SHORT COMMUNICATIONS

Effect of Reducer’s Nature on the Reduction of N-(2-Nitrophenyl)pyridinium Chlorides

R. S. Begunov, A. A. Sokolov, and T. V. Shebunina

Demidov Yaroslavl State University, Yaroslavl', 150000 Russia
e-mail: begunov@bio.uniyar.ac.ru

Received October 29, 2012

DOI: 10.1134/S1070428013050291

Pyrido[1,2-α]benzimidazoles and the other fused polycyclic imidazole derivatives containing a nodal nitrogen atom belong to the most interesting classes of organic compounds since they exhibit versatile biological activity: antitumor [1], immunomodulating [2], antiphlogistic [3], antibacterial, and fungicidal [4]. They are besides bioisosteric analogs of nitrogen bases and are capable of insertion into the DNA double helix [5]. Due to the high fluorescence activity these heterocyclic compounds are employed in the paints production [6].

Therefore a great number of publications appears describing the new or modifications of the previously known procedures for the synthesis of similar heterocyclic systems [7]. The most promising and yet the least studied is the method based on the building up of the imidazole ring of the pyrido[1,2-α]-benzimidazole system through the reductive intramolecular cyclization of 1-(2-nitrophenyl)pyridinium salts. This methods is used seldom since there are insuffcient data on the effect of various factors on the process of the reductive amination. The most essential factor is here the nature of electron donor [8, 9]. Depending on the structure of the latter a number of process may occur alternative to the intramolecular amination: the reduction of the pyridine fragment into piperidine moiety [8, 9], the formation of 1-(2-aminophenyl)derivative [9], the reaction of the pyridinium salt with the reagent (at the reduction with phenylhydrazine) [8].

The investigation of the effect of the reducer nature on the reaction direction was performed using reagents operating in the acid medium: TiCl₃, FeCl₂, SnCl₂. The use of Na₂S and the other agents for the reduction of the nitro compounds at pH > 7 is prevented by the hydrolysis of pyridinium salts occurring with the ring opening [10].

The reduction of 1-[2-nitro-4-(trifluoromethyl)phenyl]pyridinium chloride (Ia) with titanium(III) chloride in the acidic water-alcohol solution led to an intractable mixture from which we isolated in a small yield (up to 23%) a compound that according to the 1H NMR and mass spectra corresponded to the product II resulting from the reduction of the nitro group. The 1H NMR spectrum of compound II contains the signals of pyridine protons: 9.15 d (2H, H₂,6, J 8.5 Hz), 8.75 m (1H, H₄), 8.35 m (2H, H₃,5). The singlet of the amino group protons appears at 6.22 ppm due to the presence of an electron-acceptor

![Diagram](image-url)
substituent in the ortho-position (the positively charged nitrogen atom of the pyridine ring). The benzene protons are observed as an ABC system: 7.55 d (1H, H^6, J9.5 Hz), 7.35 d (1H, H^2, J1.0 Hz), 7.00 d.d (1H, H^5, J9.5, 1.0 Hz).

The formation of a multicomponent mixture at the reduction with TiCl₃ is caused apparently by the hydrolysis of the main reaction product II during the isolation under the action of hydroxide ions. The pyridine ring of product II evidently suffers ring opening under the action of hydroxide ions. The possibility of this process is confirmed by the presence in the ¹H NMR spectrum of the reaction mixture of a singlet of an aldehyde proton at 10.23 ppm.

At the use of salt Ia and SnCl₂ the product of the intramolecular reductive cyclization IIIa was obtained whose composition and structure was proved by elemental analysis, ¹H NMR and mass spectra. ¹H NMR spectrum of cyclization product IIIa contains the signals of seven aromatic and heteroaromatic protons: four signals of the pyridine ring protons 9.15 d (1H, H^9), 7.75 d (1H, H^4, J9.7 Hz), 7.66 t (1H, H^3, J8 Hz), 7.09 t (1H, H^2, J7 Hz); and three sigals of benzene ring protons 8.53 d.d (1H, H^8, J8, 2 Hz), 8.16 d (1H, H^6, J1.5 Hz), 7.68 d (1H, H^9, J8 Hz).

Thus the study of the effect of the electron donor nature on the reduction of 1-(2-nitro-4-R-phenyl)pyridinium chlorides showed that at the use of TiCl₃ formed the primary amine, whereas the intramolecular cyclization occurred under the action of FeCl₂ and SnCl₂ in acidic water-alcohol solution.

1-[2-Amino-4-(trifluoromethyl)phenyl]pyridinium chloride (II). To a solution of 1 g (3.3 mmol) of salt I in 20 ml of 2-propanol was added at 20°C 70 ml (23.1 mmol) of 5% TiCl₃ solution in 3% HCl. After 10 min the reaction mixture was alkalinized with 25% ammonia solution to pH 7–8 and extracted with several portions of chloroform (200 ml), the extract was evaporated. Yield 0.21 g (23%). Mass spectrum, m/z (Irel, %): 239 (100) [M – Cl]⁺, 170 (18), 78 (15.2), 39 (22). Found, %: C 52.08; H 3.34; N 10.19. C₁₃H₁₀ClF₃N₂. Calculated, %: C 52.46; H 3.64; N 10.20. M 239.22.

Pyrido[1,2-α]benzimidazoles IIIa–IIIk were obtained similarly. In the synthesis of compounds IIIa–IIIk 10 mmol of SnCl₂·2H₂O was used per 3.3 mmol of the salt, in the synthesis of amine III, 20 mmol.

7-(Trifluoromethyl)pyrido[1,2-α]benzimidazole (IIa). Yield 0.76 g (98%), mp 233–235°C. Mass spectrum, m/z (Irel, %): 236 (100) [M]+, 217 (20), 186 (12), 167 (4), 118 (5), 69 (5), 63 (11), 51 (17), 39 (20). Found, %: C 60.79; H 2.96; N 12.01. C₁₂H₁₀F₃N₂. Calculated, %: C 61.02; H 2.99; N 11.86. M 236.12.

7-Nitropyrido[1,2-α]benzimidazole (IIb). Yield 0.64 g (91%), mp 290–292°C. ¹H NMR spectrum, δ, ppm: 7.11 t (1H, H^6, J 7 Hz), 7.67 t (1H, H^2, J 7.5 Hz), 7.78 d (1H, H^4, J 9 Hz), 8.20 d.d (1H, H^3, J 2.0, 8.5 Hz), 8.50 d (1H, H^9, J 8.5 Hz), 8.64 d (1H, H^6, J 1.5 Hz), 9.13 d (1H, H^1, J 7 Hz). Mass spectrum, m/z (Irel, %): 213 (100) [M]+, 183 (4), 167 (91), 155 (14), 140 (28), 78 (12), 63 (11), 51 (9). Found, %: C 61.88; H 3.14; N 20.01. C₁₂H₁₀N₂. Calculated, %: C 61.97; H 2.99; N 11.86. M 213.20.

Pyrido[1,2-α]benzimidazoles-7-carbonitrile (IIc). Yield 0.61 g (96%), mp 242–244°C. ¹H NMR spectrum, δ, ppm: 7.10 t (1H, H^2, J 6.5 Hz), 7.67 t (1H, H^1, J 7 Hz), 7.74 d (1H, H^6, J 9.5 Hz), 7.75 d (1H, H^9, J 8.5 Hz), 8.35 d (1H, H^4, J 1.5 Hz), 8.51 d.d (1H, H^3, J 2.0, J 8.5 Hz), 9.15 d (1H, H^1, J 6.5 Hz). Mass spectrum, m/z (Irel, %): 193 (100) [M]+, 167 (6), 165 (4), 154 (4), 139 (9), 97 (9), 78 (8), 63 (7), 51 (12), 39 (15). Found, %: C 74.64; H 3.60; N 21.87. C₁₂H₁₀N₂. Calculated, %: C 74.61; H 3.64; N 21.76. M 193.21.

Pyrido[1,2-α]benzimidazoles-7-carboxylic acid (IId). Yield 0.65 g (93%), mp >300°C. ¹H NMR spectrum