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Synthesis of 1- and 3-Substituted Imidazo[4,5-*b*]pyridin-2-ones

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Abstract—1- and 3-Substituted imidazo[4,5-*b*]pyridin-2-ones were synthesized by heating equimolar amounts of 3-amino-2-chloropyridine or 2-chloro-3-methylaminopyridine, urea, and the corresponding arylamine at 150–210°C. The reaction of 3-amino-2-chloropyridine with urea and *p*-phenylenediamine or *p*,*p*′-diaminobiphenyl at a ratio of 2:2:1 under analogous conditions gave 1,4-bis-(2-oxoimidazo[4,5-*b*]pyridin-3-yl)benzene or 1,4-bis(2-oxoimidazo[4,5-*b*]pyridin-3-yl)biphenyl, respectively.

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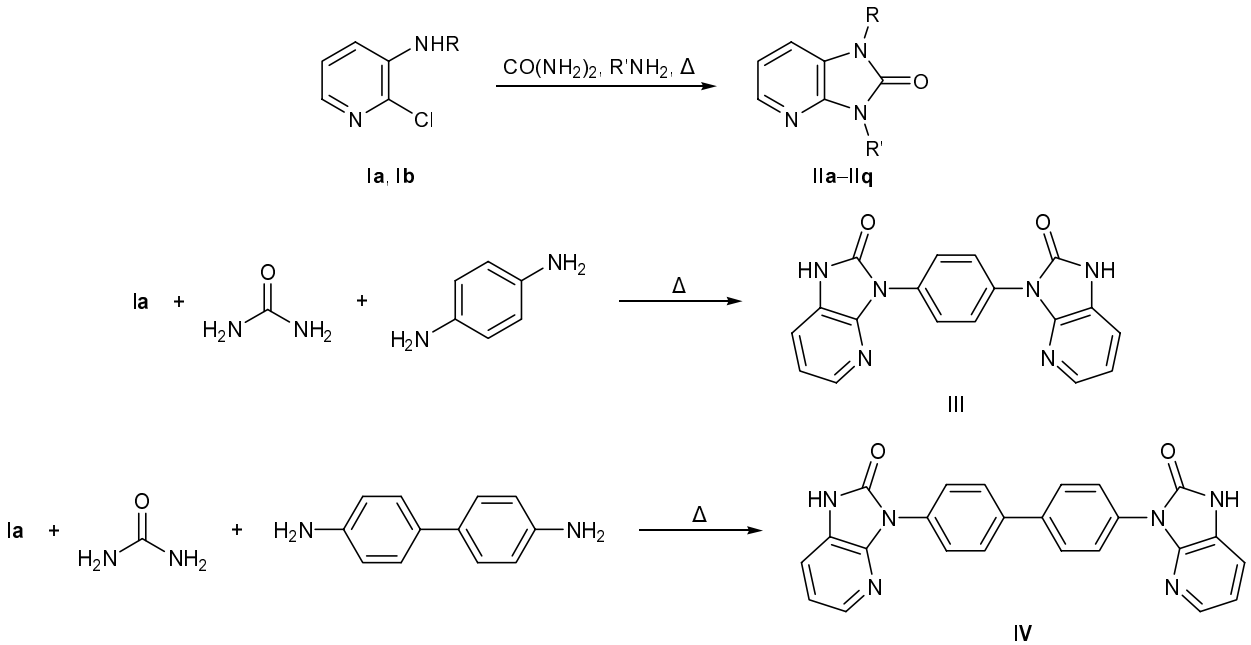
Imidazo[4,5-*b*]pyridin-2-one derivatives are structurally related to purine, and they exhibit a broad spectrum of biological properties. Some 1- and 3-alkyl(or aryl)imidazo[4,5-*b*]pyridin-2-ones were found to possess analgetic, antipyretic, antiphlogistic [1], antisecretory, antiulcer, and antidepressant activity [2]. 1- and 3-Alkyl(or aryl)-substituted 6-hetarylimidazo[4,5-*b*]-pyridin-2-ones are cardiotonic agents [3]. Compounds exhibiting pronounced antihypertensive properties were also revealed among imidazopyridine derivatives, which stimulated search for improved blocking agents of angiotensin II receptors [4].

1- and 3-Alkyl(or aryl)-substituted imidazo[4,5-*b*]-pyridin-2-ones are usually synthesized by reactions of the corresponding 2,3-diaminopyridines with urea [5], phosgene [6], ethyl formate [7], diphenylphosphoryl

Scheme 1.



I, R = H (**a**), Me (**b**); **II**, R = H, R' = $PhCH_2$ (**a**), Ph (**b**), 3-MeC_6H_4 (**c**), 4-MeC_6H_4 (**d**), 3-$MeOC_6H_4$ (**e**), 4-$MeOC_6H_4$ (**f**), 4-$EtOC_6H_4$ (**g**), 3,4-$(MeO)_2C_6H_3$ (**h**), 4-ClC_6H_4 (**i**), 4-BrC_6H_4 (**j**), 3-FC_6H_4 (**k**), 4-FC_6H_4 (**l**), 1-naphthyl (**m**), 2-naphthyl (**n**), 1,3-benzodioxol-5-yl (**o**); 2,3-dihydro-1,4-benzodioxin-6-yl (**p**); R = Me, R' = Ph (**q**).

azide [8], carbonyldiimidazole [9], and diethyl pyrocarbonate [10]. A procedure for the preparation of 3-alkyl(or aryl)imidazo[4,5-*b*]pyridin-2-ones by reaction of 2-alkyl(or aryl)aminonicotinic acid amides with urea was reported [11]. Hydroxylation of 1- and 3-alkyl-substituted imidazo[4,5-*b*]pyridines leads to the formation of the corresponding 2-oxo derivatives [12]. 5,6-Dihalo-substituted imidazo[4,5-*b*]pyridin-2-ones were obtained by halogenation of 1- and 3-alkylimidazo[4,5-*b*]pyridines in glacial acetic acid [13].

The above procedures for the synthesis of imidazo-[4,5-*b*]pyridin-2-one derivatives utilize mainly the corresponding 2,3-diaminopyridines as starting compounds; however, their preparation often involves some technical difficulties due to their increased sensitivity to atmospheric oxygen. With the goal of simplifying the synthesis of 1- and 3-substituted imidazo-[4,5-*b*]pyridin-2-one derivatives we proposed a procedure which excludes the use of 2,3-diaminopyridines [14]. The procedure is based on the reaction of equimolar amounts of 3-amino-2-chloropyridine (**Ia**) or 2-chloro-3-methylaminopyridine (**Ib**), urea, and the corresponding aromatic amine on heating at 150–210°C for 3–17 h (Scheme 1). By reaction of 3-amino-2-chloropyridine (**Ia**) with urea and *p*-phenylenediamine or *p*,*p*′-diaminobiphenyl at a ratio of 2:2:1 we obtained 1,4-bis(2-oxoimidazo[4,5-*b*]piridin-3-yl)benzene (**III**) and 1,4-bis(2-oxoimidazo[4,5-*b*]pyridin-3-yl)biphenyl (**IV**), respectively.

The IR spectra of the newly synthesized compounds contained absorption bands in the region 1690–1725 cm^{-1} due to stretching vibrations of the carbonyl group. Compounds **IIa**–**IIq**, **III**, and **IV** attract interest as potential biologically active substances; in addition, they can be subjected to further modifications.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Specord 75IR spectrometer. The purity of the products was checked by TLC on Silufol UV-254 plates using alcohol and chloroform as eluents; spots were visualized by UV irradiation or treatment with iodine vapor. Initial 3-amino-2-chloropyridine (**Ia**) and 2-chloro-3-methylaminopyridine were synthesized by the procedure described in [15].

1- and 3-Substituted imidazo[4,5-*b*]pyridin-2-ones IIa–IIq. A mixture of 10 mmol of 3-amino-2-chloropyridine (**Ia**) or 2-chloro-3-methylaminopyridine (**Ib**), 10 mmol of urea, and 10 mmol of the corresponding aromatic amine was heated for 3–17 h at 150–210°C in a stream of nitrogen. The mixture was cooled, treated with aqueous ammonia or cold water, dried, and extracted with diethyl ether or alcohol. The extract was evaporated to dryness, and the residue was recrystallized from appropriate solvent.

3-Benzyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-one (IIa). Yield 35%, mp 175–177°C (from ethanol). IR spectrum: ν(C=O) 1725 cm^{-1}. Found, %: C 69.10; H 4.81; N 18.43. $C_{13}H_{11}N_3O$. Calculated, %: C 69.32; H 4.92; N 18.62.

3-Phenyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-one (IIb). Yield 89%, mp 236–238°C (from water); published data [16]: mp 240°C. Found, %: C 68.01; H 4.19; N 19.65. $C_{12}H_9N_3O$. Calculated, %: C 68.24; H 4.29; N 19.89.

3-(3-Methylphenyl)-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-2-one (IIc). Yield 56%, mp 188–190°C (from ethanol). IR spectrum: ν(C=O) 1725 cm^{-1}. Found, %: C 69.09; H 4.78; N 18.40. $C_{13}H_{11}N_3O$. Calculated, %: C 69.32; H 4.92; N 18.62.

3-(4-Methylphenyl)-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-2-one (IId). Yield 47%, mp 220–222°C (from propan-1-ol); published data [16]: mp 222–224°C. Found, %: C 69.12; H 4.83; N 18.38. $C_{13}H_{11}N_3O$. Calculated, %: C 69.32; H 4.92; N 18.62

3-(3-Methoxyphenyl)-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-2-one (IIe). Yield 49%, mp 200–202°C (from propan-2-ol). IR spectrum: ν(C=O) 1720 cm^{-1}. Found, %: C 64.49; H 4.50; N 17.18. $C_{13}H_{11}N_3O_2$. Calculated, %: C 64.72; H 4.60; N 17.42.

3-(4-Methoxyphenyl)-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-2-one (IIf). Yield 41%, mp 255–257°C (from propan-1-ol); published data [16]: mp 257–258°C. Found, %: C 64.53; H 4.54; N 17.25. $C_{13}H_{11}N_3O_2$. Calculated, %: C 64.72; H 4.60; N 17.42.

3-(4-Ethoxyphenyl)-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-2-one (IIg). Yield 45%, mp 228–230°C (from ethanol). IR spectrum: ν(C=O) 1715 cm^{-1}. Found, %: C 65.61; H 5.03; N 16.22. $C_{14}H_{13}N_3O_2$. Calculated, %: C 65.87; H 5.13; N 16.46.

3-(3,4-Dimethoxyphenyl)-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-one (IIh). Yield 33%, mp 243–245°C (from ethanol); published data [16]: mp 245–246°C. Found, %: C 61.76; H 4.71; N 15.35. $C_{14}H_{13}N_3O_3$. Calculated, %: C 61.99; H 4.83; N 15.49.

3-(4-Chlorophenyl)-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-2-one (IIi). Yield 64%, mp 265–267°C

(from propan-1-ol); published data [16]: mp 267–269°C. Found, %: C 58.43; H 3.17; N 16.86. $C_{12}H_8ClN_3O$. Calculated, %: C 58.67; H 3.28; N 17.10.

3-(4-Bromophenyl)-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-2-one (IIj). Yield 45%, mp >250°C (from propan-1-ol). IR spectrum: ν(C=O) 1705 cm^{-1}. Found, %: C 49.42; H 2.66; N 14.29. $C_{12}H_8BrN_3O$. Calculated, %: C 49.68; H 2.78; N 14.48.

3-(3-Fluorophenyl)-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-2-one (IIk). Yield 55%, mp 220–222°C (from dioxane); published data [16]: mp 222–224°C. Found, %: C 62.64; H 3.40; N 18.08. $C_{12}H_8FN_3O$. Calculated, %: C 62.88; H 3.52; N 18.33.

3-(4-Fluorophenyl)-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-2-one (IIl). Yield 37%, mp 269–271°C (from dioxane); published data [16]: mp 271–272°C. Found, %: C 62.69; H 3.47; N 18.13. $C_{12}H_8FN_3O$. Calculated, %: C 62.88; H 3.52; N 18.33.

3-(1-Naphthyl)-2,3-dihydro-1*H*-imidazo[4,5-*b*]-pyridin-2-one (IIm). Yield 38%, mp >250°C (from water). IR spectrum: ν(C=O) 1700 cm^{-1}. Found, %: C 73.33; H 4.15; N 15.84. $C_{16}N_{11}N_3O$. Calculated, %: C 73.55; H 4.24; N 16.08.

3-(2-Naphthyl)-2,3-dihydro-1*H*-imidazo[4,5-*b*]-pyridin-2-one (IIn). Yield 34%, mp >250°C (from water). IR spectrum: ν(C=O) 1725 cm^{-1}. Found, %: C 77.31; H 4.12; N 15.80. $C_{16}H_{11}N_3O$. Calculated, %: C 73.55; H 4.24; N 16.08.

3-(3,4-Methylenedioxyphenyl)-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-one (IIo). Yield 39%, mp 226–228°C (from ethanol). IR spectrum: ν(C=O) 1725 cm^{-1}. Found, %: C 61.23; H 3.12; N 16.38. $C_{13}H_8N_3O_3$. Calculated, %: C 61.42; H 3.17; N 16.53.

3-(1,4-Benzodioxan-6-yl)-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-one (IIp). Yield 36%, mp 214–216°C (from ethanol). IR spectrum: ν(C=O) 1725 cm^{-1}. Found, %: C 63.01; H 2.98; N 15.59. $C_{14}H_{11}N_3O_3$. Calculated, %: C 63.16; H 3.03; N 15.78.

1-Methyl-3-phenyl-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-2-one (IIq). Yield 22%, mp 108–110°C (from ethanol). IR spectrum: ν(C=O) 1720 cm^{-1}. Found, %: C 62.56; H 3.45; N 24.10. $C_{14}H_{11}N_3O$. Calculated, %: C 63.32; H 4.92; N 18.65.

1,4-Bis(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-3-yl)benzene (III). A mixture of 1.3 g (10 mmol) of 3-amino-2-chloropyridine, 0.6 g (10 mmol) of urea, and 0.54 g (5 mmol) of *p*-phenylenediamine was heated for 7–10 h at 170–190°C in a stream of nitrogen. The mixture was cooled and ground with cold water, and the precipitate was filtered off, dried, and recrystallized from water. Yield 1.5 g (43%), mp >250°C. IR spectrum: ν(C=O) 1695 cm^{-1}. Found, %: C 62.56; H 3.45; N 24.10. $C_{18}H_{12}N_6O_2$. Calculated, %: C 62.79; H 3.51; N 24.41

1,4-Bis(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-3-yl)biphenyl (IV) was synthesized as described above for compound **III** from 1.3 g (10 mmol) of 3-amino-2-chloropyridine, 0.6 g (10 mmol) of urea, and 0.92 g (5 mmol) of *p*,*p*′-diaminobiphenyl. Yield 1.55 g (37%), mp >250°C (from water). IR spectrum: ν(C=O) 1690 cm^{-1}. Found, %: C 68.35; H 3.78; N 19.81. $C_{24}H_{16}N_6O_2$. Calculated, %: C 68.56; H 3.84; N 19.99.

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