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Convenient Way to the Synthesis of Polycyclic Fused Benzimidazole Derivatives with a Bridgehead Nitrogen Atom

R. S. Begunov[a],* A. A. Sokolov[a], and D. A. Gromova[a]

[a] *Demidov Yaroslavl State University, Sovetskaya ul., 14, Yaroslavl, 150003 Russia*
**e-mail: begunov@bio.uniyar.ac.ru*

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Abstract—Effective synthesis was developed for 1,2,3,4-tetrahydropyrido- and pyrido[1,2-*a*]benzimidazole-7,8-diamines that underlie the preparation of new polyazaheterocycles: pyrido[1,2-*a*]imidazo[4,5-*f*]-benzimidazole, 7*H*-pyrido[1,2-*a*]imidazo[4,5-*f*]benzotriazole, pyrido[1,2-*a*]imidazo[4,5-*g*]quinoxaline.

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A high interest in compounds containing two amino groups in *ortho*-position is due to the possibility to use them in building up various polyazaheterocycles [1–10].

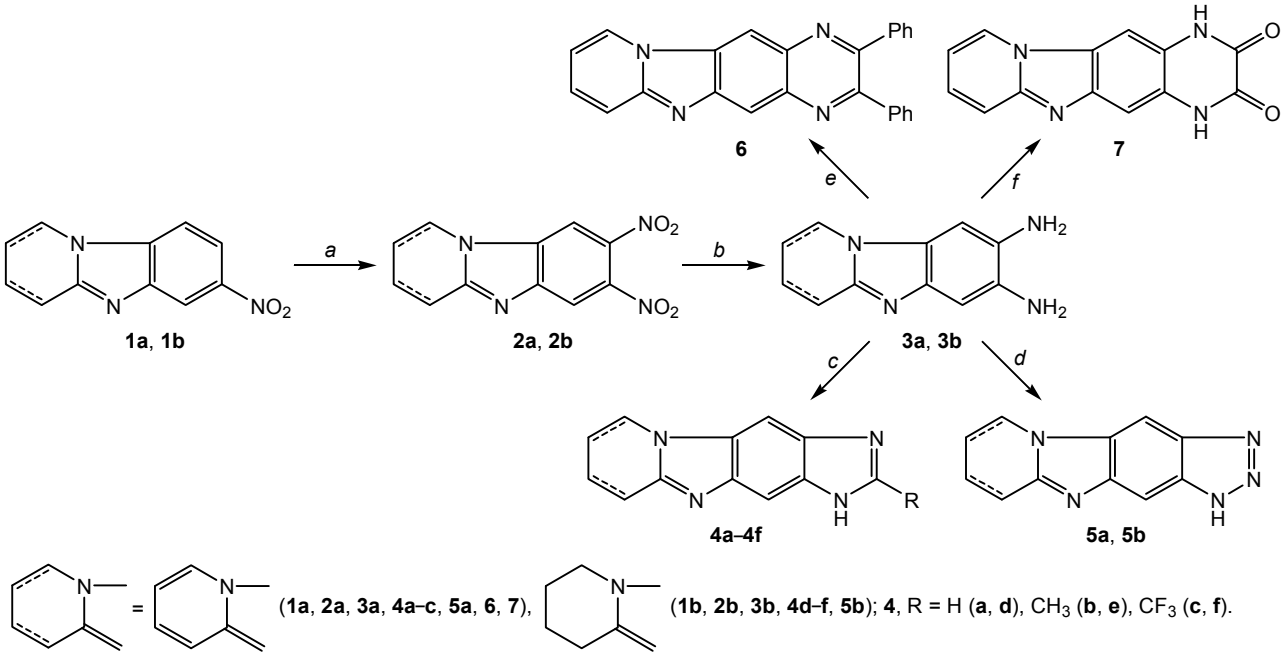
The main drawback of the traditional procedure for the preparation of (het)arenes *ortho*-diamino derivatives is the multistage character of the process and consequently low yield and purity. Commonly the corresponding scheme of the synthesis includes the following stages: reduction of a nitro compound to amino derivative, acylation, reaction with a nitrating agent, removal of acyl protection and again reduction. Another method includes reactions of nitration of halohetarenes followed by amination [11–13] and reduction. In this case problems can arise at the substitution of the halogen for amino group.

More promising seem the introducing a nitro group in the *ortho*-position with respect to already existing one. This would reduce the number of the stages of *ortho*-phenylenediamine preparation to two, but it is in conflict with the directing influence of the electron-acceptor substituents in the benzene ring. Yet for some fused benzene derivatives, e.g., benzodiazoles, the site for electrophilic attack is just the position adjacent to that of the *meta*-directing substituent [14]. This fact we established by an example of the nitration and bromination of 7-substituted pyrido[1,2-*a*]benzimidazoles [15]. It is presumable that similar direction would be observed at the nitration of 7-nitro-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole. In the course of further reduction and heterocyclization it is possible to prepare various fused polyazaheterocyclic systems.

With these observations in mind we developed an effective procedure of the synthesis of polycyclic fused benzimidazole derivatives with a bridgehead nitrogen atom.

The nitration of 7-nitropyrido- and 7-nitro-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazoles **1a** and **1b** (see the scheme) was performed by the method [15] at 30°C. Dinitro cmpounds **2a** and **2b** formed quickly (within 1.5 h) and in very high yields. As showed NMR data the nitration of compound **1b** also occurred in the position *8*. Substances **2a** and **2b** were reduced with $TiCl_3$ since at the use of $SnCl_2$ a mixture of amino products was obtained.

The fusion of imidazole, triazole, quinoxaline, and 1,4-dihydroquinoxaline-2,3-dione rings was performed applying known reactions. As a result we synthesized various, among them unknown, polynuclear fused benzimidazole derivatives with a bridgehead nitrogen atom: 8-R-pyrido- (**4a**–**4c**) and 8-R-1,2,3,4-tetrahydropyrido[1,2-*a*]imidazo[4,5-*f*]benzimidazoles **4d**–**4f**, 7*H*-pyrido[1,2-*a*]imidazo[4,5-*f*]benzotriazole **5a**, and its 1,2,3,4-tetrahydro derivative **5b**, 8,9-diphenylpyrido[1,2-*a*]imidazo[4,5-*g*]quinoxaline **6**, and 7,10-dihydropyrido[1,2-*a*]imidazo[4,5-*g*]quinoxaline-8,9-dione 7 (see the scheme). The yields of the fused polyazaheterocycles attained 91–98% indicating that the developed procedure is promising for the synthesis of polycyclic fused benzimidazole derivatives with a bridgehead nitrogen atom.



Reagents and conditions. *a*: KNO_3, H_2SO_4, 30°C, 1.5 h; *b*: $TiCl_3$, 10% HCl, *i*-PrOH, 40°C, 0.5 h; *c*: ROOH, 1–2 h; *d*: $NaNO_2$, AcOH, H_2O, 20°C, 2 h; *e*: $(PhCO)_2$, AcOH, HCl, 1 h; *f*: $(COOH)_2$, H_2O, HCl, 2 h.

EXPERIMENTAL

Melting points were measured on an apparatus Poly Therm A at the heating rate 3°C/min, the data obtained were not corrected. ^{1}H NMR spectra were registered on a spectrometer Bruker DRX500 (500.13 MHz) in DMSO-d_6. As internal reference served the residual proton signal of the solvent (δ 2.5 ppm). High resolution mass spectra were taken on an instrument Bruker micrOTOF II, ESI ionization.

Compounds 2a and 2b. General procedure. To a solution of 5 mmol of nitrosubstrate **1a** and **1b** in 20 mL of H_2SO_4 at 30°C was added dropwise within 0.5 h 0.56 g (5.5 mmol) of KNO_3 in 20 mL of H_2SO_4 and the mixture was stirred for 1 h. The reaction mixture was poured on ice, neutralized with 25% aqueous ammonia. The resulting precipitate was filtered off, several times washed with water on the filter, and dried.

7,8-Dinitropyrido[1,2-*a*]benzimidazole (2a). Yield 1.22 g (95%), yellow powder, mp 276–278°C. ^{1}H NMR spectrum, δ, ppm: 7.30 t.d (1H, H^2, *J* 6.5, 1.5 Hz), 7.85 d.d.d (1H, H^3, *J* 9.0, 6.5, 0.9 Hz), 7.87 d (1H, H^4, *J* 9.0 Hz), 8.54 s (1H, H^6), 9.39 d (1H, H^1, *J* 6.9 Hz), 9.48 s (1H, H^9). Found *m/z* 259.0463 $[M + H]^+$. $C_{11}H_7N_4O_4$. Calculated *m/z* 259.0469.

7,8-Dinitro-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole (2b). Yield 1.22 g (93%), light-brown powder, mp 219–222°C. ^{1}H NMR spectrum, δ, ppm: 1.93–2.11 m (4H, $H^{2,2,3,3}$), 3.08 t (2H, $H^{4,4}$, *J* 6.2 Hz), 4.26 t (2H, $H^{1,1}$, *J* 5.9 Hz), 8.35 s (1H, H^6), 8.50 s (1H, H^9). Found *m/z* 263.0776 $[M + H]^+$. $C_{11}H_{11}N_4O_4$. Calculated *m/z* 263.0781.

Compounds 3a and 3b. General procedure. To a solution of 3.5 mmol of 7,8-dinitrocompound **2a**, **2b** in a mixture of 10 mL of 10% HCl and 20 mL of *i*-PrOH was added 24 mL (56 mmol) of 15% solution of titanium(III) chloride in 10% HCl. The reaction mixture was stirred for 0.5 h at 40°C, cooled, treated with 25% aqueous ammonia till pH 8, extracted with several portions of hot chloroform (overall volume 250 mL), and the solvent was distilled off.

Pyrido[1,2-*a*]benzimidazole-7,8-diamine (3a). Yield 0.64 g (92%), light-yellow powder, mp 241–243°C. ^{1}H NMR spectrum, δ, ppm: 4.67 s (4H, NH_2), 6.73 t.d (1H, H^2, *J* 6.6, 1.0 Hz), 6.94 s (1H, H^6), 7.21 d.d.d (1H, H^3, *J* 9.2, 6.6, 1.3 Hz), 7.22 s (1H, H^9), 7.42 d.t (1H, H^4, *J* 9.2, 1.0 Hz), 8.54 d.t (1H, H^1, *J* 6.8, 1.0 Hz). Found *m/z* 199.0981 $[M + H]^+$. $C_{11}H_{11}N_4$. Calculated *m/z* 199.0984.

1,2,3,4-Tetrahydropyrido[1,2-*a*]benzimidazole-7,8-diamine (3b). Yield 0.66 g (94%), white powder, mp 222–225°C. ^{1}H NMR spectrum, δ, ppm: 1.85 d (2H, $H^{2,2}$, *J* 4.9 Hz), 1.96 d (2H, $H^{3,3}$, *J* 4.9 Hz), 2.80 t (2H, $H^{4,4}$, *J* 6.2 Hz), 3.84 t (2H, $H^{1,1}$, *J* 5.8 Hz), 4.27 s

(4H, $2NH_2$), 6.53 s (1H, H^6), 6.71 s (1H, H^9). Found *m/z* 203.1291 $[M + H]^+$. $C_{11}H_{15}N_4$. Calculated *m/z* 203.1297.

Compounds 4a, 4d, 4c, and 4f. General procedure. A mixture of 2.5 mmol of compound **3a**, **3b** and 5 mL of formic (at the synthesis of **4a** and **4d**) or trifluoroacetic acid (at the synthesis of **4c** and **4f**) was heated at reflux for 1 h. After cooling the reaction mixture was poured in water and neutralized with 25% aqueous ammonia till pH 8. The resulting precipitate was filtered off, several times washed with water on the filter, and dried.

Pyrido[1,2-*a*]imidazo[4,5-*f*]benzimidazole (4a). Yield 0.51 g (98%), light-brown powder, mp 296–298°C. ^{1}H NMR spectrum, δ, ppm: 6.91 t (1H, H^2, *J* 6.2 Hz), 7.43–7.53 m (1H, H^3), 7.59 d (1H, H^4, *J* 9.3 Hz), 7.86 s (1H, H^6), 8.34 s (1H, H^8), 8.52 s (1H, H^{10}), 9.12 d (1H, H^1, *J* 6.9 Hz), 12.46 s (1H, NH). Found *m/z* 209.0825 $[M + H]^+$. $C_{12}H_9N_4$. Calculated *m/z* 209.0828.

1,2,3,4-Tetrahydropyrido[1,2-*a*]imidazo[4,5-*f*]-benzimidazole (4d). Yield 0.51 g (96%), white powder, mp 300–303°C. ^{1}H NMR spectrum, δ, ppm: 1.94 d (2H, $H^{2,2}$, *J* 5.5 Hz), 2.06 d (2H, $H^{3,3}$, *J* 5.5 Hz), 2.95 t (2H, $H^{4,4}$, *J* 6.3 Hz), 4.08 t (2H, $H^{1,1}$, *J* 5.9 Hz), 7.53 s (1H, H^6), 7.62 s (1H, H^{10}), 12.21 s (1H, NH). Found *m/z* 213.1137 $[M + H]^+$. $C_{12}H_{13}N_4$. Calculated *m/z* 213.1141.

8-(Trifluoromethyl)pyrido[1,2-*a*]imidazo[4,5-*f*]-benzimidazole (4c). Yield 0.66 g (96%), yellow powder, mp >330°C. ^{1}H NMR spectrum, δ, ppm: 6.98 t (1H, H^2, *J* 6.5 Hz), 7.55–7.65 m (2H, $H^{3,4}$), 7.95 s (1H, H^6), 8.71 s (1H, H^{10}), 9.20 d (1H, H^1, *J* 6.9 Hz), 13.93 s (1H, NH). Found *m/z* 277.0700 $[M + H]^+$. $C_{13}H_8F_3N_4$. Calculated *m/z* 277.0702.

8-Trifluoromethyl-1,2,3,4-tetrahydropyrido[1,2-*a*]imidazo[4,5-*f*]benzimidazole (4f). Yield 0.66 g (94%), light-brown powder, mp 319–322°C. ^{1}H NMR spectrum, δ, ppm: 1.95 d (2H, $H^{2,2}$, *J* 4.9 Hz), 2.07 d (2H, $H^{3,3}$, *J* 4.9 Hz), 2.99 t (2H, $H^{4,4}$, *J* 6.2 Hz), 4.12 t (2H, $H^{1,1}$, *J* 5.9 Hz), 7.67 s (1H, H^6), 7.75 s (1H, H^{10}), 13.65 s (1H, NH). Found *m/z* 281.1012 $[M + H]^+$. $C_{13}H_{12}F_3N_4$. Calculated *m/z* 281.1015.

Compounds 4b and 4e. General procedure. A mixture of 2.5 mmol of compounds **3a** and **3b**, 5 mL of glacial acetic acid, and 0.05 mL of conc. HCl was heated at 100°C with a reflux condenser for 2 h. After cooling the reaction mixture was poured in water and neutralized with 25% aqueous ammonia till pH 8. The separated precipitate was filtered off, several times washed with water on the filter, and dried.

8-Methylpyrido[1,2-*a*]imidazo[4,5-*f*]benzimidazole (4b). Yield 0.53 g (95%), light-brown powder, mp >320°C. ^{1}H NMR spectrum, δ, ppm: 2.54 s (3H, CH_3), 6.89 t (1H, H^2, *J* 6.5 Hz), 7.41–7.51 m (1H, H^3), 7.57 d (1H, H^4, *J* 9.2 Hz), 7.68 s (1H, H^6), 8.39 s (1H, H^{10}), 9.09 d (1H, H^1, *J* 6.8 Hz), 12.19 s (1H, NH). Found *m/z* 223.0980 $[M + H]^+$. $C_{13}H_{11}N_4$. Calculated *m/z* 223.0984.

8-Methyl-1,2,3,4-tetrahydropyrido[1,2-*a*]imidazo[4,5-*f*]benzimidazole (4e). Yield 0.52 g (93%), light-brown powder, mp 288–293°C. ^{1}H NMR spectrum, δ, ppm: 1.92 d (2H, $H^{2,2}$, *J* 4.9 Hz), 2.05 d (2H, $H^{3,3}$, *J* 4.9 Hz), 2.48 s (3H, CH_3), 2.94 t (2H, $H^{4,4}$, *J* 6.3 Hz), 4.06 t (2H, $H^{1,1}$, *J* 6.0 Hz), 7.39 s (1H, H^6), 7.48 s (1H, H^{10}). Found *m/z* 227.1293 $[M + H]^+$. $C_{13}H_{15}N_4$. Calculated *m/z* 227.1297.

Compounds 5a and 5b. General procedure. To 2 mmol of compounds **3a** and **3b** was added 2 mL of glacial acetic acid and 3 mL of water and the mixture was stirred till the dissolution of the solid. Then at room temperature was added a solution of 0.172 g (2.5 mmol) of sodium nitrite in 2 mL of water. The reaction mixture was left standing at room temperature for 2 h with intermittent stirring. Afterwards it was treated with 25% aqueous ammonia till pH 8 and the separated precipitate was filtered off.

7*H*-Pyrido[1,2-*a*]imidazo[4,5-*f*]benzotriazole (5a). Yield 0.40 g (95%), light-brown powder, mp >305°C. ^{1}H NMR spectrum, δ, ppm: 6.98 t (1H, H^2, *J* 6.5 Hz), 7.61 m (2H, $H^{3,4}$), 7.94 s (1H, H^6), 9.00 s (1H, H^{10}), 9.20 d (1H, H^1, *J* 6.8 Hz), 15.66 s (1H, NH). Found *m/z* 210.0773 $[M + H]^+$. $C_{11}H_8N_5$. Calculated *m/z* 210.0780.

1,2,3,4-Tetrahydro-7*H*-pyrido[1,2-*a*]imidazo[4,5-*f*]benzotriazole (5b). Yield 0.41 g (97%), light brown-red powder, mp 347–350°C. ^{1}H NMR spectrum, δ, ppm: 1.94 d (2H, $H^{2,2}$, *J* 5.5 Hz), 2.06 d (2H, $H^{3,3}$, *J* 5.5 Hz), 2.99 t (2H, $H^{4,4}$, *J* 6.3 Hz), 4.12 t (2H, $H^{1,1}$, *J* 5.9 Hz), 7.80 s (1H, H^6), 7.89 s (1H, H^{10}), 15.17 s (1H, NH). Found *m/z* 214.1091 $[M + H]^+$. $C_{11}H_{12}N_5$. Calculated *m/z* 214.1093.

8,9-Diphenylpyrido[1,2-*a*]imidazo[4,5-*g*]quinoxaline (6). To 0.50 g (2.5 mmol) of compound **3a**, 0.53 g (2.52 mmol) of 1,2-bis(4-R-phenyl)ethane-1,2-dione was added 2 mL of glacial acetic acid and 0.05 mL of conc. HCl. The mixture was refluxed for 1 h, cooled,

and poured in water, neutralized with 25% aqueous ammonia till pH 8, the resulting precipitate was filtered off and dried. Yield 0.86 g (**93%**), orange powder, mp 258–260°C. ^{1}H NMR spectrum, δ, ppm: 7.10 t (1H, H^2, *J* 6.8 Hz), 7.33–7.44 m (6H, $H^{3',3'',4',4'',5',5''}$), 7.47–7.56 m (4H, $H^{2',2'',6',6''}$), 7.70–7.79 m (2H, $H^{3,4}$), 8.42 s (1H, H^6), 9.17 s (1H, H^{11}), 9.33 d (1H, H^1, *J* 6.9 Hz). Found *m/z* 373.1451 $[M + H]^+$. $C_{25}H_{17}N_4$. Calculated *m/z* 373.1454.

7,10-Dihydropyrido[1,2-*a*]imidazo[4,5-*g*]quinoxaline-8,9-dione (7). To 0.076 g (0.6 mmol) of oxalic acid dehydrate, 0.079 (0.4 mmol) of compound **3a** was added 2 mL of water and 0.05 mL of conc. HCl. The mixture was refluxed for 1 h, cooled, and poured in water, neutralized with 25% aqueous ammonia till pH 8, the resulting precipitate was filtered off and dried. Yield 92 mg (91%), light-brown powder, mp >320°C. ^{1}H NMR spectrum, δ, ppm: 6.94 t (1H, H^2, *J* 6.7 Hz), 7.47–7.52 m (2H, $H^{6,11}$), 7.59 d (1H, H^4, *J* 9.1 Hz), 7.87 t (1H, H^3, *J* 9.2 Hz), 8.95 d (1H, H^1, *J* 6.8 Hz), 12.04 s (1H, NH), 12.21 s (1H, NH). Found *m/z* 253.0713 $[M + H]^+$. $C_{13}H_9N_4O_2$. Calculated *m/z* 253.0726.

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