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SHORT COMMUNICATIONS

Simple Synthesis of Substituted Benzo[4,5]imidazo[1,2-*a*]pyridines

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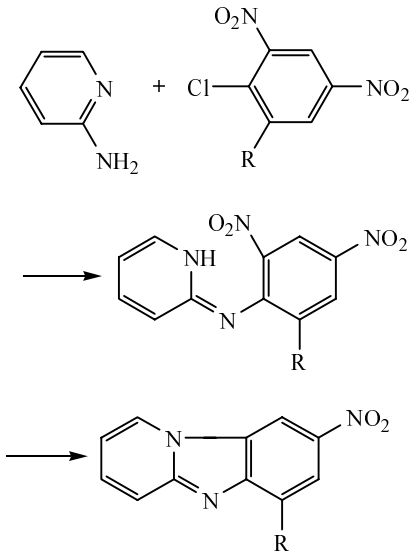
Pyridine series compounds attract traditionally great interest. Their application field is extremely wide: dyes manufacturing, agriculture, veterinary medicine, pharmacology [1–3]. A special place take here the fused pyridine derivatives. A large number of drugs belongs to this class: quinine, desoxypeganine, enteroseptol, echinopsin etc. [4]. Therefore a development of new highly selective procedures for fused puridine derivatives preparation is an urgent task.



In [5–7] various methods are described for preparation of substituted benzo[4,5]imidazo[1,2-*a*]-pyridines possessing a biological activity [8, 9] and fluorescence properties [10, 11]. However the existing procedures have significant disadvantages: application of expensive reagents, high temperature of the process, a low yield of the final products. The most common procedure of the synthesis of substituted benzo[4,5]imidazo-[1,2-*a*]-pyridines consists in condensation of benzene 1-chloro-2-nitro derivatives with 2-aminopyridine [5].

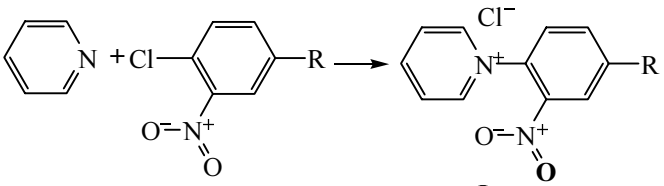
The reaction proceeds under relatively stringent conditions (190°C, 2–3 h) unsuitable for the synthesis of medicinals [12].

The procedure based on reductive cyclization of *N*-(2,4-dinitrophenyl)pyridine chloride was not widely used because of low yield of the final products and side processes. Application of Pt/C or Pd/C as reducing agents resulted in formation of 8-amino-1,2,3,4-tetrahydro-benzo[4,5]-imidazo[1,2-*a*]pyridine [13].

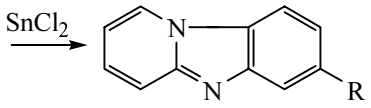
Benzo[4,5]imidazo[1,2-*a*]pyridines were obtained at the use of phenylhydrazine as cyclizing agent (boiling in acetic acid for 2 h). However the reaction under the mentioned conditions was accompanied with side processes giving a considerable amount of products and consequently reducing the yield of the target compounds (29–53%) [13].

Aiming at development of a new highly selective procedure for preparation of substituted benzo[4,5]-imidazo[1,2-*a*]pyridines we carried out a search for a convenient cyclizing agent. Its role was played by tin(II) chloride in the presence of 3% HCl. We had preliminary prepared *N*-(2-nitro-4R-phenyl)pyridines (**Ia–c**) by reaction of pyridine with *o*-nitrohaloarenes. The nitro group in the *o*-position of the pyridine ring in the compounds obtained was converted by reduction into an amino group, and then a cyclization occurred resulting from a nucleophilic attack of the amino group on the α-carbon in the pyridine ring. Thanks to the use of tin(II) chloride as reductant the cyclization occurred at room temperature within 5–10 min. Yields of the final reaction

products attained 91–98%. Inasmuch as in the *N*-(2,4-dinitrophenyl)-pyridine chloride molecule two nitro groups were present, at careful dosage of the reducing agent we succeeded in preparation both of 8-nitro- and 8-aminobenzo[4,5]imidazo[1,2-*a*]-pyridines (**IIb, d**). The primary reduction of the nitro group located in the *o*-position is due to assistance of a positively charged substituent [14].



Ia–c



IIa–d

Hence the application of tin(II) chloride as reducing agent ensured an easy and fast procedure for preparation of substituted benzo[4,5]-imidazo[1,2-*a*]pyridines in high yields.

The composition and structure of compounds obtained were proved by elemental analysis, ^{1}H NMR and mass spectra.

Compounds **Ia–c** were obtained by published method [15].

8-(Trifluoromethyl)benzo[4,5]imidazo[1,2-*a*]-pyridine (IIa). Into a flask at vigorous stirring were charged simultaneously a solution of 5 g (0.016 mol) of *N*-(2-nitro-4-trifluoromethylphenyl)-pyridinium chloride in 20 ml of ethanol and a solution of 11.13 g (0.048 mol) of $SnCl_2 \cdot 2H_2O$ in 20 ml of 3% hydrochloric acid. In 10 min the reaction mixture was alkalinized with 25% aqueous ammonia till pH 7–8, and the reaction product was extracted with several portions of chloroform (200 ml). On removing the chloroform we obtained 3.7 g (98%) of compound **IIa**, mp 233–235°C. ^{1}H, δ, ppm: 9.15 d (1H, H^4, *J* 7.5 Hz), 8.53 d.d (1H, H^7, *J* 8, 2 Hz), 8.16 d (1H, H^9, *J* 1.5 Hz), 7.75 d (1H, H^1, *J* 9 Hz), 7.68 d (1H, H^6, *J* 8 Hz), 7.66 t (1H, H^2, *J* 8 Hz), 7.09 t (1H, H^3, *J* 7 Hz). Mass spectrum, *m/z* (I_{rel}, %): 236 (100) [*M*]$^+$, 217 (20), 186 (12), 118 (5), 69 (5). Found, %: C 60.7; H 3.3; N 12.0. $C_{12}H_7N_2F_3$. Calculated, %: C 61.0; H 3.0; N 11.9.

Compounds **IIb, c** were obtained in a similar way.

8-Nitrobenzo[4,5]imidazo[1,2-*a*]pyridine (IIb). Yield 3.44 g (91%), mp 290–292°C. ^{1}H, δ, ppm: 9.13 d (1H, H^4, *J* 7 Hz), 8.64 d (1H, H^9, *J* 1.5 Hz), 8.50 d (1H, H^6, *J* 8.5 Hz), 8.20 d.d (1H, H^7, *J* 8.5, 2 Hz), 7.78 d (1H, H^1, *J* 9 Hz), 7.67 t (1H, H^2, *J* 7.5 Hz), 7.11 t (1H, H^3, *J* 7 Hz). Mass spectrum, *m/z* (I_{rel}, %): 213 (100) [*M*]$^+$, 183 (4), 167 (91), 155 (14), 140 (28), 78 (12). Found, %: C 61.6; H 3.1; N 20.0. $C_{11}H_7N_3O_2$. Calculated, %: C 62.0; H 3.3; N 19.7.

8-Cyanobenzo[4,5]imidazo[1,2-*a*]pyridine (IIc). Yield 3.54 g (96%), mp 242–244°C. ^{1}H, δ, ppm: 9.15 d (1H, H^4, *J* 6.5 Hz), 8.51 d.d (1H, H^7, *J* 8.5, 2 Hz), 8.35 d (1H, H^9, *J* 1.5 Hz), 7.75 d (1H, H^6, *J* 8.5 Hz), 7.74 d (1H, H^1, *J* 9.5 Hz), 7.67 t (1H, H^2, *J* 7 Hz), 7.10 t (1H, H^3, *J* 6.5 Hz). Mass spectrum, *m/z* (I_{rel}, %): 193 (100) [*M*]$^+$, 167 (4), 165 (4), 154 (4), 139 (4). Found, %: C 74.7; H 3.6; N 22.0. $C_{12}H_7N_3$. Calculated, %: C 74.6; H 3.6; N 21.8.

8-Aminobenzo[4,5]imidazo[1,2-*a*]pyridine (IId). To a solution of 24 g (0.107 mol) of $SnCl_2 \cdot 2H_2O$ in 20 ml of 3% hydrochloric acid was added at stirring a solution 5 g (0.0178 mol) of *N*-(2,4-dinitrophenyl)pyridinium chloride in 20 ml of ethanol. In 10 min the reaction mixture was alkalinized with 25% aqueous ammonia till pH 7–8, and the reaction product was extracted with several portions of chloroform (200 ml). On removing the chloroform we obtained 3.16 g (97%) of 8-amino-benzo[4,5]-imidazo[1,2-*a*]pyridine, mp 180–182°C. ^{1}H, δ, ppm: 8.82 d (1H, H^4, *J* 7 Hz), 7.9 d (1H, H^6, *J* 9.5 Hz), 7.47 d (1H, H^1, *J* 10 Hz), 7.38 t (1H, H^2, *J* 7.5 Hz), 6.85 t (1H, H^3, *J* 7 Hz), 6.82 d (1H, H^9, *J* 1.5 Hz), 6.7 d.d (1H, H^7, *J* 10, 2 Hz), 5.1 s (2H, NH_2). Mass spectrum, *m/z* (I_{rel}, %): 183 (100) [*M*]$^+$, 166 (4), 155 (15), 78 (12). Found, %: C 71.9; H 4.5; N 23.3. $C_{11}H_9N_3$. Calculated, %: C 72.1; H 4.9; N 23.0.

^{1}H NMR spectra were registered on spectrometer Bruker DRX-500 at operating frequency 500 MHz from solutions in DMSO-d_6. Mass spectra were measured on MKh-1310 device. The elemental analyses were carried out on a CHN-1 analyzer.

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