Monatshefte für Chemie 125, 1383–1387 (1994)

Monatshefte für Chemie
Chemical Monthly

Printed in Austria

4,5-Dihydro-5,5-dimethyl-3-oxo-3*H*-1,2,4-triazole-1-oxide. The Unpredicted Azoxy-Regioisomer

J. G. Schantl[1,*], **J. Svetlik**[2], and **V. Kettmann**[2]

[1] Institut für Organische Chemie, Universität Innsbruck, A-6020 Innsbruck, Austria
[2] Department of Analytical Chemistry, Faculty of Pharmacy, SK-83232 Bratislava, Slovakia

Summary. 4,5-Dihydro-5,5-dimethyl-3-oxo-3*H*-1,2,4-triazole (**1**) is converted to the title azoxy compound **4** by peroxytrifluoroacetic acid. The structure assignment of **4** is based on an X-ray analysis. *Ab initio* calculations were employed to rationalize the reaction path leading to the triazole-1-oxide **4** and not to the expected regioisomer triazole-2-oxide **3**.

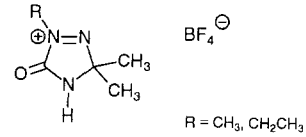
Keywords. 4,5-Dihydro-3-oxo 3*H*-1,2,4-triazole; 4,5-Dihydro-3-oxo-3*H*-1,2,4-triazole-1-oxide; Azoxy compound.

4,5-Dihydro-5,5-dimethyl-3-oxo-3*H*-1,2,4-triazol-1-oxid. Das unerwartete Regioisomere.

Zusammenfassung. 4,5-Dihydro-5,5-dimethyl-3-oxo-3*H*-1,2,4-triazol (**1**) wird mit Trifluorperessigsäure in die Titel-Azoxy-Verbindung **4** umgewandelt. Die Strukturzuordnung von **4** basiert auf einer Röntgenstrukturanalyse. Mittels *ab initio*-Rechnungen wird versucht zu erklären, weshalb die Reaktion zum Triazol-1-oxid **4** und nicht zum erwarteten regioisomeren Triazol-2-oxid **3** führt.

Introduction

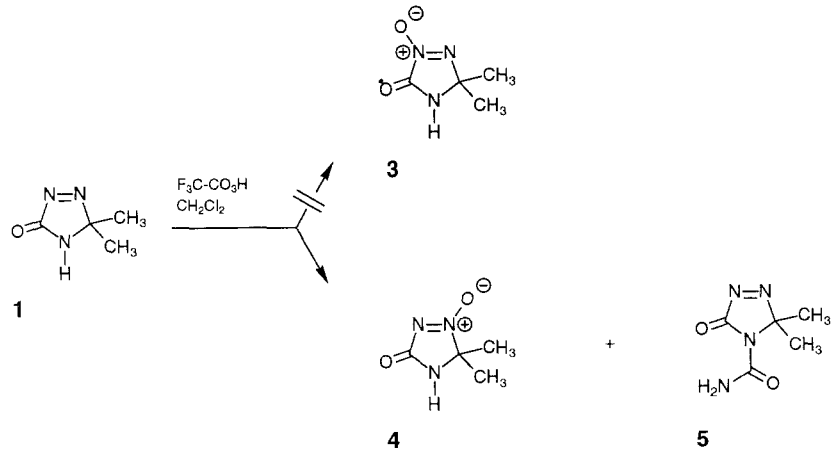
Azoxy compounds (diazene oxides) are of interest because of their potential as biologically active compounds. Some natural products incorporating an azoxy function exhibit antibiotic activity [1, 2]. Other azoxy compounds are potential carcinogens due to their alkylating capability [2]. Although acyclic azoxy compounds represent a well known class of compounds, cyclic analogs are less abundant [1, 3]. In the course of the investigation of the reactivity of 4,5-dihydro-5,5-dimethyl-3-oxo-3*H*-1,2,4-triazole (**1**) [4–6] it seemed to be of interest to explore the site of electrophilic attack at the diazene function. Alkylation with *Meerwein* salts (R_3O^+ BF_4^-) was reported to occur at the N-2 position furnishing 2-alkyl-triazolium salts **2** [6]. By analogy, electrophilic oxygenation was supposed to take place at the same N-2 position giving rise to the azoxy derivative **3**.



2

Results and Discussion

Common reagents for N-oxidation like *m*-chloroperbenzoic acid, performic acid, peracetic acid, magnesium monoperoxyphthalate, and similarly dimethyldioxirane [7] failed to react with triazole **1**. Only peroxytrifluoroacetic acid [8], considered to be one of the most powerful oxygen transfer reagents, worked as expected. The reaction of triazole **1** with peroxytrifluoroacetic acid in dichloromethane at reflux temperature led to one major product which turned out to be the azoxy derivative **4** (*vide infra*) rather than its regioisomer **3** (Scheme 1). In addition, a small amount of 4-aminocarbonyl-4,5-dihydro-5,5-dimethyl-3-oxo-3*H*-1,2,4-triazole (**5**) [4] was formed. It appears to be the self-carbamoylation product of compound **1**. Both products **4** and **5** were separated and purified from intractable material by column chromatography.



1 3 4 5

Scheme 1

Elemental analysis and mass spectra provided proof of the molecular formula of the oxygenation product emerging from the peracid treatment of **1**. The EI-MS exhibited the molecular ion at $m/z = 129$, and the parent ion at $m/z = 85$ indicated the loss of N_2O. Moreover, the strong IR-absorption at 1549 cm^{-1} is typical of the azoxy moiety [9, 10]. These data did not provide any clue as to the azoxy regioisomer **3** or **4** formed. The NMR spectra were not conclusive either. The ^1H NMR spectra of **1** and the azoxy product were nearly identical. The ^{13}C NMR chemical shift differences between the starting compound **1** [5] and the azoxy derivative were not significant enough to draw an unambiguous conclusion as to the oxygenation site in the azoxy product. Eventually, the structure of the oxygenation product was determined by single crystal X-ray analysis. As revealed

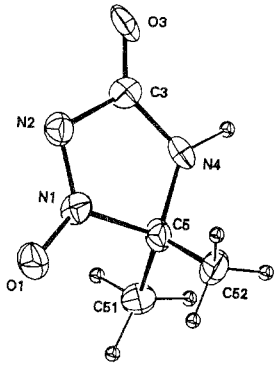


Fig. 1. ORTEP plot of **4**

by the ORTEP view (Fig. 1), oxygen is attached to the N-1 atom, thus proving structure **4** for the azoxy product derived from **1** [11].

This result is in striking contrast with the expectation based on experience and literature [12]. According to a study on the oxygenation of substituted azobenzenes with perbenzoic acid, the more nucleophilic nitrogen atom of the diazene function is oxygenated [12]. Accounting for electronic effects, the N-2 position of **1** was considered to be the more nucleophilic site of the two diazene nitrogen atoms. This was reflected by the alkylation of **1** with trialkyloxonium tetrafluoroborate, affording the 2-alkyltriazolium salts **2** (*vide supra*) [6].

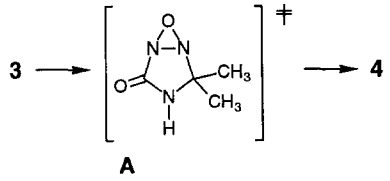
Ab initio MO calculations of the electron distribution in **1** substantiated the higher electron density at the N-2 position as compared to N-1. Thus, the N-2 atom was envisioned to be the more susceptable site for oxygenation by the peracid reagent giving rise to the triazole-oxide **3**.

However, contrary to the theoretically based prediction, the azoxy compound **4** was actually obtained. Perhaps, the formation of **4** could be rationalized by thermodynamics favoring this regioisomer. The comparison of the total energy E_{tot} of both regioisomers **3** and **4** (as calculated using *ab initio* RHF/STO-3G MO models) seemed to confirm this suggestion: $E_{tot}(\mathbf{3}) = -462.47822$ Hartree, $E_{tot}(\mathbf{4}) = -462.49032$ Hartree. The energy difference of $\Delta E_{tot} = 31.8$ kJ/mol is sufficiently large to provide for the formation of isomer **4** only.

Table 1. 4–31G calculated total charge densities of **1**. The geometry was optimized using the SCF restricted *Hartrees-Fock* (RHF) method within the GAUSSIAN 90 program package [13] employing the internal STO-3G basis set. The net atomic charges were calculated at the RHF/4–31G level.

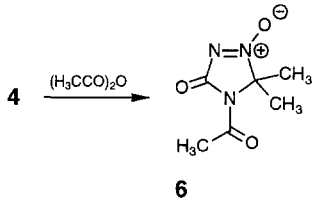
N-1	−0.1328	C-51	−0.4361
N-2	−0.2396	H1-51	0.2070
C-3	0.9230	H2-51	0.1764
O-3	−0.5763	H3-51	0.1858
N-4	−0.9013	C-52	−0.4361
H-4	0.4115	H1-52	0.2070
C-5	0.2491	H2-52	0.1764
		H3-52	0.1858

In order to comply with both the anticipated nucleophilic reactivity at the N-2 position of the starting compound **1** and the formation of the thermodynamically favored azoxy product **4** (oxygen atom attached to the N-1 atom), the following rationalization is offered [14]. Oxygenation of **1** may occur first at the N-2 position. The resultant intermediate **3**, in turn, undergoes a rearrangement *via* the oxadiaziridine-like transition state **A** to afford the isomeric azoxy product **4** (Scheme 2). Alternatively, the oxygenation of **1** may directly proceed *via* **A**.



Scheme 2

The azoxy compound **4** was found to be remarkably sensitive toward alkali leading to rapid decomposition under gas evolution. This behaviour parallels and exceeds the instability of **1** towards bases [6]. Attempts to alkylate the azoxy compound **4** with methyl iodide, dimethyl sulfate, and *Meerwein* reagent failed.



Scheme 3

Acetylation with acetyl chloride did not work, but refluxing **4** in acetic anhydride afforded the acetyl derivative **6** (Scheme 3). Contrary to the parent compound **1**, carbamoylation with phenylisocyanate could not be achieved. Also an attempt to employ the azoxy function of **4** as a 1,3-dipole in a cycloaddition reaction with dimethyl acetylenedicarboxylate was not successful.

Experimental

The following instrumentation was used: M.p., Kofler hot stage microscope [Reichert]; FT-IR: Mattson Galaxy 3020; ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz): Bruker AM 300; MS: Varian MAT 44S (70 eV); X-Ray: Synthex $P2_1$.

4,5-Dihydro-5,5-dimethyl-3-oxo-3H-1,2,4-triazole-1-oxide (**4**)

To a stirred mixture of 90% hydrogen peroxide (1.0 ml, 0.029 mol) and dichloromethane (40 ml) at 0 °C trifluoroacetic anhydride (2.8 ml, 0.02 mol) was added dropwise. After 1 h at this temperature, a solution of **1** (0.77 g, 0.0068 mol) in dichloromethane (20 ml) was added and the mixture was heated at reflux temperature for 8 h. After removal of the solvent, the oily residue was subjected to column chromatography on silica. Ether was used to elute first **5** [4] (40 mg, 7.5%). Subsequent elution with acetone gave **4** (0.46 g, 52%, colorless crystals after recrystallization from methanol/diethyl ether).

M.p.: 155–156 °C (decomp.); IR (KBr): 3216 (NH), 1753 (CO), 1549 cm^{-1} (NNO); ^1H NMR (*DMSO*-d_6): $\delta = 1.61$ (s, 6H, 2 CH_3), 9.81 (br, s, 1H, NH); ^{13}C NMR (*DMSO*-d_6): $\delta = 25.58$ (CH_3), 98.84 (C-5), 159.67 (CO); EI-MS (*m/z* (%)): 129 (28, $MH^{+\cdot}$), 105 (12), 85 (100), 84 (83), 83 (32); CI-MS (isobutane): 130 (MH^+); anal.: calcd. for $C_4H_7N_3O_2$ (129.12): C 37.21, H 5.46, N 32.54; found: C 37.50, H 5.51, N 32.82.

4-Acetyl-4,5-dihydro-5,5-dimethyl-3-oxo-3H-1,2,4-triazole-1-oxide (**6**)

A solution of **4** (0.40 g, 0.0031 mol) in acetic anhydride (5 ml) was heated at 95 °C for 2 h. After evaporation of the solvent, a gelatinous residue (0.39 g, 73%) was obtained which could not be crystallized.
IR (KBr): 1780 (CO), 1718 (CO), 1549 cm^{-1} (NNO); ^1H NMR (*DMSO*-d_6): $\delta = 1.83$ (s, 6H, $2CH_3$), 2.51 (s, 3H, CH_3); ^{13}C NMR (*DMSO*-d_6): $\delta = 23.94$ (2 CH_3), 25.28 (CH_3CO), 98.55 (C-5), 156.87 (CO), 168.05 (CO); CI-MS (isobutane): 172 (MH^+).

Acknowledgment

This work has been supported by the *Österreichische Nationalbank* (*Jubiläumsfonds*, Project No. 4247).

References

[1] Schantl J. C. (1993) In: Kropf H., Schaumann E. (eds) Houben-Weyl, Methoden der Organischen Chemie, vol. E15/1. G. Thieme, Stuttgart, 1090
[2] Lang Fugmann S., Pawlenko S. (1992) In: Klamann D (ed) Houben-Weyl, Methoden der Organischen Chemie, vol. E16d/1. G. Thieme, Stuttgart, 119
[3] Snyder J. P., Lee L., Bandurco V. T., Yu C. Y., Boyd R. J. (1972) J. Am. Chem. Soc. **94**: 3260, and references cited therein
[4] Schantl J. G., Gstach H., Lanznaster N. (1987) Synthesis 986
[5] Schantl J. G., Gstach H., Lanznaster N., Gieren A., Lamm V. (1987) J. Heterocycl. Chem. **24**: 1401
[6] Schantl J. G., Lanznaster N., Gstach H. (1990) Heterocycles **31**: 825
[7] Adam W., Curci R., Edwards J. O. (1989) Acc. Chem. Res. **22**: 205. Adam W., Bialas J., Hadjiarapoglou L. (1991) Chem. Ber. **124**: 2377
[8] Carruthers W. (1971) In: Some Modern Methods of Organic Synthesis. Cambridge University Press, London, p 264
[9] Langley B. W., Lythgoe B., Rayner L. S. (1952) J. Chem. Soc. 4191
[10] Freeman J. P. (1962) J. Org. Chem. **27**: 1309
[11] The full details of the crystal and molecular structure of the triazole-oxide **4** will be given elsewhere: Kettmann, V., Svetlik, J., Schantl, J. G. (1994) Acta Cryst. C. (submitted)
[12] Mitsuhashi T., Simamura O., Tezuka Y. (1970) J. Chem. Soc., Chem. Commun. 1300.
[13] Frisch M. J., Head-Gordon M., Trucks G. W., Foresman J. B., Schlegel H. B., Raghavachari K., Robb M. A., Binkley J. S., Gonzalez C., DeFrees D. J., Fox D. J., Whiteside R. A., Seeger R., Melius C. F., Baker J., Martin R. L., Kahn L. R., Stewart J. J. P., Topiol S., Pople J. A. (1990) GAUSSIAN 90, Revision H, Gaussian Inc., Pittsburgh.
[14] A similar rationalization based on kinetic measurements has been used to explain the oxidation of 1,3-diaryltriazenes with perbenzoic acid: Mitsuhashi T., Simamura O. (1970) J. Chem. Soc. B 705.

Received June 29, 1994. Accepted July 18, 1994