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Ring Transformation of 7-Nitro-1-(4-nitrophenyl)-4,5-dihydro-1*H*-imidazo- and -[1,2,3]triazolo[4,5-*c*]pyridin-4-ones

Yu. M. Yutilov, N. N. Smolyar, A. B. Eres'ko, and S. V. Gres'ko

Litvinenko Institute of Physical Organic and Coal Chemistry, National Academy of Sciences of Ukraine, ul. R. Lyuksemburg 70, Donetsk, 83114 Ukraine
e-mail: yutilov@skif.net

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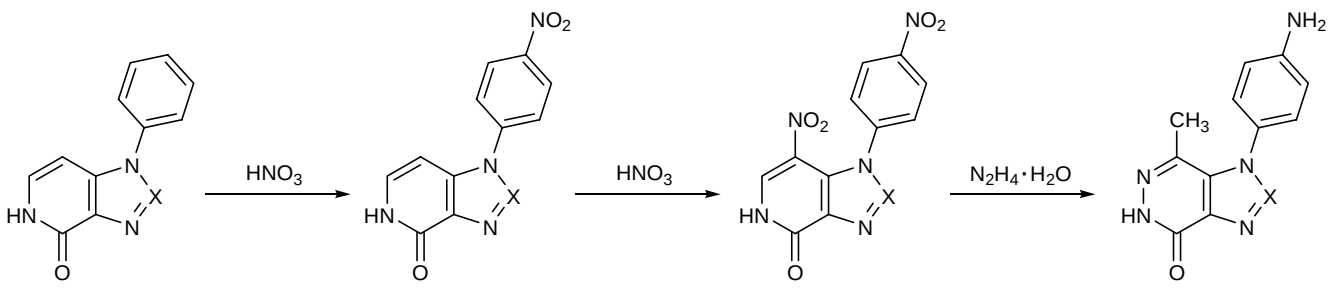
Abstract—Nitration of 1-phenyl-4,5-dihydroimidazo- and -1,2,3-triazolo[4,5-*c*]pyridin-4-ones initially occurs at the *para* position of the phenyl ring, and the subsequent nitration yields the corresponding 7-nitro-1-(4-nitrophenyl) derivatives. Treatment of the latter with hydrazine hydrate leads to formation of 1-(4-aminophenyl)-7-methyl-4,5-dihydroimidazo- and -1,2,3-triazolo[4,5-*d*]pyridazin-4-ones.

We previously reported on a new ring transformation of fused 5-nitropyridin-2-ones under conditions of profound hydrazinolysis. For example, the reaction with 7-nitro-4,5-dihydroimidazo[4,5-*c*]pyridin-4-one leads to formation of pyridazine derivative [1, 2]. The general character of this transformation was demonstrated with a series of bicyclic 5-nitropyridin-2-ones having fused imidazole, triazole, benzene, pyridine, and thiophene rings [2–5]. Apart from high yields of pyridazine derivatives, a specific feature of this reaction is reduction of one CH group of the pyridine fragment to methyl. On the basis of experimental data, a probable mechanism of the ring transformation was proposed [4]. The discovered reaction considerably extends preparative potential of the synthesis of difficultly accessible pyridazine derivatives, e.g., substituted 1-phenyl-4,5-dihydroimidazo- and -[1,2,3]triazolo[4,5-*d*]pyridazines.

It seemed to be interesting to examine the behavior of the nitration products of 1-phenyl-4,5-dihydroimidazo- and -[1,2,3]triazolo[4,5-*c*]pyridin-4-ones **Ia** and **Ib** in the reaction with hydrazine hydrate. Initial compounds **Ia** and **Ib** were prepared by acid hydrolysis of 4-chloro-1-phenyl-4,5-dihydroimidazo- and -[1,2,3]-triazolo[4,5-*c*]pyridines according to the procedure described in [6]. However, it remained unclear whether the nitration of compounds **Ia** and **Ib** will occur initially at position *7* of the pyridine fragment or at the N^1-phenyl group.

We have found that treatment of compounds **Ia** and **Ib** with excess nitrating mixture under mild conditions initially leads to introduction of a nitro group into the *para* position of the phenyl ring to give compounds **IIa** and **IIb**; the subsequent nitration of mononitro derivatives **IIa** and **IIb** afforded 7-nitro-1-(4-nitrophenyl)-4,5-dihydroimidazo- and -[1,2,3]triazolo[4,5-*c*]pyridin-

Scheme 1.



Ia, **Ib** **IIa**, **IIb** **IIIa**, **IIIb** **IVa**, **IVb**

X = CH (**a**), N (**b**).

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4-ones **IIIa** and **IIIb**. The latter products can also be obtained in fairly high yields by prolonged treatment of **Ia** and **Ib** with excess nitrating mixture. The structure of the products was confirmed by the IR and ^{1}H NMR spectra.

Hydrazinolysis of compounds **IIIa** and **IIIb** under conditions analogous to those described in [2] gave new products which were identified as 1-(4-aminophenyl)-7-methyl-4,5-dihydroimidazo- and -[1,2,3]triazolo[4,5-*d*]pyridazin-4-ones **IVa** and **IVb**. Their ^{1}H NMR spectra contain signals from protons of the C-methyl groups (δ 2.50–2.52 ppm), aromatic protons of the *p*-phenylene fragment, and NH protons (δ 5.66–5.68 ppm). The presence of an aromatic amino group was confirmed by a distinct color test with sodium hypobromite and by the absence in the IR spectrum of absorption bands typical of stretching vibrations of nitro group.

Ring transformation products **IVa** and **IVb** attract interest for pharmacological screening, since some imidazo[4,5-*d*]pyridazine derivatives were found to exhibit clearly pronounced cardiotonic, antithrombotic, antioxidant, and mycostatic activity [7–10].

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Telsa BS-467C spectrometer (80 MHz) in CF_3COOH, as well as on a Gemini-200 instrument (200 MHz), in acetone-d_6 and DMSO-d_6, using HMDS as internal reference. The IR spectra were measured on a UR-20 spectrometer from samples dispersed in mineral oil. The purity of the products was checked by TLC on Silufol UV-254 plates using alcohol as eluent; spots were visualized under UV light or by treatment with iodine vapor.

1-Phenyl-4,5-dihydroimidazo[4,5-*c*]pyridin-4-one hydrochloride (Ia). A mixture of 1.5 g (6.35 mmol) of 4-chloro-1-phenyl-4,5-dihydroimidazo[4,5-*c*]pyridine [11] and 15 ml of 85% of formic aid was heated for 2 h under reflux. Formic acid was distilled off, 10 ml of concentrated hydrochloric acid was added to the residue, and the resulting solution was heated for 1 h and evaporated to dryness. The residue was ground with 5 ml of 2-propanol, and the precipitate was filtered off and recrystallized from alcohol. Yield 1.6 g (99%), colorless substance, mp 260–263°C. IR spectrum, ν, cm^{-1}: 1660 (C=O). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 6.80 d (1H, 7-H, J = 7.3 Hz), 7.63 d (1H, 6-H, J = 7.3 Hz), 7.67–7.70 m (5H, 1-Ph), 9.55 s (1H, 2-H). Found, %: C 58.02; H 4.05; N 16.72. $C_{12}H_9N_3O\cdot HCl$. Calculated, %: C 58.19; H 4.07; N 16.96.

1-Phenyl-4,5-dihydro[1,2,3]triazolo[4,5-*c*]pyridin-4-one hydrochloride (Ib) was synthesized in a similar way from 4-chloro-1-phenyl-4,5-dihydro-[1,2,3]triazolo[4,5-*c*]pyridine [11]. Yield 98%, mp 267–270°C. IR spectrum, ν, cm^{-1}: 1665 (C=O). ^{1}H NMR spectrum (CF_3COOH), δ, ppm: 7.33 s (5H, 1-Ph), 7.83 d (1H, 7-H, J = 7.0 Hz), 8.28 (1H, 6-H, J = 7.0 Hz). Found, %: C 52.99; H 3.61; N 22.34. $C_{11}H_8N_4O\cdot HCl$. Calculated, %: C 53.13; H 3.65; N 22.53.

1-(4-Nitrophenyl)-4,5-dihydroimidazo[4,5-*c*]pyridin-4-one (IIa). Hydrochloride **Ia**, 1.4 g (5.65 mmol), was dissolved on stirring and cooling to –5 to 0°C in 12 ml of concentrated sulfuric acid, 1.12 g (11.09 mmol) of potassium nitrate was added, and the mixture was stirred for 2 h at that temperature, allowed to slowly warm up to room temperature, and poured onto ice. The precipitate was filtered off, washed with 2-propanol, and dried. Yield 1.0 g (69%), light yellow crystals, mp > 300°C. IR spectrum, ν, cm^{-1}: 1355 (NO_2, sym.), 1530 (NO_2, asym.), 1700 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.61 d (1H, 7-H, J = 7.0 Hz), 7.30 d (1H, 6-H, J = 7.0 Hz), 7.91 d (2H, 2'-H, 6'-H, J = 8.0 Hz), 8.44 d (2H, 3'-H, 5'-H, J = 8.0 Hz), 8.47 s (1H, 2-H), 11.51 s (1H, 5-H). Found, %: C 56.09; H 3.10; N 21.79. $C_{12}H_8N_4O_3$. Calculated, %: C 56.25; H 3.15; N 21.87.

1-(4-Nitrophenyl)-4,5-dihydro[1,2,3]triazolo-[4,5-*c*]pyridin-4-one (IIb) was synthesized from hydrochloride **Ib** as described above for compound **IIa**. Yield 81%, mp > 300°C (from DMSO). ^{1}H NMR spectrum (CF_3COOH), δ, ppm: 6.91 d (1H, 7-H, J = 7.0 Hz), 7.30 d (1H, 6-H, J = 7.0 Hz), 7.64 d (2H, 2'-H, 6'-H, J = 8.0 Hz), 8.19 d (2H, 3'-H, 5'-H, J = 8.0 Hz). Found, %: C 51.21; H 2.70; N 27.08. $C_{11}H_7N_5O_3$. Calculated, %: C 51.37; H 2.74; N 27.23.

7-Nitro-1-(4-nitrophenyl)-4,5-dihydroimidazo-[4,5-*c*]pyridin-4-one (IIIa). *a.* Potassium nitrate, 1.5 g (14.85 mmol), was added under stirring and cooling to 0–5°C to a solution of 1.3 g (5.08 mmol) of compound **IIa** in 13 ml of concentrated sulfuric acid, and the mixture was stirred for 2 h at that temperature. It was then allowed to warm up to room temperature, heated for 2 h at 60–65°C, cooled, and poured onto ice. The precipitate was filtered off, washed with cold water and 2-propanol, and dried. Yield 0.92 g (60%), mp > 300°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.78 d (2H, 2'-H, 6'-H, J = 8.5 Hz), 8.36 d (2H,

3'-H, 5'-H, *J* = 8.5 Hz), 8.39 s (1H, 6-H), 8.53 s (1H, 2-H), 11.30 s (1H, 5-H). Found, %: C 47.71; H 2.30; N 23.12. $C_{12}H_7N_5O_5$. Calculated, %: C 47.85; H 2.34; N 23.25.

b. Compound **Ia**, 1.4 g (5.65 mmol), was dissolved in 14 ml of concentrated sulfuric acid, 2.3 g (22.77 mmol) of potassium nitrate was added in portions under stirring and cooling (–5 to 0°C), and the mixture was stirred for 2 h at –5 to 0°C, allowed to warm up to room temperature, stirred for 48 h, poured onto ice, and treated as described above in *a*. Yield 1.1 g (65%), mp > 300°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.79 d (2H, 2'-H, 6'-H, *J* = 8.5 Hz), 8.36 d (2H, 3'-H, 5'-H, *J* = 8.5 Hz), 8.38 s (1H, 6-H), 8.53 s (1H, 2-H), 11.29 s (1H, 5-H). Found, %: C 47.63; H 2.29; N 23.07. $C_{12}H_7N_5O_5$. Calculated, %: C 47.85; H 2.34; N 23.25.

7-Nitro-1-(4-nitrophenyl)-4,5-dihydro[1,2,3]triazolo[4,5-*c*]pyridin-4-one (IIIb) was synthesized as described above for compound **IIIa** (method *a*) using **IIb** as starting compound. Yield 50%, light yellow crystals, mp > 300°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.78 d (2H, 2'-H, 6'-H, *J* = 8.0 Hz), 8.16 d (2H, 3'-H, 5'-H, *J* = 8.0 Hz), 8.80 d (1H, 6-H). Found, %: C 43.52; H 1.96; N 27.65. $C_{11}H_6N_6O_5$. Calculated, %: C 43.72; H 2.00; N 27.81.

Compound **IIIb** was also synthesized from hydrochloride **Ib** following the procedure described for **IIIa** (method *b*). Yield 60%, mp > 300ºC. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.76 d (2H, 2'-H, 6'-H, *J* = 8.0 Hz), 8.17 d (2H, 3'-H, 5'-H, *J* = 8.0 Hz), 8.82 s (1H, 6-H). Found, %: C 43.49; H 1.93; N 27.60. $C_{11}H_6N_6O_5$. Calculated, %: C 43.72; H 2.00; N 27.81.

1-(4-Aminophenyl)-7-methyl-4,5-dihydroimidazo[4,5-*d*]pyridazin-4-one (IVa). A mixture of 0.8 g (2.66 mmol) of compound **IIIa** and 12 ml of hydrazine hydrate was heated for 3–5 h at 135–140°C. Excess hydrazine hydrate was distilled off, the residue was ground with cold water, and the precipitate was filtered off, washed with 2-propanol, and dried. Yield 0.4 g (62%), snow-white crystals, mp > 300°C. IR spectrum, ν, cm^{-1}: 1675 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.50 s (3H, CH_3), 5.68 s (2H, NH_2), 6.66 d (2H, 2'-H, 6'-H, *J* = 8.0 Hz), 7.18 d (2H, 3'-H, 5'-H, *J* = 8.0 Hz), 8.23 s (1H, 2-H), 12.52 s (1H, 5-H). Found, %: C 59.60; H 4.57; N 28.88. $C_{12}H_{11}N_5O$. Calculated, %: C 59.74; H 4.60; N 29.03.

1-(4-Aminophenyl)-7-methyl-4,5-dihydro[1,2,3]triazolo[4,5-*d*]pyridazin-4-one (IVb) was synthesized as described above for compound **IVa** from triazolopyridine **IIIb**. Yield 67%, snow-white crystals, mp > 300°C. IR spectrum, ν, cm^{-1}: 1680 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.52 s (3H, CH_3), 5.66 s (2H, NH_2), 6.77 d (2H, 2'-H, 6'-H, *J* = 8.0 Hz), 7.37 d (2H, 3'-H, 5'-H, *J* = 8.0 Hz), 12.55 s (1H, 5-H).

REFERENCES

1. Yutilov, Yu.M. and Svertilova, I.A., *Khim. Geterotsikl. Soedin*., 1982, p. 705.
2. Yutilov, Yu.M. and Svertilova, I.A., *Russ. J. Org. Chem*., 1999, vol. 35, p. 583.
3. Yutilov, Yu.M. and Smolyar, N.N., *Khim. Geterotsikl. Soedin*., 1984, p. 132.
4. Yutilov, Yu.M. and Smolyar, N.N., *Zh. Org. Khim*., 1986, vol. 22, p. 1793.
5. Yutilov, Yu.M., Smolyar, N.N., and Gres'ko, S.V., *Russ. J. Org. Chem*., 1995, vol. 31, p. 273.
6. Temple, C., Smith, B.H., and Montgomery, J.A., *J. Org. Chem*., 1972, vol. 37, p. 3601.
7. FRG Patent Appl. no. 3347290, 1985; *Ref. Zh., Khim*., 1986, no. 13O79P.
8. FRG Patent Appl. no. 3445299, 1986; *Ref. Zh., Khim*., 1987, no. 3O147P.
9. Gerhardt, G.A., Aldous, D.L., and Castle, R.N., *J. Heterocycl. Chem*., 1965, vol. 2, p. 247.
10. Yutilov, Yu.M., Svertilova, I.A., Kirichenko, V.V., and Afanas'ev, B.E., USSR Inventor's Certificate no. 1187438, 1983; *Byull. Izobret*., 1997, no. 29.
11. Svertilova, I.A., Smolyar, N.N., and Yutilov, Yu.M., *Ukr. Khim. Zh*., 1996, vol. 62, nos. 3–4, p. 64.