Synthesis of β-Aminonitrones by Regioselective Oxidation of 4*H*-Imidazoles [1])

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Abstract. A new regioselective synthesis for aminonitrones of type **4** *via* oxidative modification of 4*H*-imidazoles **1** has been developed. An X-ray structural analysis revealed an unexpected tautomeric fixation of the hydrogen atom in **4**. NMR investigations of the ^{15}N-labelled derivative **4b** showed that this fixation is also present in solution. All new synthesized aminonitrones reported here are unusually stable which can be explained by contribution of anionic as well as cationic delocalized mesomeric structures. Treatment of **4** with acetic anhydride leads to formation of the *O*-acylated hydroxylamine derivatives **5**.

We recently reported a new synthesis of the deeply coloured 4*H*-imidazoles of type **1** [1]. These heterocycles can be regarded as 1,3,6-triazafulvenes and have received particular attention not only from structural and theoretical [2] but also from synthetical points of view. For example, the amphoteric properties of **1** allows the introduction of electrophilic [3] as well as nucleophilic [4] building blocks. Furthermore, due to the acceptor properties of the 1,4-diaza-1,3-dien substructure, **1** can be readily reduced by alkali metals. Subsequent reaction of the preformed trianion with various electrophiles constitutes a convenient route to highly substituted imidazoles, substituted heterospiranes as well as macrocyclic imidazole derivatives [5]. Continuing our work involving the chemistry of cycloamidines, we here now have studied the oxidative modification of the 4*H*-imidazoles **1**.

Whereas no reaction was observed using oxidation agents such as H_2O_2 and *tert*-butyl-hydroperoxide, *m*-chloroperoxybenzoic acid and especially dimethyldioxirane proved to be efficient oxygen transfer reagents. In both cases, dark red crystals could be isolated in nearly quantitative yield. We first thought that, due to the low field absorption of the NH-hydrogen in the ^{1}H NMR-spectra a typical conversion of secondary amines to the corresponding hydroxylamine derivative **2** had occurred [6]. However, the X-ray structure analysis of the tolyl-substituted derivative **4a** did not confirm the expected constitution of **2**. In the solid state, the hydrogen atom is localized at the exocyclic nitrogen and the resulting nitronsubstructure **4** is stabilized by strong hydrogen bonds. This structural fixation could also be shown *via* NMR-spectroscopical investigations on the ^{15}N-labelled derivative **4b**. In solution, the NH-signal is split into a doublet ($^1J(^{15}N,H)$ = 91.32 Hz) which can be readily detected even at room temperature. This finding indicates that the zwitterionic π-bond system of the tautomeric nitron structure is preferred. A possible tautomerism between **4** and **2** can be excluded since broadening of the signal pattern was observed neither at −80 °C nor by heating the sample up to 60 °C. The regioselective oxygen transfer reaction most likely starts with the addition of oxygen to the exocyclic imine C–N-bond. The resulting oxaziridine **3** is then able to rearrange into the more stable open-chained nitron substructure [7].

Both mesomeric resonance structures **4'** and **4"** have to be discussed as a basic criterion for the stability of **4**. On the one hand, a negative charge can be delocalized in the imidazole ring system which results in an aromatic structure **4'**. For example, the anion of **1** shows an unusual high stability which allows the complex formation of the counter-ion by one molecule of water [3]. On the other hand, **1** readily abstracts a proton. Quantum mechanical calculations [2] have proposed a delocalized (4n)π-bond system [8] for these protonated derivatives.

In the X-ray structure of **4a**, the N4–O bond length (1.323(3) Å) indicates that it is not a typical single bond (N–O 1.392 Å; N=O 1.215 Å [9]). In addition, the C–N-bonds in the molecule show only a slight alternation in their bond lengths thus indicating that the resonance

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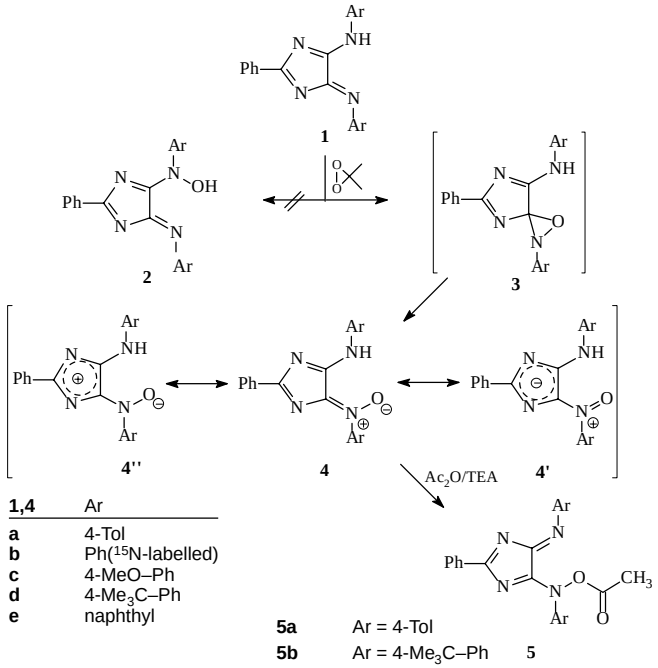

Scheme 1 Regioselective oxidation reaction of 4*H*-imidazoles **1**

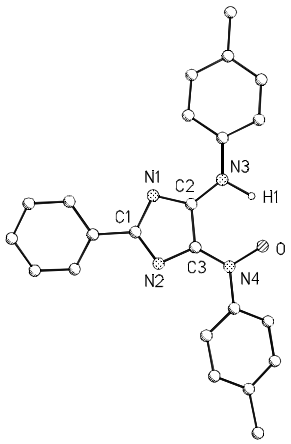

Fig. 1 Perspective drawing of **4a**; the numbering corresponds to that used for the X-ray analysis. Selected distances [Å] and angles [°]: O–N4 1.323(3), N1–C11.390(3), N1–C2 1.330(3), N2–C1 1.339(3), N2–C3 1.369(3), N3–C2 1.349(3), N4–C3 1.337(3), C2–C3 1.478(3), C2–N1–C1 102.8(2), C1–N2–C3 102.0(2), N2–C1–N1 118.0(2), N1–C2–C3 108.4(2), O–N4–C3 119.2(2).

structures **4**' and **4**'' participate in the stabilization of the nitron derivative **4**. At the same time, these experimental findings emphasize the amphotheric properties of the 4*H*-imidazoles **1**.

Except for compound **4**, only a few amino-substituted nitrones are known to date [10]. For example, α-aminonitrones were recently obtained as new class of metabolites by the P4502C3 enzymatic *N*-oxygenation of *N*-substituted benzamidines [11]. The synthesis of these compounds was realized by the oxidation of the same substrates with *m*-chloroperbenzoic acid [12].

The delocalization of the π-bond system strongly influences the chemical properties and compound **4** thus shows only a restricted reactivity as compared to typical aminonitrones [13]. In contrast to the well-known ability of nitrones to undergo 1,3-dipolar cycloaddition reactions [7], **4** is stable towards dipolarophilic reagents. Neither variation of the reaction conditions (temperature, solvent) nor employing powerful dipolarophilic compounds, such as acetylene-dicarboxylate, lead to spiro-heterocycles. This low reactivity is reflected by the high thermical stability of **4.** Neither decomposition nor isomerisation could be observed upon heating without solvents at 250 °C for 12 hours.

Compound **4** however, reacts quantitatively with acetic anhydride in the presence of triethylamine to give the acylated derivatives **5**. The NMR-spectra of **5** provided the expected signal set but considering the regioselectivity of this acylation reaction, no further statements could be made. The mass spectra of **5** indicated that an *O*-acylated substructure was formed due to the strong fragmentation of $[CH_3COO]^+$ observed.

In accordance with the slight alteration of the chromophoric system of **1**, all derivatives of **5** as well as the starting material **4** are intensely red compounds (**5a**: λ_{max} = 501 nm). *O*-Acylated hydroxylamine derivatives are used for the generation of radicals by homolysis of the *N–O* bond. Formation of radicals could accordingly be demonstrated for a solution of **5a** by adding 2,6-di-*tert*-butyl-4-methylphenol and irradiation of the solution (mercury high-pressure lamp, λ = 546 nm) followed by subsequent EPR-spectroscopical measurements. Due to the integration of the radical producing group in the chromophoric system of **1**, an application of these easy available compounds as initiator for photopolymerization and other radical chain reactions becomes apparent. We are continuing our study on the properties of **5** and will report the results in a forthcoming paper.

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Experimental

All reagents were of commercial quality (Aldrich, Fluka, Merck) and were used as received. Solvents were dried and purified using standard techniques. Reactions were monitored by thin layer chromatography (TLC), on plastic plates coated with neutral alumina with fluorescence indicator (Polygram ALOX N/UV_{254} from Macherey-Nagel). Separations by flash chromatography were carried out on neutral alumina (Merck, aluminium oxide 90 active neutral, activity V, particle size 0.063 mm – 0.2 mm, 70 – 230 mesh ASTM). Melting points were measured with a Galen III (Boëtius system) from Cambridge Instruments, and are uncorrected. UV/Vis-spectra were

obtained using a Perkin Elmer Lambda 19 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were obtained on Bruker DRX 400 (400 MHz) and Bruker AC 250 (250 MHz) spectrometers (^{1}H NMR shifts: relative to ^{1}H signals of the solvent). Mass spectra were taken from measurements on a Finnigan MAT SAQ 710 mass spectrometer. Elemental analyses were carried out in-house with an automatic analyzer LECO CHNS 932.

Crystal Structure Determination

Data Collection: The intensity data for the compound were collected on a Nonius KappaCCD diffractometer, using graphite-monochromated Mo-K_α radiation. Data were corrected for Lorentz and polarization effects, but not for absorption [14]. The structure was solved by direct methods (SHELXS [15]). and refined by full-matrix least squares techniques against Fo^2 (SHELXL-97 [16]). The hydrogen atoms were included at calculated positions with fixed thermal parameters. All nonhydrogen atoms were refined anisotropically [16]. Crystal Data for **4a** [17]: $C_{23}H_{20}N_4O$, Mr = 368.43 gmol^{-1}, red prism, size 0.40 × 0.30 × 0.10 mm^3, monoclinic, space group $P2_1/n$, a = 13.5101(5), b = 7.0572(3), c = 20.1236(6) Å, β = 99.672(2)°, V = 1891.4(1) Å^3, T = −90 °C, Z = 4, $\rho_{calcd.}$ = 1.294 gcm^{-3}, μ (Mo-K_α) = 0.82 cm^{-1}, F(000) = 776, 4906 reflections in h(−14/15), k(−7/0), l(−22/22), measured in the range 3.06° ≤ Θ ≤ 23.26°, completeness Θ_{max} = 98.6%, 2624 independent reflections, R_{int} = 0.027, 2507 reflections with $F_o > 4\sigma(F_o)$, 256 parameters, 0 restraints, R^1_{obs} = 0.051, wR^2_{obs} = 0.144, R^1_{all} = 0.069, wR^2_{all} = 0.171, GOOF = 1.047, largest difference peak and hole: 0.431/−0.260 e Å^{-3}.

Synthesis of the Nitrone-Derivatives 4 (General Procedure)

To a solution of 1.0 mmol of the appropriate imidazole **1** in 30 ml acetone, 1 ml of a 1M dimethyldioxirane solution [18] was added at −10 °C. The reaction mixture was allowed to warm to room temp. and stirring was continued for 1h. After completion of the reaction (control by TLC), the solvent was evaporated and the residue was purified by column chromatography (ethylacetate/heptane 1:10) or by recrystallization from acetone.

4-((E)-Oxido-p-tolylimino)-2-phenyl-N-p-tolyl-4H-imidazol-5-amine (**4a**)

Yield 0.34 g (93%), red crystals *m.p.* 206−207 °C. − ^{1}H NMR (250 MHz, $CDCl_3$): δ/ppm = 12.41 (s, 1H, NH), 8.44 (d, 2H, *o*-Ph), 8.18 (d, 2H, Tol), 7.96 (d, 2H, Tol), 7.49 (m, 3H, *m*-, *p*-Ph), 7.33 (d, 2H, Tol), 7.26 (d, 2H, Tol), 2.44 (s, 3H, CH_3–Tol), 2.38 (s, 3H, CH_3–Tol)). − ^{13}C NMR (62 MHz, $CDCl_3$): δ/ppm = 143.2, 141.4, 135.6, 135.2, 132.4, 132.2, 130.0, 129.8, 129.6, 129.2, 128.5, 124.4, 121.4, 21.4, 21.1. − MS *m/z* (%): 369 [M$^+$] (100), 353 (41), 122 (6). − UV/Vis (CH_2Cl_2) λ_{max} (lg ε) = 283 (4.22), 382 (4.17), 501 nm (4.12).

$C_{23}H_{20}N_4$	Calcd.:	C 74.96	H 5.47	N 15.21
(368.21)	Found:	C 75.21	H 5.88	N 14.89.

4-((E)-Oxido-phenyl-^{15}N-imino)-2-phenyl-N-phenyl-4H-imidazol-5-^{15}N-amine (**4b**)

Yield 0.29 g (86%), red crystals, *m.p.* 176 °C. − ^{1}H NMR (400 MHz, THF-d_8): δ/ppm = 12.40 (d, 1H, $^1J(^{15}N,H)$ = 91.32 Hz, NH), 8.40 (d, 4H), 8.18 (d, 2H), 7.47 (m, 8H), 7.15 (m, 1H). − ^{13}C NMR (100 MHz, THF-d_8): δ/ppm = 174.4, 161.9, 154.4, 146.8, 139.2, 133.6, 132.8, 131.5, 130.3, 130.1, 129.3, 129.2, 126.1, 125.5. − MS *m/z* (%): 343 [M$^+$] (100), 327 (17), 243 (48). − UV/Vis (CH_2Cl_2) λ_{max} (lg ε) = 274 (4.25), 481 nm (3.27).

$C_{21}H_{16}N_2{}^{15}N_2O$	Calcd.:	C 73.71	H 4.71	N 16.95
(342.16)	Found:	C 73.82	H 4.97	N 16.75.

4-((E)-Oxido-p-methoxy-phenylimino)-2-phenyl-N-p-methoxy-phenyl-4H-imidazol-5-amine (**4c**)

Yield 0.37 g (92%), red crystals, *m.p.* 200 °C. − ^{1}H NMR (400 MHz, DMSO-d_6, 333 K): δ/ppm = 12.19 (s, 1H, NH), 8.33 (d, 2H), 8.29 (d, 2H), 7.56 (m, 3H), 7.15 (d, 2H), 7.08 (d, 2H). − ^{13}C NMR (100 MHz, DMSO-d_6, 333 K): δ/ppm = 171.8, 160.8, 159.6, 156.9, 151.7, 138.2, 131.8, 131.7, 130.5, 128.5, 128.3, 125.6, 122.5, 114.4, 113.6, 55.4, 55.1. − MS *m/z* (%): 401 MS *m/z* (%): (100), 385 (33), 138 (22). − UV/Vis (CH_2Cl_2) λ_{max} (lg ε) = 284 (4.29), 394 (4.28), 516 nm (4.29).

$C_{23}H_{20}N_4O_3$	Calcd.:	C 68.99	H 5.03	N 13.99
(400.41)	Found:	C 68.98	H 5.30	N 13.67.

4-((E)-Oxido-p-tert-butyl-phenylimino)-2-phenyl-N-p-tert-butyl-phenyl-4H-imidazol-5-amine (**4d**)

Yield 0.43 g (96%), red crystals, *m.p.* 255 °C. − ^{1}H NMR (250 MHz, $CDCl_3$): δ/ppm = 12.40 (s, 1H, NH), 8.57 (d, 2H), 8.46 (d, 2H), 8.23 (d, 2H), 7.50 (m, 7H), 1.37 (s, 9H), 1.35 (s, 9H). − ^{13}C NMR (62 MHz, $CDCl_3$): δ/ppm = 174.5, 160.9, 154.4, 153.4, 148.9, 143.1, 135.2, 132.4, 132.2, 129.6, 128.4, 126.3, 125.7, 124.2, 35.0, 34.6, 31.3, 31.2. − MS *m/z* (%): 453 [M$^+$] (100), 437 (26), 397 (12), 159 (7). − UV/Vis (CH_2Cl_2) λ_{max} (lg ε) = 283 (4.26), 359 (4.18), 502 nm (4.04).

$C_{29}H_{32}N_4O$	Calcd.:	C 77.00	H 7.13	N 12.39
(452.57)	Found:	C 76.77	H 7.34	N 12.17.

4-((E)-Oxido-naphthyllimino)-2-phenyl-N-p-naphthyl-4H-imidazol-5-amine (**4e**)

Yield 0.41 g (93%), red crystals, *m.p.* 180 °C. − ^{1}H NMR (250 MHz, $CDCl_3$): δ/ppm = 13.35 (s, 1H, NH), 9.22 (d, 1H), 8.37 (d, 2H), 8.31 (d, 1H), 7.92 (m, 4H), 7.84 (m, 2H), 7.49 (m, 9H). − ^{13}C NMR (62 MHz, $CDCl_3$): δ/ppm = 175.4, 160.5, 156.3, 141.0, 134.3, 134.0, 133.0, 132.4, 132.1, 131.1, 129.8, 129.0, 128.4, 128.2, 127.8, 127.3, 127.0, 126.5, 126.3, 126.1, 125.0, 124.6, 123.2, 122.9, 120.1, 119.4. − MS m/z (%): 441 [M$^+$] (100), 411 (11), 298 (10), 158 (14), 144 (6). − UV/Vis (CH_2Cl_2) λ_{max} (lg ε) = 277 (4.24), 324 (4.20), 402 (4.17), 503 nm (4.13).

$C_{29}H_{20}N_4O$	Calcd.:	C 79.07	H 4.58	N 12.72
(440.48)	Found:	C 78.77	H 4.80	N 12.58.

Synthesis of the O-acylated Hydroxylamines 5 (General Procedure)

To a solution of 1.0 mmol of the appropriate nitrone derivative **4** in 5 ml chloroform, 0.2 g (2.0 mmol) of triethylamine and 0.2 g (2.0 mmol) of acetic anhydride were added. The solution was stirred at room. temp. overnight. After completion of the reaction (control by TLC), the organic layer was washed twice with 10 ml of water and than dried over anhydrous sodium sulfate. After filtration, the solvent was removed *in vacuo* and the residue was purified by recrystallization from ether/heptane.

O-Acetyl-N-[2-phenyl-4-((Z)-p-tolylimino)-4H-imidazol-5-yl]-N-p-tolylhydroxylamine (**5a**)

Yield 0.4 g (98%), red crystals, *m.p.* 201–204 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): δ/ppm = 8.39 (d, 2H), 7.72 (m, 4H), 7.53 (d, 2H), 7.45 (d, 2H), 7.27 (d, 2H), 7.19 (d, 2H), 2.40 (s, 3H), 2.37 (s, 3H), 2.33 (s, 3H). – ^{13}C NMR (62 MHz, $CDCl_3$): δ/ppm = 168.0, 138.4, 138.2, 135.3, 133.7, 133.3, 130.2, 129.7, 129.6, 129.4, 129.2, 128.4, 126.9, 123.6, 123.0, 119.8, 21.3, 21.2, 20.9. – MS *m/z* (%): 411 [M^+] (85), 367 [$M^+ - COCH_3$] (17), 351 [$M^+ - CO_2CH_3$] (100), 269 (77), 248 (8), 107 (6). – UV/Vis (CH_2Cl_2) λ_{max} (lg ε) = 510 nm (4.12).

$C_{25}H_{22}N_4O_2$	Calcd.:	C 73.15	H 5.40	N 13.65
(410.45)	Found:	C 73.18	H 5.38	N 13.14.

O-Acetyl-N-[2-phenyl-4-((Z)-p-tert.butyl-phenylimino)-4H-imidazol-5-yl]-N-p-tert butyl-phenylhydroxylamine (**5b**)

Yield 0.47 g (95%), red crystals, *m.p.* 187–188 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): δ/ppm = 8.42 (d, 2H), 7.66 (m, 3H), 7.48 (m, 8H), 2.39 (s, 3H), 1.36 (s,18H). – ^{13}C NMR (62 MHz, $CDCl_3$): δ/ppm = 188.9, 171.9, 168.0, 151.4, 144.8, 138.1, 135.2, 133.3, 131.8, 130.3, 126.6, 126.0, 125.8, 122.2, 116.8, 34.8, 31.3, 18.4. – MS(EI) *m/z* (%): 494 [M^+] (20), 450 (25), 435 (46), 393 (34), 379 (57), 276 (23), 247 (34), 144(47), 116 (32), 44 (100). – UV/Vis (CH_2Cl_2) λ_{max} (lg ε) = 334 (4.18), 407 (4.03), 482 nm (4.11).

$C_{31}H_{34}N_4O_2$	Calcd.:	C 75.27	H 6.93	N 11.33
(494.61)	Found:	C 75.08	H 6.83	N 11.24.

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