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On the Lead Tetraacetate Oxidation of 4-Amino-1,2,4-triazoles, 1-Amino- and 2-Amino-1,2,3-triazoles

Short Communication

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Lead tetraacetate oxidation of 4-amino-1,2,4-triazoles, 1-amino- and 2-amino-1,2,3-triazoles affords mainly fragmentation to nitriles or acetylenes, even in the presence of intramolecularly attached double bonds.

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Über die Bleitetraacetatoxidation von 4-Amino-1,2,4-triazolen, 1-Amino- und 2-Amino-1,2,3-triazolen (Kurze Mitteilung)

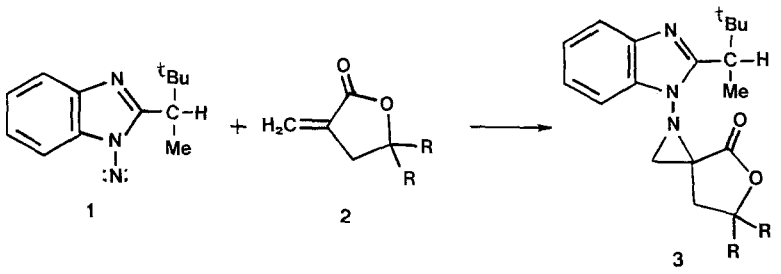
Bei der Oxidation von 4-Amino-1,2,4-triazolen, 1-Amino- und 2-Amino-1,2,3-triazolen mit Bleitetraacetat entstanden hauptsächlich Nitrile bzw. Acetylene durch Fragmentierung — trotz der Gegenwart von intramolekularen Doppelbindungen.

Although the addition of C-nitrenes to alkenes yields aziridines in low yield or in a non-stereospecific way [1], most N-nitrenes can be trapped by alkenes to give good yields of aziridines [2]. The singlet ground state of N-nitrenes allows their additions to be stereospecific and without competition from insertion to C–H bonds.

Moreover, *Atkinson* has recently demonstrated that chirality can be transferred to aziridines from the chiral (but racemic) N-nitrene **1** to prochiral alkenes. Indeed, a 5.3 : 1 mixture of diastereoisomers of the adduct **3** was obtained by addition of **1** to the α-methylene-γ-butyrolactone **2** (R = H) (Scheme 1), but only a single isomer was detected in the NMR spectrum of the crude product when the reaction was performed on **2** ($R = Me$) [3].

Thus, aziridination of alkenes by N-nitrenes is endowed with a considerable synthetic potential, although the interest of this reaction has been only recently recognized, in contrast to the well known merits of epoxidation, its oxygen-counterpart. The aziridine-linked heterocycle could be removed by a number of ways and, like epoxides, aziridines can be opened in a selective way, providing an useful entry to more complex nitrogen-containing synthetic targets.

Scheme 1



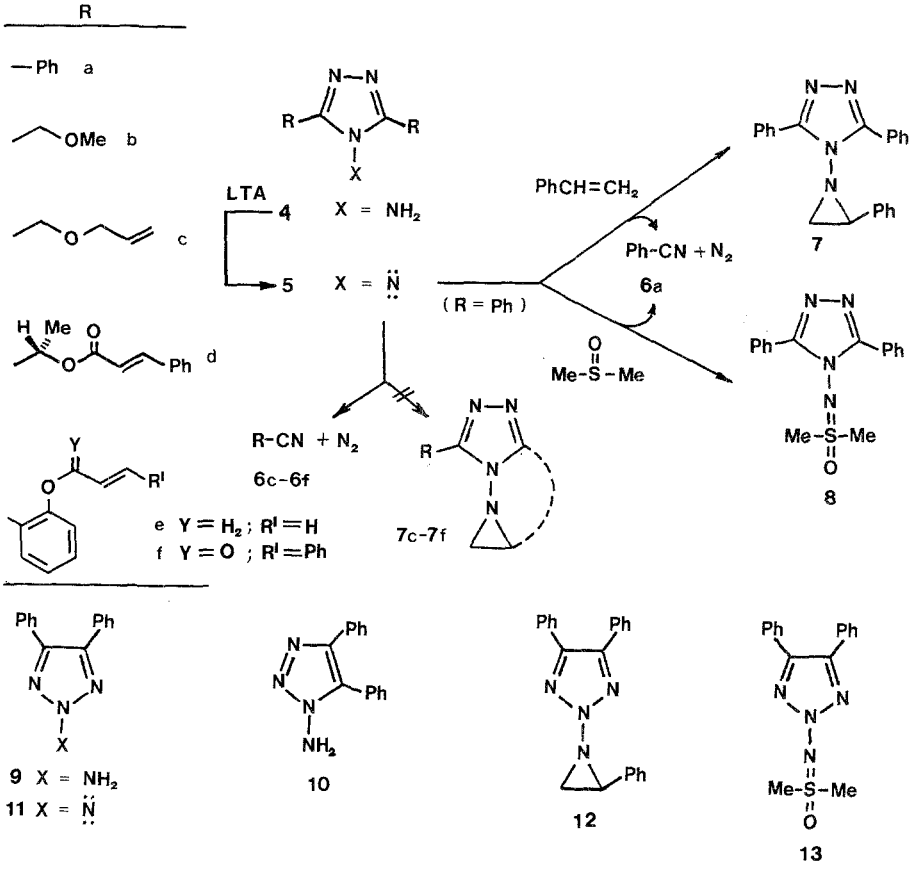
Apart from N-aminobenzimidazoles, examples of azolyl derived N-nitrenes are rare, 4-amino-1,2,4-triazole being one of the best known examples. Lead tetraacetate (*LTA*) oxidation of 4-amino-1,2,4-triazoles **4** causes fragmentation of the heterocycle, yielding nitrogen and nitriles **6** (hydrogen cyanide in the case of the parent 4-amino-1,2,4-triazole) as the main products [4]. However, in the case of the diphenyl derivative **4a** the hypothetical N-nitrene intermediate **5a** was trapped in the presence of a large excess of styrene and other alkenes as scavengers, and variable amounts of triazolyl-aziridines **7** were isolated [5, 6]. When the reaction of **4a** with *LTA* was carried out in the presence of dimethyl sulfoxide (*DMSO*), and no alkene was added, the corresponding sulfoximine **8** was the only identified product [5].

In our hands, the results for the *LTA* oxidation of **4a** in the presence of a large excess of styrene (cf. Refs. [5, 6]) were fully reproducible, benzonitrile (36%) and the triazolyl-aziridine **7a** (30%) being the only isolated compounds. Analogously, the oxidation in the presence of *DMSO* yielded benzonitrile (51%) and the dimethylsulfoximine **8** (43%) (Scheme 2).

Yields for **7a** and **8** correspond to pure, isolated compounds. Reactions were carried out in methanol (0 °C, 1 h) with an equimolar amount of *LTA* and a large excess of styrene or *DMSO* (molar ratios $\geqslant 40:1$). The crude mixtures were quantitatively analyzed for benzonitrile content by GC/MS. No other volatile compounds were identified. Data for aziridine **7a**: M.p. (hexane-ethyl acetate) 204–205 °C (lit. [5] 204–206 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.95 (m, 4H), 7.6–7.1 (m, 9H), 6.8 (m, 2H), 3.06 (dd, 1H), 2.62 and 2.38 (2 dd, 2H). EI-MS *m/z* (rel. abund.): 338 (M^+, 37), 310 (22), 309 (14), 118 (20), 104 (74), 103 (100), 91 (75), 89 (73). Data for sulfoximine **8**: M.p. (hexane-ethyl acetate) 236 °C (lit.

[5] 236–237 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.13 (m, 4 H), 7.5–7.3 (m, 6 H), 2.75 (s, 6 H). EI-MS *m/z* (rel. abund.): 312 (M^+, 51), 234 (0.5), 221 (1.5), 104 (10), 103 (100), 89 (4), 78 (48), 76 (24), 63 (20).

Scheme 2



One could expect that introduction of a double bond in the triazolyl substituents at positions 3 and 5, as in **4c** and **4d**, would reasonably enhance the probability of nitrene addition.

Compound **4c** was obtained in 67% yield from 4-amino-3,5-bis(chloromethyl)-1,2,4-triazole [7] and sodium allyl alkoxide. Oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.0–5.8 (m, 2 H), 5.4–5.2 (m, 4 H), 5.2 (br s, 2 H), 4.70 (s, 4 H), 4.08 (m, 4 H). EI-MS *m/z* (rel. abund.): 223 (4), 208 (16), 194 (57), 168 (100), 155 (24), 112 (53), 110 (64), 97 (71), 82 (54), 66 (87). Compound **4d** was obtained in 62% yield from (*S,S*)-4-amino-3,5-bis(1-hydroxyethyl)-1,2,4-triazole [7] and cinnamoyl chloride (r. t., 48 h, dichloromethane-pyridine). ^{1}H NMR

(200 MHz, $CDCl_3$): δ 7.68 (d, $J = 16$ Hz, 2H), 7.6–7.1 (m, 10H), 6.41 (d, $J = 16$ Hz, 2H), 6.11 (q, $J = 6.8$ Hz, 2H), 5.55 (br s, 2H), 1.84 (d, $J = 6.8$ Hz, 6H). EI-MS *m/z* (rel. abund.): 250 (5), 147 (17), 131 (100), 103 (39), 77 (32).

Compounds **4c** and **4d** constitute examples of differently activated double bonds. Moreover, the chirality of **4d** offers a chance for chirality transfer to obtain optically active aziridines. However, nitriles **6c** and **6d** were the only detected (and isolated) reaction products.

Data for nitrile **6c**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.1–5.8 (m, 1H), 5.4–5.2 (m, 2H), 4.66 (s, 2H), 4.15 (m, 2H). EI-MS *m/z* (rel. abund.: 68 (36), 41 (100), 39 (57). Data for nitrile **6d** (yield 70%): ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.78 (d, $J = 16$ Hz, 1H), 7.6–7.3 (m, 5H), 6.43 (d, $J = 16$ Hz, 1H), 5.54 (q, $J = 6.9$ Hz, 1H), 1.71 (d, $J = 6.9$ Hz, 3H). EI-MS *m/z* (rel. abund.): 201 (M^+, 24), 186 (0.5), 172 (0.5), 156 (19), 147 (18), 131 (100), 103 (73), 77 (60).

In the case of **6d**, the compound was found to be optically pure [$[\alpha]_D^{25} = -20.8$ °C ($c = 0.8$, ethanol)], since the NMR signals of **6d** were shifted downfield but without splitting upon addition of small amounts of Eu(*tfc*)$_3$. Therefore, racemization does not take place during fragmentation of the triazole.

The lack of addition in **4c** and **4d** could be explained by the aliphatic character of the substituents of the triazole ring. Indeed, no nitrene addition was observed by *Sauer* in the parent 4-amino-1,2,4-triazole nor in its 3,5-dimethyl substituted derivative [5]. Similarly, reaction of **4b** [7] with *LTA* in the presence of a large excess of styrene afforded methoxyacetonitrile as the only identified compound. Thus, the two 3,5-diarylsubstituted triazoles **4e** and **4f** were synthetised.

Compound **4e** was obtained by alkylation of 4-amino-3,5-bis(2-hydroxyphenyl)-1,2,4-triazole [8] with allyl bromide under phase transfer conditions (acetonitrile, sodium carbonate, tetrabutylammonium bisulfate, yield 85%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.7–6.8 (m, 8H), 6.1–5.8 (m, 2H), 5.4–5.1 (m, 4H), 5.04 (br s, 2H), 4.58 (m, 4H). EI-MS *m/z* (rel. abund.) 348 (M^+, 13), 347 (13), 332 (16), 318 (35), 317 (42), 307 (52), 302 (31), 276 (28), 262 (32), 235 (30), 162 (37), 120 (61), 104 (38), 91 (100), 77 (49), 65 (46). The same substrate afforded **4f** in 64% yield by acylation with cinnamoyl chloride as for **4d**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.8–6.8 (m, 20H), 6.47 (d, $J = 16$ Hz, 2H), 4.88 (br s, 2H). EI-MS *m/z* (rel. abund.): 528 (M^+, 1), 380 (8), 253 (23), 147 (28), 131 (100), 103 (73), 77 (45).

However, intramolecular addition of nitrenes derived from **4e** and **4f** was neither observed, nitriles **6e** and **6f** being again the only detected products.

Data for nitrile **6e** (yield 80%): ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.7–7.4 (m, 2H), 7.1–6.9 (m, 2H), 6.2–5.9 (m, 1H), 5.6–5.2 (m, 2H), 4.68 (m, 2H). EI-MS *m/z* (rel. abund.): 159 (M^+, 100), 130 (12), 119 (52), 91 (54), 75 (13), 64 (34), 63 (32). Data for nitrile **6f** (yield 69%): ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.96 (d, $J = 16$ Hz, 1H), 7.8–7.1 (m, 9H), 6.67 (d, $J = 16$ Hz, 1H). EI-MS *m/z* (rel. abund.): 249 (M, 1.5), 231 (0.5), 131 (100), 103 (45), 77 (40).

In order to further extend the study of this reaction to other N-aminoazoles, we submitted the two isomeric N-amino-1,2,3-triazoles **9** and **10**, obtained by amination of the corresponding triazole, to the same reaction conditions.

Product distribution in the amination reaction of 1,2,3-triazoles closely resembles methylation [9]. Thus, amination of 4,5-diphenyl-1,2,3-triazole with excess of hydroxylamine-O-sulfonic acid (KOH-H_2O, 60 °C, 2 h) gave a 3 : 1 mixture of **9** : **10**, which were separated by column chromatography. Total yield, based in transformed triazole, was 94%.

In the case of 2-amino-4,5-diphenyl-1,2,3-triazole **9**, one could anticipate a similar fragmentation path as for the 1,2,4-triazolyl series from nitrene **11** (i.e., formation of benzonitrile and the corresponding nitrene-addition compounds). However, with styrene no aziridine **12** was detected, although only 54% of benzonitrile were isolated. This fact revealed the enhanced unstability of nitrene **11** compared to **5**. Indeed, the reaction in the presence of *DMSO* afforded benzonitrile (63%), but in this case the dimethylsulfoximine **13** was isolated, though only in 1% yield.

Finally, *LTA* oxidation of 1-amino-4,5-diphenyl-1,2,3-triazole **10**, in the presence of either styrene or dimethyl sulfoxide afforded diphenylacetylene, in 60 and 62% yields, respectively. No traces of aziridines, sulfoximines, nor nitriles were detected.

Data for **12**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.58 (m, 4 H), 7.45–7.3 (m, 6 H), 3.42 (s, 6 H). EI-MS *m/z* (rel. abund.): 312 (M^+, 54), 104 (20), 103 (100), 89 (16), 78 (64), 76 (37), 63 (44).

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