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Selective reduction of the azido groups of 2,4,6-triazidopyridines

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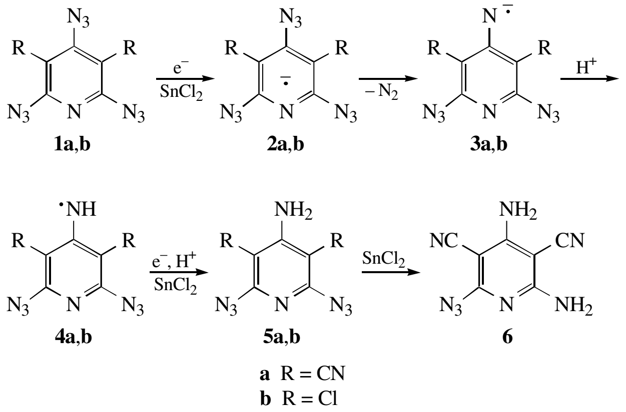
Upon treatment with $SnCl_2$ in methanol at room temperature, 2,4,6-triazidopyridines undergo selective reduction of the γ-azido groups to give the corresponding 4-amino-2,6-diazidopyridines in high yields.

The reduction of azides to amines is an important reaction in organic synthesis.[1] In the last decade, much attention was focused on the development of methods allowing the selective and mild reduction of the azido groups in polyfunctional compounds bearing carbon–carbon double bonds, nitro and carbonyl groups and other functionalities.[2] However, because of the lack of suitable model compounds, the selective reduction of nonequivalent azido groups in aromatic polyazides was not studied. Recently, we have shown that 2,4,6-triazidopyridines are characterised by the nonequivalent distribution of bonding electron density in the α- and γ-azido groups and, as a result, readily undergo selective derivatization in reactions with electron-rich[3] and electron-deficient dipolarophiles,[4] nucleophilic addition[5] and upon photolysis.[6] This work is devoted to the selective reduction of nonequivalent azido groups in 2,4,6-triazidopyridines.[1(a),(b)]

$SnCl_2$ was chosen for study owing to its ability to efficiently reduce various aromatic azides to amines[7] under mild conditions. The reactions of **1a**,**b** with an equivalent amount of $SnCl_2$ in methanol at room temperature for 30 min afforded amines **5a**,**b** in high yields.[†] The structures of **5a**,**b** were supported by elemental analysis and spectroscopic investigations.[‡] Thus, for instance, the presence of only three signals at δ_C 80.4 (C-3, C-5), 160.6 (C-4) and 161.0 ppm (C-2, C-6) for the carbon atoms of the pyridine ring of **5a** and at δ_C 100.0 (C-3, C-5), 147.7 (C-2, C-6) and 150.8 ppm (C-4) for the carbon atoms of the pyridine ring of **5b** in the ^{13}C NMR spectra unambiguously demonstrates that the amino groups of these compounds are located at the 4-position of the pyridine ring. Upon treatment with an excess of $SnCl_2$ in methanol at room temperature, aminodiazide **5a** was readily reduced to diaminoazide **6**[‡] in 87% yield. By contrast, due to weaker electron-withdrawing substituents at the pyridine ring, chlorine-substituted diazide **5b** did not react with $SnCl_2$ even after prolonged reflux in methanol.



The selective reduction of the γ-azido groups in **1a**,**b** can be rationalised by an analysis of the bonding electron density distribution in these molecules. According to the theory,[1] the first step of the reaction involves a single electron transfer from reductant to azide. The most prominent feature of the azide radical anions thereby formed is the considerable bending of the azido group (from about 170° in starting azides to about 130° in radical anions) and a dramatic decrease in the activation energy of $N–N_2$ bond dissociation (from 35 to 6 kcal mol^{-1}, respectively).[8] As can be seen in Figure 1, the γ-azido groups in **1a**,**b** have the lowest bonding orbital density at the N_α and N_β atoms, so the structural changes in these groups on the way from **1a**,**b** to **2a**,**b** should[6(b)] require less energy, making the dissociation of the γ-groups in **2a**,**b** the more facile process. This assumption is supported by PM3 computations[§] of **2a**

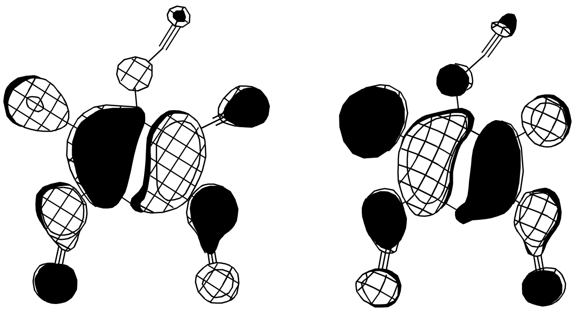

HOMO of **1a**   HOMO of **1b**

Figure 1 The orbital density distribution in the HOMO of **1a**,**b**. The lower bonding orbital density at the N_α atom of the γ-azido groups in the HOMO of **1a**,**b** indicates that these groups more easily achieve the geometry of the azide radical anions.

[†] *Typical procedure for the synthesis of 4-amino-2,6-diazidopyridines* **5a**,**b**. A powder of $SnCl_2$ (1 mmol) was slowly added in small portions to a stirred solution of triazide **1a**,**b** (1 mmol) in 50 ml of methanol at room temperature. The mixture was kept at room temperature for 30 min, and then the solvent was evaporated under reduced pressure. The solid residue was chromatographed on a silica gel column using a mixture of benzene and ethyl acetate (4:1 for **5a**, 9:1 for **5b**) as an eluent. Yields: **5a**, 88%; **5b**, 78%.

[‡] **5a**: mp 155–156 °C (decomp.). ^1H NMR ([$^2H_6$]acetone) δ: 7.24 (br. s, 2H, NH_2). ^{13}C NMR ([$^2H_6$]acetone) δ: 80.4 (C-3, C-5), 113.0 (CN), 160.6 (C-4), 161.0 (C-2, C-6). IR (microcrystalline film, ν_{max}/cm^{-1}): 3352 (s, ν_{as} NH), 3232 (s, ν_s NH), 2234 (s, CN), 2158 and 2143 (s and s, N_3), 1683 (s, δ_s NH), 1588 and 1560 (s and vs, C=N, C=C), 1411 (vs), 1321 (m), 1233 (w), 1199 (w), 767 (m), 665 (w), 592 (m), 544 (w), 515 (w), 492 (w). Found (%): C, 37.31; H, 0.97; N, 61.72. Calc. for $C_7H_2N_{10}$ (%): C, 37.19; H, 0.85; N 61.96.

5b: mp 170–171 °C (decomp.). ^1H NMR ([$^2H_6$]acetone) δ: 6.28 (br. s, 2H, NH_2). ^{13}C NMR ([$^2H_6$]acetone) δ: 100.0 (C-3, C-5), 147.7 (C-2, C-6), 150.8 (C-4). IR (microcrystalline film, ν_{max}/cm^{-1}): 3502 (s, ν_{as} NH), 3399 (s, ν_s NH), 2172 and 2143 (s and s, N_3), 1629 (s, δ_s NH), 1576 and 1544 (w and s, C=N, C=C), 1413 (vs), 1390(vs), 1354 (w), 1316 (w), 1230 (s), 1096 (s), 1004 (w), 828 (m), 737 (s), 678 (w), 635 (w), 540 (m). Found (%): C, 24.68; H, 0.93; N, 45.62. Calc. for $C_5H_2Cl_2N_8$ (%): C, 24.51; H, 0.82; N 45.73.

6: mp 177–178 °C (decomp.). ^1H NMR ([$^2H_6$]acetone) δ: 6.77 (br. s, 2H, 4-NH_2), 6.60 (br. s, 2H, 2-NH_2). ^{13}C NMR ([$^2H_6$]acetone) δ: 71.9 (C-3), 74.6 (C-5), 114.3 and 115.2 (CN), 160.9 (C-4), 161.4 (C-6), 162.8 (C-2). IR (microcrystalline film, ν_{max}/cm^{-1}): 3378 and 3338 (s and s, ν_{as} 2-NH and 4-NH), 3234 and 3225 (s and s, ν_s 2-NH and 4-NH), 2210 (vs, CN), 2140 (s, N_3), 1660 and 1618 (s and vs, δ_s 2-NH and 4-NH), 1574 and 1553 (vs and vs, C=N, C=C), 1473 (m), 1386 (s), 1332 (m), 772 (w), 669 (w), 497 (w), 477 (w), 438 (m). Found (%): C, 42.16; H, 2.14; N, 55.70. Calc. for $C_7H_4N_8$ (%): C, 42.01; H, 2.01; N 55.98.

($S = {}^1/_2$, $q = -1$), which yield the γ-azido group distorted (the N–N–N angle is about 127°, the N–N_2 bond length is about 1.40 Å) conformer of **2a** by preference. Computations of the α-azido group distorted (the N–N–N angle is about 128°, the N–N_2 bond length is about 1.40 Å) conformer of **2a** were performed using the computational bending of the α-azido group in **2a** to 125° prior the geometry optimization. As expected, the α-azido group distorted conformers of **2a**,**b** appeared to be 3 and 6 kcal mol^{-1} higher in energy than the respective γ-azido group distorted conformers of **2a**,**b**. This confirms that generation of low-energy conformers of the γ-azido group of **2a**,**b** from **1a**,**b** is indeed the less energy consuming process and supports the electron density bonding arguments.

Selective reduction of nonequivalent azido groups in aromatic polyazides can be a useful method for the preparation of new organic compounds. Obviously, the greater the difference in the HOMO orbital density distribution on the azido groups in polyazides, the higher the selectivity of the reduction.

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[§] The structures of the α- and γ-isomers of radical anions **2a**,**b** ($S = {}^1/_2$, $q = -1$) were calculated with the full optimization of geometrical parameters using the PM3 method (UHF, SCF level).[9]