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Synthesis of 2-Hetarylimidazo[4,5-*d*]pyridazine Derivatives

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Abstract—2-Chloropyridine-3,4-diamine reacted with hetarenecarboxylic acids (pyridine-2-, pyridine-3-, and pyridine-4-carboxylic acids and 6-oxo-1,6-dihydropyridazine-3-carboxylic acid) in polyphosphoric acid at 160–170°C to give the corresponding 2-hetarylimidazo[4,5-*c*]pyridin-4-ones. Nitration of the latter with a mixture of concentrated nitric and sulfuric acids led to the formation of 2-hetaryl-7-nitroimidazo[4,5-*c*]pyridin-4-ones which were converted into 2-hetaryl-7-methylimidazo[4,5-*d*]pyridazin-4-ones by the action of hydrazine hydrate at 140–150°C.

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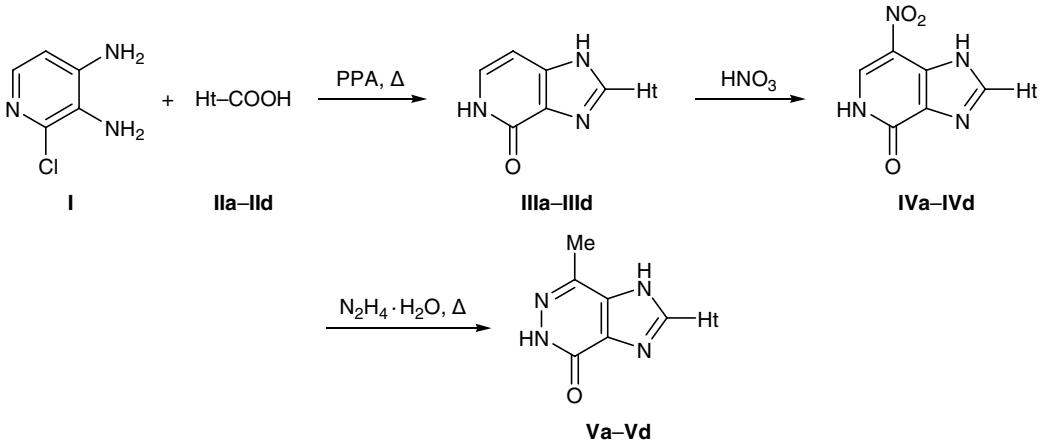
Some imidazo[4,5-*d*]pyridazine derivatives were found to exhibit strong antithrombotic, cardiotonic, and antioxidant activity [1–3]. The existing methods for the synthesis of imidazo[4,5-*d*]pyridazines are based on cyclizations of 4,5-diaminopyridazines with formic acid, formamide, and triethyl orthoformate [4, 5]. Substituted imidazo[4,5-*d*]pyridazines were also obtained by reaction of 4,5-diaminopyridazines with aromatic aldehydes in nitrobenzene or with arenecarboxylic acids in polyphosphoric acid (PPA) [2, 3, 6]. Cyclization of 2-substituted diethylimidazo[4,5-*d*]-pyridazines with aromatic aldehydes or compounds having an activated methyl group in the presence of elemental sulfur was reported to lead to analogous results [7].

While continuing our studies in the field of synthesis of substituted imidazo[4,5-*d*]pyridazines [7], we tried to obtain 2-hetarylimidazo[4,5-*d*]pyridazine derivatives by analogy with the transformation of fused 5-nitropyridin-2-ones by the action of hydrazine hydrate, which was revealed by us previously [8]. The corresponding fused 5-nitropyridin-2-ones were synthesized from 2-chloropyridine-3,4-diamine (**I**) and pyridine-2-, pyridine-3-, and pyridine-4-carboxylic and 6-oxo-1,6-dihydropyridazine-3-carboxylic acids **IIa**–**IId**, followed by nitration with a mixture of concen-

Scheme 1.

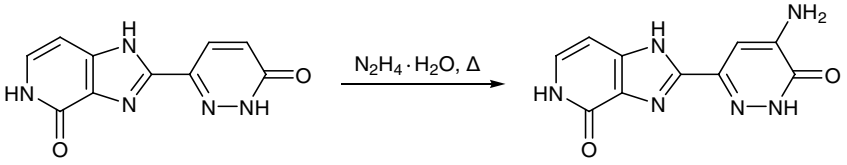


I **IIa–IId** **IIIa–IIId** **IVa–IVd** **Va–Vd**

Ht = 2-pyridyl (**a**), 3-pyridyl (**b**), 4-pyridyl (**c**), 6-oxo-1,6-dihydropyridazin-3-yl (**d**).

[†] Deceased.

Scheme 2.



trated sulfuric and nitric acids (Scheme 1). The reaction of 2-chloropyridine-3,4-diamine (**I**) with hetarenecarboxylic acids **IIa**–**IId** in polyphosphoric acid at 160–170°C (4 h) led to closure of imidazole ring and was accompanied by acid hydrolysis with replacement of the chlorine atom by oxo group. The ^{1}H NMR spectra of 2-hetarylimidazo[4,5-*c*]pyridin-4-ones **IIIa**–**IIId** thus formed contained two doublets from the vicinal 6-H and 7-H protons in the pyridine fragment and signals from protons in the hetaryl substituent. Compounds **IIIa**–**IIId** showed in IR spectra carbonyl absorption at 1650–1670 cm^{-1}.

Oxoimidazopyridines **IIIa**–**IIId** were subjected to nitration with a mixture of concentrated nitric and sulfuric acids according to the procedure reported in [9]. The ^{1}H NMR spectra of the nitration products, 2-hetaryl-7-nitroimidazo[4,5-*c*]pyridin-4-ones **IVa**–**IVd**, displayed a singlet from the 6-H proton at δ 8.58–9.01 ppm and signals from protons in the hetaryl substituent. In the IR spectra of **IVa**–**IVd**, absorption bands due to stretching vibrations of the carbonyl and nitro groups were present.

Nitro compounds **IVa**–**IVd** underwent recyclization into 7-methyl-2-hetarylimidazo[4,5-*d*]pyridazin-4-one derivatives **Va**–**Vd** on heating with excess hydrazine hydrate for 3–4 h at 140–150°C. In the reaction with compound **IVd**, the transformation of the pyridine fragment into pyridazine was accompanied by introduction of an amino group into the 4-position of the pyridazine fragment attached to the imidazole ring. Analogous amination (cf. [10]) occurred when compound **IIId** was heated with hydrazine hydrate; as a result, 2-(5-amino-6-oxo-1,6-dihydropyridazin-3-yl)imidazo[4,5-*c*]pyridin-4-one (**VI**) was formed (Scheme 2).

The structure of compounds **III**–**VI** was confirmed by the ^{1}H NMR and IR spectra and elemental analyses. 2-Hetarylimidazo[4,5-*d*]pyridazine derivatives **IVa**–**IVd** attract interest as potential pharmacologically active compounds [11]. The procedure described in the present communication may be regarded as a preparative method of synthesis of imidazo[4,5-*d*]pyridazines, which supplements the existing procedures and extends their potential.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded from solutions in DMSO-d_6, CD_3COOD, and pyridine-d_5 on a Varian Gemini-200 spectrometer (200 MHz) using hexamethyldisiloxane as internal reference. The IR spectra were obtained on a UR-20 spectrometer from samples dispersed in mineral oil and on a Specord 75 IR instrument from samples prepared as KBr pellets. The purity of the products was checked by TLC on Silufol UV-254 plates using alcohol and chloroform as eluents; spots were visualized under UV light or by treatment with iodine vapor. 2-Chloropyridine-3,4-diamine (**I**) was synthesized according to the procedure reported in [12]. The synthesis of 6-oxo-1,6-dihydropyridazine-3-carboxylic acid (**II**) was described in [13].

2-Hetarylimidazo[4,5-*c*]pyridin-4-ones IIIa–IIId (*general procedure*). Polyphosphoric acid, 6 ml, was added to a mixture of 5.0 mmol of compound **I** and 5 mmol of acid **IIa**–**IId**, and the mixture was heated for 4 h at 160–170°C, cooled, diluted with 15–20 ml of water, and neutralized with ammonium carbonate. The precipitate was filtered off, dried, and recrystallized from appropriate solvent.

2-(2-Pyridyl)imidazo[4,5-*c*]pyridin-4-one (IIIa). Yield 65%, mp >250°C (decomp., from water). IR spectrum, ν, cm^{-1}: 1650 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.51 d (1H, 7-H, J = 6.0 Hz), 7.15 t (1H, 5′-H), 7.52 d (1H, 6-H, J = 6.0 Hz), 8.01 t (1H, 4′-H), 8.26 d (1H, 3′-H, J = 7.0 Hz), 8.72 d (1H, 6-H, J = 7.0 Hz), 11.30 br.s (1H, NH). Found, %: C 62.08; H 3.74; N 26.25. $C_{11}H_8N_4O$. Calculated, %: C 62.26; H 3.80; N 26.40.

2-(3-Pyridyl)imidazo[4,5-*c*]pyridin-4-one (IIIb). Yield 87%, mp >250°C (decomp., from water). IR spectrum, ν, cm^{-1}: 1665 (C=O). ^{1}H NMR spectrum (CD_3COOD), δ, ppm: 7.08 d (1H, 6-H, J = 6.0 Hz), 7.44 t (1H, 5′-H), 7.77 d (1H, 7-H, J = 6.0 Hz), 8.74 d (1H, 6′-H, J = 6.0 Hz), 8.83 d (1H, 4′-H, J = 6.0 Hz), 9.41 s (1H, 2′-H). Found, %: C 62.10; H 3.72; N 26.28. $C_{11}H_8N_4O$. Calculated, %: C 62.26; H 3.80; N 26.40.

2-(4-Pyridyl)imidazo[4,5-*c*]pyridin-4-one (IIIc). Yield 61%, mp >250°C (decomp., from water). IR

spectrum, ν, cm^{-1}: 1670 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 6.70 d (1H, 7-H, J = 6.0 Hz), 7.30 d (1H, 6-H, J = 6.0 Hz), 8.15 d (2H, 2′-H, 6′-H, J = 7.0 Hz), 8.81 d (2H, 3′-H, 5′-H, J = 7.0 Hz), 11.45 br.s (1H, NH). Found, %: C 62.12; H 3.75; N 26.22. $C_{11}H_8N_4O$. Calculated, %: C 62.26; H 3.80; N 26.40.

2-(6-Oxo-1,6-dihydropyridazin-3-yl)imidazo-[4,5-*c*]pyridin-4-one (IIId). Yield 72%, mp >300°C (decomp., from water). IR spectrum, ν, cm^{-1}: 1650–1660 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 6.51 d (1H, 7-H, J = 6.3 Hz), 7.12 d (1H, 4′-H, J = 9.6 Hz), 7.25 d (1H, 6-H, J = 6.3 Hz), 8.19 d (1H, 5′-H, J = 9.6 Hz), 11.28 br.s (1H, 5-H), 13.31 br.s (1H, 1′-H), 13.55 br.s (1H, 1-H). Found, %: C 52.24; H 3.03; N 30.41. $C_{10}H_7N_5O_2$. Calculated, %: C 52.40; H 3.08; N 30.56.

2-Hetaryl-7-nitroimidazo[4,5-*c*]pyridin-4-ones IVa–IVd (*general procedure*). Compound **IIIa–IIId**, 1.5 mmol, was dissolved on cooling (~10°C) in 3.6 ml of concentrated sulfuric acid, the solution was cooled to 5°C, and a solution of 0.75 ml of concentrated nitric acid (d = 1.5 g/cm^3) in 0.5 ml of concentrated sulfuric acid was added dropwise. After 0.5–1.0 h, the mixture was gradually warmed up to 50–60°C, kept for 2 h at that temperature, cooled, and poured onto ice. The precipitate (compound **IVc**) was filtered off, washed with a small amount of cold water until neutral washings, and dried. Compound **IVa** separated when the solution was adjusted to pH 3–4. Nitro compounds **IVb** and **IVd** were isolated by neutralization of the solution with ammonium carbonate. Compounds **IVa–IVd** were purified by recrystallization from water.

7-Nitro-2-(2-pyridyl)imidazo[4,5-*c*]pyridin-4-one (IVa). Yield 51%, mp 180–182°C (from water). IR spectrum, ν, cm^{-1}: 1660 (C=O), 1530 (NO_2, sym.), 1355 (NO_2, asym.). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 7.25 t (1H, 5′-H), 8.10 t (1H, 4′-H), 8.58 d (1H, 3′-H, J = 7.0 Hz), 8.62 d (1H, 6′-H, J = 7.0 Hz), 8.92 s (1H, 6-H). Found, %: C 51.27; H 2.69; N 27.09. $C_{11}H_7N_5O_3$. Calculated, %: C 51.39; H 2.74; N 27.24.

7-Nitro-2-(3-pyridyl)imidazo[4,5-*c*]pyridin-4-one (IVb). Yield 46%, mp >250°C (decomp., from water). IR spectrum, ν, cm^{-1}: 1660 (C=O), 1535 (NO_2, sym.), 1355 (NO_2, asym.). ^1H NMR spectrum (pyridine-d_5), δ, ppm: 7.65 t (1H, 4′-H), 8.64 s (1H, 6-H), 8.70 d (1H, 5′-H, J = 7.0 Hz), 8.76 d (1H, 6′-H, J = 7.0 Hz), 9.47 s (1H, 2′-H). Found, %: C 51.25; H 2.67; N 27.11. $C_{11}H_7N_5O_3$. Calculated, %: C 51.39; H 2.74; N 27.24.

7-Nitro-2-(4-pyridyl)imidazo[4,5-*c*]pyridin-4-one (IVc). Yield 48%, mp >250°C (decomp., from water). IR spectrum, ν, cm^{-1}: 1660 (C=O), 1535 (NO_2, sym.), 1355 (NO_2, asym.). ^1H NMR spectrum (pyridine-d_5), δ, ppm: 8.20 d (2H, 2′-H, 6′-H, J = 7.0 Hz), 8.85 d (2H, 3′-H, 5′-H, J = 7.0 Hz), 9.01 s (1H, 6-H). Found, %: C 51.23; H 2.70; N 27.06. $C_{11}H_7N_5O_3$. Calculated, %: C 51.39; H 2.74; N 27.24.

7-Nitro-2-(6-oxo-1,6-dihydropyridazin-3-yl)-imidazo[4,5-*c*]pyridin-4-one (IVd). Yield 63%, mp >300°C (decomp., from water). IR spectrum, ν, cm^{-1}: 1660 (C=O), 1535 (NO_2, sym.), 1355 (NO_2, asym.). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 7.05 d (1H, 4′-H, J = 9.9 Hz), 8.16 d (1H, 5′-H, J = 9.9 Hz), 8.58 s (1H, 6-H), 12.41 br.s (1H, 5-H), 13.48 br.s (1H, 1′-H). Found, %: C 43.62; H 2.15; N 30.51. $C_{10}H_6N_6O_4$. Calculated, %: C 43.80; H 2.21; N 30.65.

2-Hetaryl-7-methylimidazo[4,5-*d*]pyridazin-4-ones Va–Vd (*general procedure*). A mixture of 1.2 mmol of nitro compound **IVa–IVd** and 24 mmol of hydrazine hydrate was heated for 3–4 h at 140–150°C. Excess hydrazine hydrate was distilled off together with water, and traces of the latter were removed by azeotrope distillation with benzene or toluene. The solid residue was recrystallized from appropriate solvent.

7-Methyl-2-(2-pyridyl)imidazo[4,5-*d*]pyridazin-4-one (Va). Yield 55%, mp >250°C (decomp., from propan-1-ol). IR spectrum, ν, cm^{-1}: 1665 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.57 s (3H, CH_3), 7.56 t (1H, 5′-H), 8.05 t (1H, 4′-H), 8.29 d (1H, 3′-H, J = 7.0 Hz), 8.79 d (1H, 6′-H, J = 7.0 Hz), 12.45 br.s (1H, 5-H). Found, %: C 58.01; H 3.93; N 30.65. $C_{11}H_9N_5O$. Calculated, %: C 58.15; H 4.00; N 30.82.

7-Methyl-2-(3-pyridyl)imidazo[4,5-*d*]pyridazin-4-one (Vb). Yield 50%, mp >250°C (decomp., from ethanol). IR spectrum, ν, cm^{-1}: 1665 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.57 s (3H, CH_3), 7.55 d (1H, 5′-H, J = 8.0 Hz), 8.60 d (1H, 4′-H, J = 8.0 Hz), 8.72 d (1H, 6′-H, J = 8.0 Hz), 9.40 s (1H, 2′-H), 12.45 br.s (1H, 5-H). Found, %: C 57.98; H 3.95; N 30.67. $C_{11}H_9N_5O$. Calculated, %: C 58.15; H 4.00; N 30.82.

7-Methyl-2-(4-pyridyl)imidazo[4,5-*d*]pyridazin-4-one (Vc). Yield 77%, mp >250°C (decomp., from propan-2-ol). IR spectrum, ν, cm^{-1}: 1665 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.55 s (3H, CH_3), 8.16 d (2H, 2′-H, 6′-H, J = 7.0 Hz), 8.72 d (2H,

3′-H, 5′-H, J = 7.0 Hz), 12.50 br.s (1H, 5-H). Found, %: C 57.96; H 3.94; N 30.69. $C_{11}H_9N_5O$. Calculated, %: C 58.15; H 4.00; N 30.82.

2-(5-Amino-6-oxo-1,6-dihydropyridazin-3-yl)-7-methylimidazo[4,5-*d*]pyridazin-4-one (Vd). Yield 53%, mp >300°C (decomp., from water). IR spectrum, ν, cm^{-1}: 1660 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.61 s (3H, CH_3), 7.57 br.s (2H, NH_2), 7.79 s (1H, 3′-H), 11.19 br.s (1H, 5-H), 12.71 br.s (1H, 1′-H). Found, %: C 46.2; H 3.43; N 37.67. $C_{10}H_9N_7O_2$. Calculated, %: C 46.33; H 3.50; N 37.82.

2-(5-Amino-6-oxo-1,6-dihydropyridazin-3-yl)-imidazo[4,5-*d*]pyridin-4-one (VI). Yield 70%, mp >300°C (decomp., from water). IR spectrum, ν, cm^{-1}: 1650–1660 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 6.45 d (1H, 7-H, J = 6.0 Hz), 6.53 s (1H, 4′-H), 7.21 d (1H, 6-H, J = 6.0 Hz), 11.11 br.s (1H, 5-H), 12.85 br.s (2H, 1-H, 1′-H). Found, %: C 49.03; H 3.25; N 34.28. $C_{10}H_8N_6O_2$. Calculated, %: C 49.18; H 3.30; N 34.41.

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