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REACTIONS OF 7-NITROPYRIDO[1,2-*a*]BENZIMIDAZOLIUM SALTS WITH HYDRAZINES AND HYDROXYLAMINE

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We are the first to show that quaternary 7-nitropyrido[1,2-a]benzimidazolium salts are cleaved by hydrazine, phenylhydrazine, and hydroxylamine to form 2-pyrazolinemethyl- and 2-isoxazoline-methyl-6-nitrobenzimidazoles.

Keywords: isoxazolinemethylnitrobenzimidazole, pyrazolinemethylnitrobenzimidazole, 7-nitropyridobenzimidazolium salts, pyridine ring opening.

N-Methylimidazo[1,2-*a*]pyridinium [1, 2] and 7-nitropyrido[1,2-*a*]benzimidazolium salts [3] are cleaved rather readily by the action of secondary amines to give (1*E*,3*E*)-1-amino-4-(hetaryl)-1,3-butadienes. The reaction of such salts with hydrazines and hydroxylamine has not been studied.

We have shown that 5-methyl-7-nitropyrido[1,2-*a*]benzimidazolium iodide (**1**) and 5-allyl-7-nitropyrido[1,2-*a*]benzimidazolium bromide (**2**) are converted by the action of hydrazine in acetonitrile at reflux into 2-dihydropyrazolylmethyl-6-nitrobenzimidazoles **3** and **4**, respectively, as a consequence of cleavage of the pyridine fragment.

We assume that 1-hydrazino-4-nitrobenzimidazolyl-1,3-butadienes **A** are initially formed in the nucleophilic cleavage of salts **1** and **2** and then converted to pyrazolylmethylnitrobenzimidazoles **B** as a result of a Michael 1,2-addition of the hydrazine fragment to the diene system. Prototropic isomerization of the Δ^3-pyrazoline fragment in nitrobenzimidazoles **B** to a Δ^2-pyrazoline fragment leads to benzimidazoles **3** and **4**. This scheme for the formation of compounds **3** and **4** was confirmed by convergent synthesis of pyrazolylmethyl derivative **3** from (1*E*,3*E*)-1-dimethylamino-4-(6-nitrobenzimidazol-2-yl)-1,3-butadiene (**5**) [3] and hydrazine. The removal of a dimethylamino group at a double bond by the action of primary amines is commonly used in organic synthesis [4]. Acetylation of imidazoles **3** and **4** by acetic anhydride gives only monoacetyl derivatives **6** and **7**, which supports the proposed structure of the pyrazoline ring. The ^{1}H NMR spectra of compounds **3** and **4**, in which one vinyl proton signal as a triplet with $^3J = 1.4$ and 1.7 ppm is found at 6.85 and 6.74 ppm, respectively, are in good accord with this conclusion.

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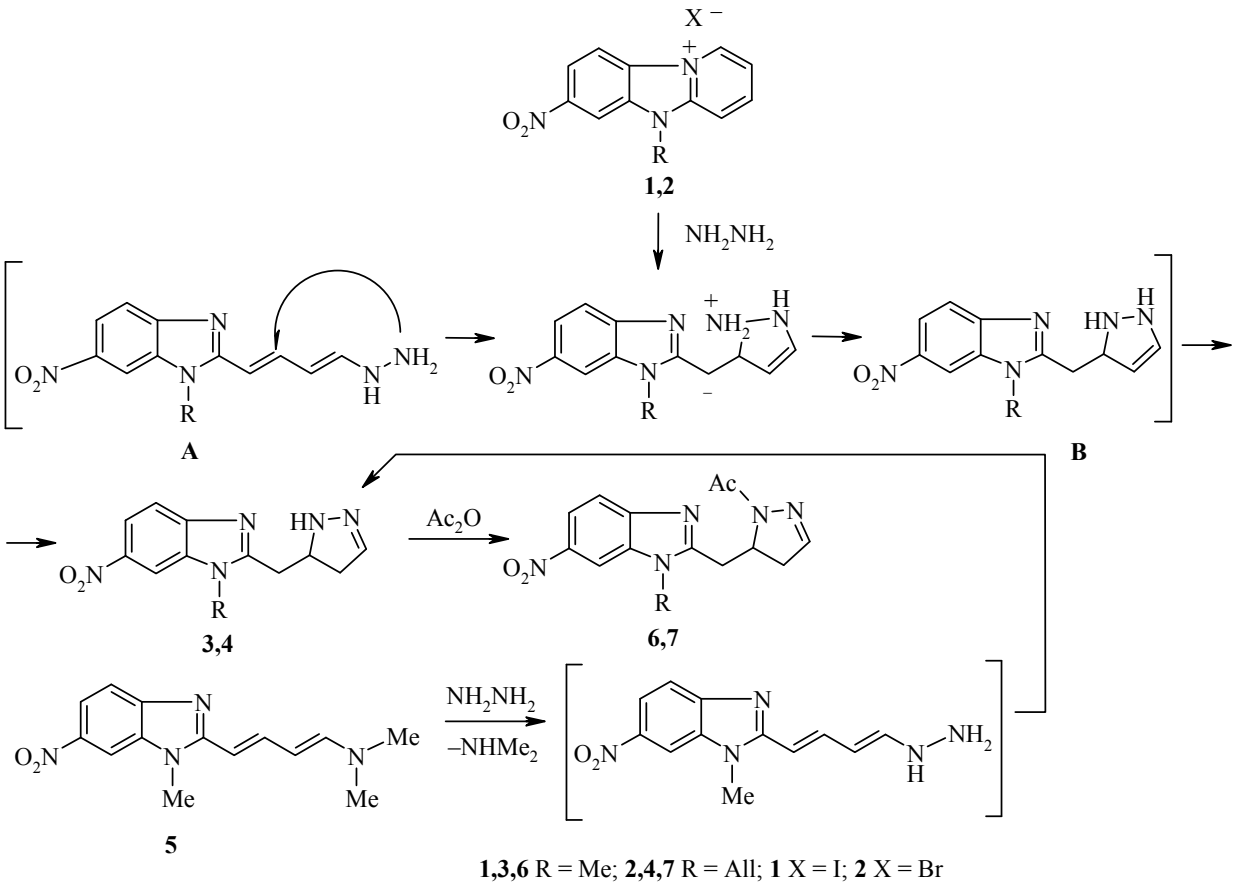
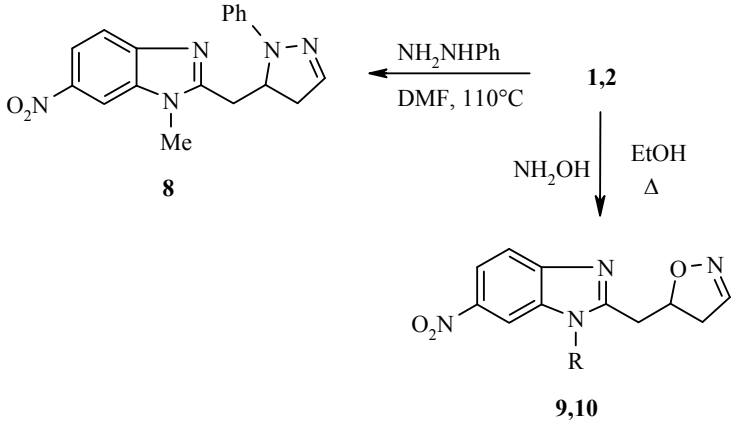


1,3,6 R = Me; **2,4,7** R = All; **1** X = I; **2** X = Br

Cleavage of salt **1** by phenylhydrazine proceeds under more rigorous conditions (in DMF at 110°C) than for the cleavage with hydrazine, probably due to the lower nucleophilicity of phenylhydrazine. N-Phenylpyrazolinylmethylnitroimidazole **8** was obtained in 33% yield.



9 R = Me, **10** R = allyl

Analogous cleavage of salts **1** and **2** by the action of hydroxylamine proceeds in ethanol at reflux. Isoxazolinylmethylnitrobenzimidazoles **9** and **10** were obtained in 20 and 27% yield, respectively.

The mass spectra of all the pyrazolinyl- and isoxazolinylmethylbenzimidazoles **3**, **4**, and **6-10** show molecular ion peaks of various intensity corresponding to their chemical formulas. The signals of all the protons with chemical shifts and coupling constants corresponding to their position are found in the ^{1}H NMR spectra of **3**, **4**, and **6-10**. The signals of the methylene group protons are not equivalent and are observed as AB systems. The signal of vinyl proton H-3' of the pyrazoline and isoxazoline rings is seen at 6.74-7.12 ppm as a triplet or multiplet due to spin-spin coupling with the protons of the adjacent methylene group.

Thus, in this work, we are the first to have shown the feasibility of transforming 7-nitropyridobenzimidazolium salts into pyrazolinyl- and isoxazolinylmethyl-6-nitrobenzimidazoles.

EXPERIMENTAL

The IR spectra were taken on an Infralum FT-801 Fourier spectrometer for KBr pellets. The ^{1}H NMR spectra were taken on a Bruker WP-400 spectrometer at 400 MHz in $CDCl_3$ with TMS as the internal standard. The electrospray ionization mass spectra were taken on a Finnigan MAT Incos 50 mass spectrometer with direct sample inlet into the ion source at 70 eV ionization voltage. Thin-layer chromatography was carried out on Silufol UV-254 plates with development by iodine vapor. Neutral Fluka 507 alumina (0.05-0.15 mm) was used for the column chromatography.

2-(4,5-Dihydro-1H-pyrazol-5-yl)methyl-1-methyl-6-nitrobenzimidazole (3). A. A solution of 9-methyl-7-nitropyridobenzimidazolium iodide (**1**) (1.6 g, 5 mmol) and hydrazine hydrate (10 ml) in acetonitrile (10 ml) was heated at reflux for 5 h with monitoring by thin-layer chromatography. Acetonitrile was distilled off in vacuum. The residue was washed with 10 ml water and subjected to column chromatography using ethyl acetate as the eluent to give 0.7 g (44%) benzimidazole **3** as pale-yellow crystals; mp 138-140°C (ethyl acetate). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.98 (1H, ddd, *J* = 1.5, *J* = 8.4, *J* = 16.8, H-4'*a*); 3.07 (1H, ddd, *J* = 1.5, *J* = 9.8, *J* = 16.8, H-4'*b*); 3.10 (1H, s, 2-CH_2); 3.20 (1H, s, 2-CH_2); 3.83 (3H, s, N–CH_3); 4.10 (1H, m, H-5'); 6.85 (1H, t, *J* = 1.4, H-3'); 7.74 (1H, d, *J* = 8.9, H-4); 8.08 (1H, dd, *J* = 2.1, *J* = 8.9, H-5); 8.52 (1H, d, *J* = 2.1, H-7). Found, %: C 55.23; H 5.18; N 27.19. $C_{16}H_{18}N_4O_2$. Calculated, %: C 55.59; H 5.02; N 27.02.

B. A solution of diene **5** (0.8 g, 2.9 mmol) and hydrazine hydrate (10 ml) in acetonitrile (10 ml) was heated at reflux for 6 h with monitoring by thin-layer chromatography. Acetonitrile was distilled off in vacuum. The residue was treated as in Method A to give 0.53 g (70%) benzimidazole **3** as pale-yellow crystals; mp 140-141°C. A mixed melting point with a sample obtained by Method A was undepressed.

2-(1-Acetyl-4,5-dihydro-1H-pyrazol-5-yl)methyl-1-methyl-6-nitrobenzimidazole (6). Benzimidazole **3** (1 g, 4 mmol) in acetic anhydride (5 ml) was heated at reflux for 1 h. Acetic anhydride was distilled off in vacuum. The residue was made basic by adding saturated aqueous sodium carbonate (20 ml) and extracted with two 30-ml chloroform portions. The extract was dried over $MgSO_4$. The residue after removal of the chloroform was recrystallized from ethyl acetate to give 0.6 g (60%) acetylbenzimidazole **6** as white crystals; mp 210-212°C. IR spectrum, ν, cm^{-1}: 1670 (N–C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.34 (3H, s, CH_3CO); 3.04 (1H, dd, *J* = 9.6, *J* = 14.5, 2-CH_2); 3.10 (1H, ddd, *J* = 1.7, *J* = 4.8, *J* = 17.9, H-4'*a*); 3.20 (1H, ddd, *J* = 1.4, *J* = 10.7, *J* = 17.9, H-4'*b*); 3.70 (1H, dd, *J* = 2.9, *J* = 14.5, 2-CH_2); 3.93 (3H, s, N–CH_3); 4.80 (1H, m, H-5'); 8.30 (1H, d, *J* = 2.1, H-8). Found, %: C 55.83; H 4.93; N 23.45. $C_{14}H_{14}N_5O_3$. Calculated, %: C 56.00; H 4.67; N 23.33.

2-(1-Acetyl-4,5-dihydro-1H-pyrazol-5-yl)methyl-1-allyl-6-nitrobenzimidazole (7). Pyrazolylmethylnitrobenzimidazole **4** (0.7 g), obtained as described above from salt **2** (1.5 g, 4.5 mmol) and hydrazine hydrate (10 ml), in acetic anhydride (5 ml) was heated at reflux for 1 h with monitoring by thin-layer chromatography. Acetic anhydride was distilled off in vacuum. The residue was made basic by adding aqueous sodium carbonate and extracted by two 30-ml chloroform portions. The extract was dried over $MgSO_4$. Chloroform was distilled off and the residue was recrystallized from ethyl acetate to give 0.34 g (60%) acetylbenzimidazole **7** as colorless

crystals; mp 222-224°C. IR spectrum, ν, cm^{-1}: 1675 (N–C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.34 (3H, s, CH_3CO); 2.87 (1H, dd, *J* = 10.2, *J* = 14.5, 2-CH_2); 3.02 (1H, ddd, *J* = 1.6, *J* = 10.8, *J* = 18.9, H-4'*b*); 3.17 (1H, ddd, *J* = 1.6, *J* = 4.9, *J* = 18.9, H-4'*a*); 3.62 (1H, dd, *J* = 2.7, *J* = 14.5, 2-CH_2); 4.67 (1H, m, H-5'); 4.72 (2H, m, CH_2–C=); 4.99 (1H, m, C<u>H</u>=CH_2); 5.23 (1H, m, C<u>H$_2$</u>=CH); 5.96 (1H, m, C<u>H$_2$</u>=CH); 6.85 (1H, m, H-3'); 7.72 (1H, d, *J* = 8.8, H-4); 8.15 (1H, dd, *J* = 2.1, *J* = 8.8, H-5); 8.26 (1H, d, *J* = 2.1, H-7). Found, %: C 59.00; H 5.38; N, 22.91. $C_{16}H_{17}N_5O_3$. Calculated, %: C 58.72; H 5.20; N 22.89.

1-Methyl-6-nitro-2-(1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)methylbenzimidazole (8). A solution of salt **1** (1 g, 3 mmol) and phenylhydrazine (2 g, 18 mmol) in DMF (15 ml) was heated at 110°C for 24 h with monitoring by thin-layer chromatography. DMF was distilled off in vacuum. Water (15 ml) was added to the residue and the mixture was extracted with two 30-ml chloroform portions. The extract was dried over $MgSO_4$. Chloroform was distilled off and the residue was purified by chromatography on an alumina column to give 0.2 g (33%) methylnitropyrazolylbenzimidazole **8** as colorless crystals; mp 148-150°C (ethyl acetate). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.04 (2H, m, H-4'*a* + H-4'*b*); 3.29 (2H, s, 2-CH_2); 3.36 (3H, s, N–CH_3); 4.94 (1H, m, H-5'); 6.78 (1H, m, H-3'); 6.83-7.22 (5H, m, H arom); 7.77 (1H, d, *J* = 8.7, H-4); 8.19 (1H, d, *J* = 1.2, H-7); 8.22 (1H, dd, *J* = 2.1, *J* = 8.7, H-5). Found, %: C 62.93; H 5.42; N 21.53. $C_{17}H_{17}N_5O_2$. Calculated, %: C 63.16; H 5.26; N 21.67.

2-(4,5-Dihydroisoxazol-5-yl)methyl-1-methyl-6-nitrobenzimidazole (9). A solution of salt **1** (1.5 g, 4.2 mmol), hydroxylamine hydrochloride (3 g, 42 mmol), and sodium acetate (3.4 g, 42 mmol) in ethanol (30 ml) was heated at reflux for 10 h with monitoring by thin-layer chromatography. Ethanol was distilled off in vacuum and 50 ml water was added to the residue. The mixture was extracted with two 30-ml chloroform portions. The extract was dried over $MgSO_4$. Chloroform was distilled off and the residue was purified by chromatography on an alumina column to give 0.4 g (27%) benzimidazole **9** as white crystals; mp 148-150°C (ethyl acetate). ^{1}H NMR spectrum δ, ppm (*J*, Hz): 3.11 (1H, m, H-4'*a*), 3.20 (1H, m, H-4'*b*); 3.30 (2H, s, 2-CH_2); 3.88 (3H, s, N–CH_3); 5.11 (1H, m, H-5'); 7.08 (1H, m, H-3'); 7.71 (1H, d, *J* = 8.8, H-4); 8.17 (1H, dd, *J* = 2.1, *J* = 8.8, H-5); 8.28 (1H, d, *J* = 2.1, H-7). Found, %: C 55.47; H 4.65; N 21.41. $C_{12}H_{12}N_4O_3$. Calculated, %: C 55.38; H 4.62; N 21.53.

1-Allyl-2-(4,5-dihydroisoxazol-5-yl)methyl-6-nitrobenzimidazole (10). By a method similar to the procedure described above for the preparation of benzimidazole **9**, salt **2** (2 g, 2.8 mmol) and hydroxylamine hydrochloride (3.9 g, 28 mmol) in the presence of sodium acetate (4.6 g, 28 mmol) gave 0.6 g (20%) benzimidazole **10** as white crystals; mp 168-170°C (ethyl acetate). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.09 (1H, ddd, *J* = 1.9, *J* = 6.5, *J* = 17.8, H-4'*a*); 3.21 (2H, m, 2-CH_2); 3.29 (1H, ddd, *J* = 1.7, *J* = 10.4, *J* = 17.8, H-4'*b*); 4.74 (2H, m, CH_2–C=); 4.89 (1H, m, H-5'); 5.03 (1H, m, CH_2=); 5.24 (1H, m, CH_2=); 5.60 (1H, m, C<u>H</u>=CH_2); 7.12 (1H, m, H-3'); 7.75 (1H, d, *J* = 8.9, H-4); 8.16 (1H, d.d, *J* = 2.1, *J* = 8.9, H-5); 8.25 (1H, d, *J* = 2.1, H-7). Found, %: C 58.56; H 4.53; N 19.03. $C_{14}H_{14}N_4O_3$. Calculated, %: C 58.74; H 4.90; N 19.59.

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