
$^1$H NMR (CD$_2$Cl$_2$)
Reaction of \(N\)-methyl-\(N\)-nitrosourea
with TIOPr at -60 °C
\(^{15}\text{N},^{1}\text{H} \text{gHMBCAD (CD}_2\text{Cl}_2)\)
Reaction of aq. KOH with 34
$^1$H NMR (CD$_2$Cl$_2$)

$-20 \degree$C

trans-2-butenal

CH$_3$CHO

$\delta$ (ppm)

13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
Reaction of DIPA with 34
^1H NMR (CD_2Cl_2)
room temperature
Reaction of TEMP with 34
$^1$H NMR (CD$_2$Cl$_2$)
room temperature

CH$_3$CHO

Denitrosated 34

TEMP

CH$_3$CHO
Reaction of 34 with NaOMe at -40 °C
$^1$H NMR (THF-d$_8$)
44
gHSQCAD (CDCl₃)
Reaction of 44 with TIOPr at -40 °C

$^1$H NMR (THF-$d_8$)
Reaction of 43 with TIOPr

$^1$H NMR (CD$_2$Cl$_2$)

$-20 \, ^{\circ}\text{C}$

$\text{CH}_3\text{CHO}$

$\text{CH}_2\text{N}_2$

$\text{CH}_3\text{CHO}$
Reaction of 18 with QN$_3$

$^1$H NMR (CDCl$_3$)

$-45 \, ^\circ$C

52

CH$_3$N$_3$
$^1$H NMR of 52
CDCl$_3$

52

After recondensation of reaction mixture
Reaction of 18 with $QN_3$

$^{13}$C NMR (CDCl$_3$)

$-45 \, ^{\circ}\text{C}$

52
Reaction of 18 with TMGA
$^1$H NMR (CDCl$_3$)
$-45 \, ^\circ\mathrm{C}$
Reaction of 18 with TMGA
$^{13}$C NMR (CDCl$_3$)
$-45$ °C
Recondensed CH$_3$N$_3$ from QN$_3$ reaction with 18
$^1$H NMR (CDCl$_3$)
~20 °C
Recondensed CH$_3$N$_3$ from QN$_3$ reaction with 18
$^1$H NMR (CDCl$_3$)
-20 °C
Recondensed CH₃N₃ from TMGA reaction with 18
¹³C NMR (CDCl₃)
-20 °C
Reaction of 18 with QI
$^1$H NMR (CDCl$_3$)
room temperature

53a and 53b
(mixture of rotamers)
Reaction of 18 with QI
$^{13}$C NMR (CDCl$_3$)
room temperature

53a and 53b

(mixture of rotamers)
Reaction of 18 with QBr

$^1H$ NMR (CDCl$_3$)

54a and 54b
Reaction of 18 with QBr to C NMR (CDCl₃)

54a and 54b only signals of major rotamer seen
Reaction of 18 with QSCN

$^1$H NMR (CDCl$_3$)

55a and 55b
Reaction of 18 with QSCN

$^{13}$C NMR (CDCl$_3$)

55a and 55b
$^{1}H$ NMR (CD$_2$Cl$_2$)
$^{13}$C NMR (CD$_2$Cl$_2$)
$^{13}$C NMR (CDCl$_3$)

$72 \quad \quad 73$ (minor)

$\delta$ (ppm)

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

-89.250
-86.302
-65.445
-63.037
29.623
29.157
27.968
27.218
21.642
19.494
$^1$H NMR (CDCl$_3$)
$^{13}$C NMR (CDCl$_3$)

67

$^{13}$C NMR (CDCl$_3$)
$^{13}$C NMR (CDCl$_3$)
$^1$H NMR (CDCl$_3$)
$^{13}$C NMR (CDCl$_3$)
\(^1\)H NMR (CDCl\(_3\))

![NMR Spectrum](image)

δ (ppm)
$^{13}$C NMR (CDCl$_3$)
Crystal structure data for 3-methyl-4,5-dihydro-1,2,3-oxadiazolium tosylate (18)

**Figure S1.** ORTEP representation (50% probability level) of the molecular structure of the asymmetric unit of 18 with atom numbering scheme; hydrogen atoms in calculated positions are omitted for clarity.

**Figure S2.** ORTEP representation (30% probability level) of the one-dimensional hydrogen bridge bond network of 18 with selected atom numbering scheme.
Figure S3. Packing of 18 (grey: carbon; red: oxygen; blue: nitrogen; yellow: sulfur; black: hydrogen).

The packing consists of cationic oxadiazolinium layers parallel to [010], which are separated by the tosylate anions forming the hydrogen bridge-bond network (Figure SI3). The non-polar parts of the tosylate molecules are arranged in a zipper-type structure with the adjacent layer without any interactions between both layers.

Temperature (T): 110 K

Radiation: Mo–Kα, λ = 0.71073 Å
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<td>O(6)–S(2)</td>
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<tr>
<td>O(8)–H(103)</td>
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<tr>
<td>O(8)–H(108)</td>
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<td>O(8)–H(208)</td>
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</tr>
<tr>
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<td>119.6(3)</td>
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<td>121.7(2)</td>
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<tr>
<td>C(3)–C(4)–C(5)</td>
<td>118.5(2)</td>
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<td>C(3)–C(4)–C(7)</td>
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<td>C(5)–C(6)–C(1)</td>
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<td>Angle (°) ± Error</td>
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<td>C(12)-C(13)-C(8)</td>
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<td>C(8)-C(9')-H(9')</td>
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<td>C(10')-C(9')-H(9')</td>
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<td>C(11)-C(10')-C(9')</td>
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<td>C(11)-C(10')-H(10')</td>
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<td>C(9')-C(10')-H(10')</td>
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<td>C(13')-C(12')-C(11)</td>
<td>121.6(5)</td>
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\begin{align*}
C(13')-C(12')-H(12') & \quad 119.2 \\
C(11)-C(12')-H(12') & \quad 119.2 \\
C(12')-C(13')-C(8) & \quad 117.1(5) \\
C(12')-C(13')-H(13') & \quad 121.4 \\
C(8)-C(13')-H(13') & \quad 121.4 \\
C(11)-C(14)-H(14A) & \quad 109.5 \\
C(11)-C(14)-H(14B) & \quad 109.5 \\
H(14A)-C(14)-H(14B) & \quad 109.5 \\
C(11)-C(14)-H(14C) & \quad 109.5 \\
H(14A)-C(14)-H(14C) & \quad 109.5 \\
H(14B)-C(14)-H(14C) & \quad 109.5 \\
O(7)-C(15)-C(16) & \quad 103.65(19) \\
O(7)-C(15)-H(15A) & \quad 111.0 \\
C(16)-C(15)-H(15A) & \quad 111.0 \\
O(7)-C(15)-H(15B) & \quad 111.0 \\
C(16)-C(15)-H(15B) & \quad 111.0 \\
H(15A)-C(15)-H(15B) & \quad 109.0 \\
N(1)-C(16)-C(15) & \quad 100.21(19) \\
N(1)-C(16)-H(16A) & \quad 111.7 \\
C(15)-C(16)-H(16A) & \quad 111.7 \\
N(1)-C(16)-H(16B) & \quad 111.7 \\
C(15)-C(16)-H(16B) & \quad 111.7 \\
H(16A)-C(16)-H(16B) & \quad 109.5 \\
N(1)-C(17)-H(17A) & \quad 109.5 \\
N(1)-C(17)-H(17B) & \quad 109.5 \\
H(17A)-C(17)-H(17B) & \quad 109.5 \\
N(1)-C(17)-H(17C) & \quad 109.5 \\
H(17A)-C(17)-H(17C) & \quad 109.5 \\
H(17B)-C(17)-H(17C) & \quad 109.5 \\
N(2)-N(1)-C(17) & \quad 120.1(2)
\end{align*}
N(2) – N(1) – C(16) : 115.6(2)
C(17) – N(1) – C(16) : 124.3(2)
N(1) – N(2) – O(7) : 110.84(19)
N(2) – O(7) – C(15) : 109.69(18)
H(1O3) – O(8) – H(1O8) : 108(3)
H(1O3) – O(8) – H(2O8) : 113(4)
H(1O8) – O(8) – H(2O8) : 111(4)
O(1) – S(1) – O(2) : 115.47(11)
O(1) – S(1) – O(3) : 110.39(10)
O(2) – S(1) – O(3) : 110.78(11)
O(1) – S(1) – C(1) : 107.25(12)
O(2) – S(1) – C(1) : 106.82(11)
O(3) – S(1) – C(1) : 105.53(11)
O(5) – S(2) – O(4) : 113.65(11)
O(5) – S(2) – O(6) : 113.01(11)
O(4) – S(2) – O(6) : 111.16(11)
O(5) – S(2) – C(8) : 107.04(12)
O(4) – S(2) – C(8) : 105.55(10)
O(6) – S(2) – C(8) : 105.73(11)
Torsion angles [deg]

C(6) - C(1) - C(2) - C(3)  -0.9(4)
S(1) - C(1) - C(2) - C(3)  179.2(2)
C(1) - C(2) - C(3) - C(4)  0.4(4)
C(2) - C(3) - C(4) - C(5)  -0.1(4)
C(2) - C(3) - C(4) - C(7)  178.7(3)
C(3) - C(4) - C(5) - C(6)  0.2(4)
C(7) - C(4) - C(5) - C(6)  -178.6(3)
C(4) - C(5) - C(6) - C(1)  -0.6(4)
C(2) - C(1) - C(6) - C(5)  1.0(4)
S(1) - C(1) - C(6) - C(5)  -179.1(2)
C(9') - C(8) - C(9) - C(10) -80(2)
C(13) - C(8) - C(9) - C(10) -5.6(10)
C(13') - C(8) - C(9) - C(10) 35.0(10)
S(2) - C(8) - C(9) - C(10)  -177.7(7)
C(8) - C(9) - C(10) - C(11)  -2.1(13)
C(10') - C(11) - C(10) - C(9) 77(3)
C(12) - C(11) - C(10) - C(9)  11.0(11)
C(12') - C(11) - C(10) - C(9) -29.8(10)
C(14) - C(11) - C(10) - C(9)  -178.4(7)
C(10') - C(11) - C(12) - C(13) -34.4(9)
C(10) - C(11) - C(12) - C(13)  -12.2(9)
C(12') - C(11) - C(12) - C(13)  73.8(7)
C(14) - C(11) - C(12) - C(13)  177.2(5)
C(11) - C(12) - C(13) - C(8)  4.5(10)
C(9') - C(8) - C(13) - C(12)  29.3(8)
C(9) - C(8) - C(13) - C(12)  4.5(9)
C(13') - C(8) - C(13) - C(12) -88.4(9)
S(2) - C(8) - C(13) - C(12)  176.7(5)
C(9)–C(8)–C(9′)–C(10′) 84(2)
C(13)–C(8)–C(9′)–C(10′) −31.8(8)
C(13′)–C(8)–C(9′)–C(10′) 6.5(9)
S(2)–C(8)–C(9′)–C(10′) −178.7(5)
C(12)–C(11)–C(10′)–C(9′) 32.8(10)
C(10)–C(11)–C(10′)–C(9′) −90(3)
C(12′)–C(11)–C(10′)–C(9′) −7.4(10)
C(14)–C(11)–C(10′)–C(9′) 179.9(6)
C(8)–C(9′)–C(10′)–C(11) 0.9(12)
C(10′)–C(11)–C(12′)–C(13′) 7.2(9)
C(12)–C(11)–C(12′)–C(13′) −79.6(7)
C(10)–C(11)–C(12′)–C(13′) 31.7(8)
C(14)–C(11)–C(12′)–C(13′) −179.9(5)
C(11)–C(12′)–C(13′)–C(8) −0.7(9)
C(9′)–C(8)–C(13′)–C(12′) −6.2(8)
C(9)–C(8)–C(13′)–C(12′) −32.2(8)
C(13)–C(8)–C(13′)–C(12′) 72.8(8)
S(2)–C(8)–C(13′)–C(12′) 178.7(5)
O(7)–C(15)–C(16)–N(1) 2.4(2)
C(15)–C(16)–N(1)–N(2) −2.2(3)
C(15)–C(16)–N(1)–C(17) 176.8(2)
C(17)–N(1)–N(2)–O(7) −178.1(2)
C(16)–N(1)–N(2)–O(7) 1.0(3)
N(1)–N(2)–O(7)–C(15) 0.8(3)
C(16)–C(15)–O(7)–N(2) −2.1(3)
C(6)–C(1)–S(1)–O(1) −18.7(2)
C(2)–C(1)–S(1)–O(1) 161.1(2)
C(6)–C(1)–S(1)–O(2) −143.1(2)
C(2)–C(1)–S(1)–O(2) 36.8(2)
C(6)–C(1)–S(1)–O(3) 99.0(2)
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Curriculum Vitae

Personal Information

Name: Neeraj Singh
Date of Birth: February 25, 1987
Place of Birth: Ghazipur, India
Nationality: Indian

Education

2000–2002 High School, Mahanagar Boys' Inter College
2002–2004 Intermediate, Mahanagar Boys' Inter College
2005–2008 Bachelor of Science, University of Lucknow, India
2008–2010 Master of Science in Chemistry, University of Lucknow, India

Awards

- Fifth rank in the entire university in B.Sc. examination.
- Satish Chandra Vinod Chandra Gold Medal for obtaining highest marks in Zoology in B.Sc.
- First rank in the entire university in M.Sc. examination.
- Qualified Lecturer eligibility test conducted by CSIR-UGC, India.
- Received DST (Department of Science and Technology, India) Inspire fellowship.
- Received DAAD PhD Scholarship to pursue doctoral research work under the supervision of Prof. Dr. Klaus Banert, TU Chemnitz, Chemnitz, Germany.
- A2 level Deutsch Certificate from InterDaf Leipzig.

Publications

2) 4.5-Dihydro-1,2,3-oxadiazole: A Very Elusive Key Intermediate in Very Important Chemical Transformations. K. Banert, N. Singh, B. Fiedler, J.

**Posters presented**


Selbstständigkeitserklärung

Hiermit erkläre ich an Eides statt, dass ich die vorliegende Arbeit selbstständig und nur unter Verwendung der angegebenen Quellen und Hilfsmittel angefertigt habe.

Neeraj Singh,

Neeraj Singh  Chemnitz  16.09.2015

Unterschrift  Ort  Datum