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Nucleophilic replacement of the azido groups by amines in 2,4,6-triazido-3-chloro-5-cyanopyridine

Sergei V. Chapyshev

Institute of Problems of Chemical Physics, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russian Federation. Fax: +7 496 515 3588; e-mail: chap@icp.ac.ru

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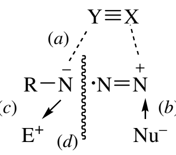
2,4,6-Triazido-3-chloro-5-cyanopyridine reacts with pyrrolidine and piperidine to form corresponding 2-azido-4,6-diamino-3-chloro-5-cyanopyridines in high yields.

Aromatic azides are important starting materials in organic synthesis.[1] All of the known reactions of azido groups are divided into four types: (*a*) cycloaddition of dipolarophiles to the N_α and N_γ atoms, (*b*) addition of nucleophiles to the terminal N_γ atoms, (*c*) addition of electrophiles to the N_α atoms and (*d*) dissociation of the N–N_2 bonds due to photolysis, thermolysis, electron impact or electron transfer from reductants (Scheme 1).[1(d)] Previously, it was found that reactions of triazides **1a–c** with norbornene,[2] acetylenes,[2(d),3] PPh_3[4] or $SnCl_2$[5] give azides **2–6** (Scheme 2), which were used in the photochemical syntheses of high-spin nitrenes.[6] Here, a new type of reactions of aromatic azides involving the formal nucleophilic replacement of the azido groups by amines is considered.

A short-time reflux (5 min) of triazide **1c**[†] in pyrrolidine or piperidine leads to the formation of new products. Chromatographic analysis showed that only one new compound is formed in each reaction. According to published data,[7] aromatic nitriles readily react with amines to form amidines. Because triazide **1c** has a rather active cyano group, it would be expected that new compounds from the reactions of triazide **1c** with pyrrolidine and piperidine are amidines **7a**,**b** (Scheme 2). Surprisingly, IR spectroscopy[‡] showed that new compounds contain both azido (2130 cm^{-1}) and cyano (2205 cm^{-1}) groups. Moreover, elemental



Scheme 1

analyses and ^{13}C NMR spectra[‡] indicated that these compounds were the products of the replacement of two azido groups in triazide **1c** by amines, which was impossible to predict *a priori*.

In order to determine the positions of amino substituents in the pyridine ring of new azides, theoretical ^{13}C NMR spectra of three possible isomers (2,4-, 2,6- and 4,6-diaminoazido-3-chloro-5-cyanopyridine) were simulated.[§] The best agreement between experimental and theoretical ^{13}C NMR spectra was found for 4,6-diaminopyridines **10a**,**b**. Thus, for instance, according to theoretical predictions, azide **10a** should display five signals in the ^{13}C NMR spectra of the pyridine ring at 78.1 (C-5), 94.1 (C-3), 154.0 (C-2), 161.9 (C-4) and 164.0 ppm (C-6) that are close to experimentally observed values of 78.9, 95.9, 155.5, 155.9 and 157.3 ppm. Note that the ^{13}C NMR simulation program is almost insensitive to the nature of amino substituents and predicts the same chemical shifts for the carbon atoms of the pyridine ring in azides **10a** and **10b**. In comparison with pyrrolidino substituents, piperidino substituents are conformationally more flexible and less electron-donating. Due to

† The syntheses of triazide **1c** was described elsewhere.[2(a)]

‡ *A typical procedure for the synthesis of diaminopyridines* **10a**,**b**. A solution of triazide **1c** (3 mmol) in 5 ml of pyrrolidine or piperidine was boiled for 5 min, cooled to room temperature and poured into 50 ml of water. The solid material was filtered off, washed with water and recrystallised from methanol.

10a: yield 88%, yellow crystals; mp 118–120 °C (decomp.). ^1H NMR ($CDCl_3$) δ: 1.98 (m, 8H, β-CH_2), 3.68 (t, 4H, α-CH_2, *J* 7.5 Hz), 3.78 (t, 4H, α-CH_2, *J* 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 25.4 and 25.9 (C_β), 50.3 and 51.7 (C_α), 78.9 (C-5), 95.9 (C-3), 117.4 (CN), 155.5 (C-2), 155.9 (C-4), 157.3 (C-6). IR (microcrystalline film, ν_{max}/cm^{-1}): 2969 (m) and 2876 (m) (CH), 2205 (m) (CN), 2130 (vs) (N_3), 1565 (vs) and 1520 (m) (C=N, C=C), 1485 (s), 1480 (s), 1373 (m), 1341 (m), 1230 (m), 1178 (w), 1102 (w), 1067 (w), 869 (m), 743 (m). Found (%): C, 53.28; H, 4.92; N, 30.56. Calc. for $C_{14}H_{16}ClN_7$ (%): C, 52.91; H, 5.07; N 30.85.

10b: yield 92%, yellow crystals; mp 121–122 °C (decomp.). ^1H NMR ($CDCl_3$) δ: 1.5–1.8 (m, 12H, β-CH_2 and γ-CH_2), 3.40 (t, 4H, α-CH_2, *J* 7.5 Hz), 3.60 (4H, α-CH_2, *J* 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 23.8 and 24.3 (C_γ), 25.6 and 26.3 (C_β), 49.4 and 52.6 (C_α), 83.7 (C-5), 100.9 (C-3), 117.7 (CN), 153.5 (C-2), 160.7 (C-4), 161.6 (C-6). IR (microcrystalline film, ν_{max}/cm^{-1}): 2937 (s) and 2853 (m) (CH), 2205 (m) (CN), 2130 (vs) (N_3), 1534 (vs) and 1475 (m) (C=N, C=C), 1442 (s), 1369 (s), 1348 (m), 1303 (m), 1286 (m), 1257 (m), 1230 (m), 1156 (m), 1108 (m), 1025 (m), 988 (m), 893 (w), 855 (m), 759 (w). Found (%): C, 55.22; H, 5.77; N, 28.56. Calc. for $C_{16}H_{20}ClN_7$ (%): C, 55.57; H, 5.83; N, 28.35.

§ Theoretical ^{13}C NMR spectra of isomeric azidodipyrrolidin-1-yl-3-chloro-5-cyanopyridines and azidodipiperidin-1-yl-3-chloro-5-cyanopyridines were simulated using the standard ChemDraw Ultra 10.0 program.

2-Azido-4,6-dipyrrolidin-1-yl-3-chloro-5-cyanopyridine, δ: 25.5 (C_β), 50.9 and 51.4 (C_α), 78.1 (C-5), 94.1 (C-3), 114.5 (CN), 154.0 (C-2), 161.9 (C-4), 164.0 (C-6).

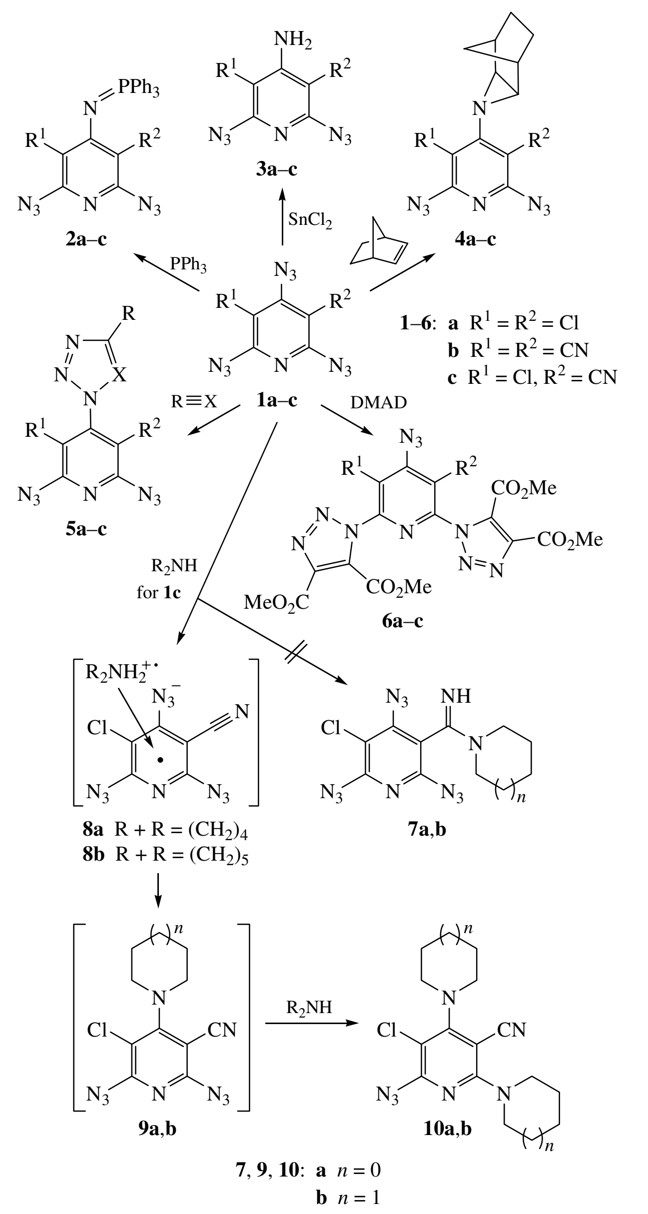
4-Azido-2,6-dipyrrolidin-1-yl-3-chloro-5-cyanopyridine, δ: 25.5 (C_β), 51.4 (C_α), 85.0 (C-5), 107.0 (C-3), 117.0 (CN), 145.0 (C-4), 162.0 (C-6), 164.0 (C-2).

6-Azido-2,4-dipyrrolidin-1-yl-3-chloro-5-cyanopyridine, δ: 25.5 (C_β), 50.9 and 51.4 (C_α), 74.4 (C-5), 104.0 (C-3), 117.0 (CN), 152.0 (C-6), 161.9 (C-4), 166.0 (C-2).

2-Azido-4,6-dipiperidin-1-yl-3-chloro-5-cyanopyridine, δ: 24.5 (C_γ), 25.5 (C_β), 49.7 and 51.3 (C_α), 78.1 (C-5), 94.1 (C-3), 114.5 (CN), 154.0 (C-2), 161.9 (C-4), 164.0 (C-6).

4-Azido-2,6-dipiperidin-1-yl-3-chloro-5-cyanopyridine, δ: 24.5 (C_γ), 25.5 (C_β), 49.7 (C_α), 85.0 (C-5), 107.0 (C-3), 117.0 (CN), 145.0 (C-4), 162.0 (C-6), 164.0 (C-2).

6-Azido-2,4-dipiperidin-1-yl-3-chloro-5-cyanopyridine, δ: 24.5 (C_γ), 25.5 (C_β), 49.7 and 51.3 (C_α), 74.4 (C-5), 104.0 (C-3), 117.0 (CN), 152.0 (C-6), 161.9 (C-4), 166.0 (C-2).



Scheme 2

these effects, five signals of the pyridine ring in the experimental ^{13}C NMR spectrum of azide **10b** occur at δ 83.9 (C-5), 100.9 (C-3), 153.5 (C-2), 160.7 (C-4) and 161.6 ppm (C-6).

The formation of diaminoazidopyridines **10a**,**b** in reactions of triazide **1c** with pyrrolidine and piperidine represents a new type of reactions of aromatic azides involving the formal nucleophilic replacement of the azido groups by amines. Most probably, these reactions occur by a radical mechanism[8] involving electron transfer from the HOMOs of amines to the LUMOs of electron-deficient triazide **1c** followed by the collapse of diradical complexes **8** into aminopyridine and gaseous HN_3 (Scheme 2). The fact that the azido groups are replaced by amines in pyridine **1c** at *ortho* positions to the cyano group supports this hypothesis. Quantum-chemical PM3 calculations[¶] showed that these positions in the radical anions of **1c** and **9a**,**b** bear the highest spin populations and should be most reactive toward radical cations. The reactions stop at the stage of diamination due to the high LUMO energies of azides **10a**,**b**. Similar effects have been observed during the reduction of triazide **1b** with $SnCl_2$ in methanol to form 2,4-diamino-6-azido-3,5-dicyanopyridine.[5]

In conclusion, the new reactions of aromatic azides involving the nucleophilic replacement of the azido groups by amines can be used for the amination of aromatic nitriles because the direct amination of halogenated aryl nitriles often stops at the stage of monoamination.[9] By contrast, many halogenated aryl nitriles readily react with sodium azide to form di- and triazides,[2(*a*),3(*a*)] the azido groups of which can be replaced by amino functions.

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¶ The structures of radical anions for **1c** and **9a**,**b** were calculated with the full optimization of geometrical parameters using the PM3 method (HyperChem 7.52, UHF, $S = 1/2$, Total Charge –1, Polak-Ribiere Algorithm).

Calculated spin-populations for the carbon atoms in the pyridine ring.

Radical anion of **1c**: –0.008 (C-2), 0.016 (C-3), –0.036 (C-4), 0.002 (C-5), 0.002 (C-6).

Radical anion of **9a**: 0.003 (C-2), –0.010 (C-3), 0.003 (C-4), 0.003 (C-5), –0.029 (C-6).

Radical anion of **9b**: 0.008 (C-2), –0.018 (C-3), 0.009 (C-4), –0.002 (C-5), –0.028 (C-6).