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SYNTHESIS OF NAPHTHO[1,2-*e*]-PYRAZOLO[5,1-*b*][1,3]OXAZINES

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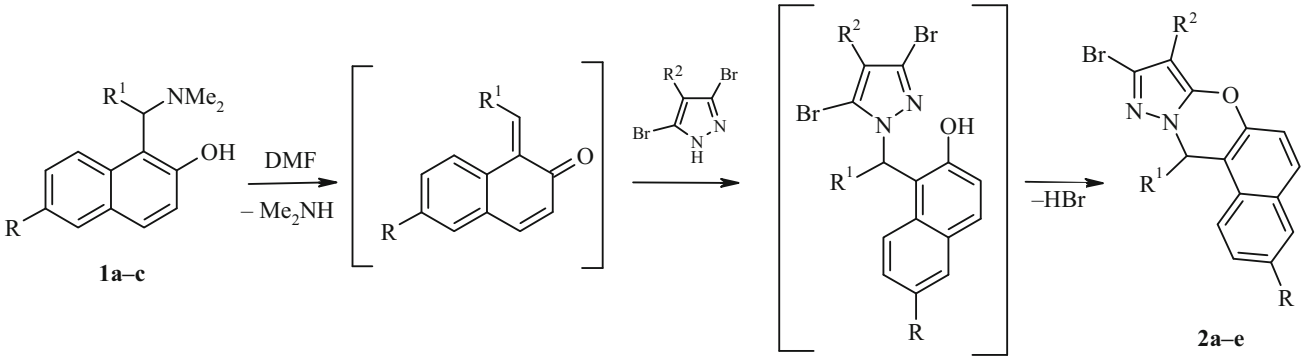
The previously unknown heterocyclic system naphtho[1,2-e]pyrazolo[5,1-b][1,3]oxazine was synthesized by the condensation of 1-dimethylaminomethyl-2-naphthols with bromopyrazoles. It is proposed that the highly reactive o-methylenequinone of the naphthalene series is formed as an intermediate.

Keywords: 2-bromopyrazoles, *o*-methylenequinones, naphtho[1,2-*e*]pyrazolo[5,1-*b*][1,3]oxazines, Mannich bases, cascade reactions.

1,3-Benzoxazines, annelated with nitrogen-containing heterocycles, are of interest as intercalating and antibacterial agents [1–3] and also as photochromic materials [4, 5]. However, the choice of suitable methods for preparing them is limited and includes thermolysis of imidoylketenes [6], condensation of thiophosgene with 2'-aminosalicylanilides [7], interaction of 2-azidomethylphenols with cyanogen bromide [8], and the reaction of tetrahydrocarbazoles with 2-chloromethylphenols [9].



1a, **2a,d** R = R^1 = H, **1b**, **2b** R = 1-Ad, R^1 = H, **1c**, **2c,e** R = H, R^1 = 4-$MeOC_6H_4$; **2 a–c** R^2 = Br, **d,e** R^2 = NO_2

We have shown that the new heterocyclic system of naphtho[1,2-*e*]pyrazolo[5,1-*b*][1,3]oxazines **2a–e** are formed on the interaction of Mannich bases of the naphthalene series **1a–c** with 3,4,5-tribromopyrazole or 3,5-dibromo-4-nitropyrazole in boiling DMF.

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In the case of 3,4,5-tribromopyrazole the condensation was carried out in the presence of K_2CO_3 to accelerate the conversion of the intermediate 1-(3,4,5-tribromo-1H-pyrazol-1-ylmethyl)-2-naphthols into naphtho-[1,2-*e*]pyrazolo[5,1-*b*][1,3]oxazines **2a–c**. The substituents in the starting materials do not appear to have a substantial effect on the yields of the final products.

The reaction is cascade and include several stages: deamination of the Mannich base – formation of the corresponding *o*-methylenequinone; addition of the bromopyrazole to the *o*-methylenequinone, and intramolecular nucleophilic substitution of the bromine atom in the pyrazole unit [10].

The absorptions corresponding to the vibrations of the OH bond are absent in IR spectra of compounds **2a–e** which confirms the cyclic structure of these compounds. In the ^{1}H NMR spectra of compounds **2a,b,d** the methylene protons resonate in the 5.53–5.62 ppm region. The signals of aliphatic methyne protons in compounds **2c,e** are strongly shifted to weak field and appear in the 6.86–7.30 ppm region.

Thus we have proposed an effective method for the synthesis of naphtho[1,2-*e*]pyrazolo[5,1-*b*]-[1,3]oxazines, the advantage of which is the use of available starting materials, the absence of oligomerization products of the corresponding *o*-methylenequinones, and the high yields of the final products.

EXPERIMENTAL

IR spectra of KBr tablets were recorded with a Shimadzu FTIR-8400S spectrometer. ^{1}H, ^{13}C, and DEPT NMR spectra were taken with a JEOL JNM-ECX400 spectrometer (400 and 100 MHz respectively) in $CDCl_3$ (compounds **2a–d**) and DMSO-d_6 solutions (compound **2e**) with TMS as internal standard. Elemental analysis was carried out on an Euro Vector EA-3000 automatic CHNS-analyzer.

The starting Mannich bases **1a–c** were obtained from 2-naphthols by known methods [11, 12].

8,9-Dibromo-12H-naphtho[1,2-*e*]pyrazolo[5,1-*b*][1,3]oxazine (2a). A mixture of 1-(dimethylaminomethyl)-2-naphthol (**1a**) (1 g, 5 mmol), 3,4,5-tribromopyrazole (1.51 g, 5 mmol), and K_2CO_3 (1.38 g, 10 mmol) in DMF (15 ml) was boiled with stirring for 5 h, then cooled and poured into cold water (50 ml). The precipitate was filtered off, washed with water, purified by column chromatography (toluene as eluent), and recrystallized from a methanol–DMF mixture, to give compound **2a** (1.29 g, yield 68%) as colorless crystals; mp 229–230°C. IR spectrum, ν, cm^{-1}: 3047 (CH Ar), 2920, 2870 (CH_2), 1628, 1605, 1570, 1516, 1462, 1389, 1377, 1354, 1246, 1211, 1014, 972, 810. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.56 (2H, s, CH_2); 7.40 (1H, d, *J* = 8.7, H Ar); 7.50–7.60 (1H, m, H Ar); 7.60–7.70 (2H, m, H Ar); 7.85–7.95 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 45.20 (CH_2); 107.28 (C); 117.08 (CH); 121.57 (CH); 125.92 (CH); 128.12 (CH); 128.46 (C); 128.97 (CH); 129.83 (C); 130.42 (CH); 130.61 (C); 145.10 (C). Found, %: C 44.20; H 2.09; N 7.41. $C_{14}H_8Br_2N_2O$. Calculated, %: C 44.25; H 2.12; N 7.37.

3-(1-Adamantyl)-8,9-dibromo-12H-naphtho[1,2-*e*]pyrazolo[5,1-*b*][1,3]-oxazine (2b) was made analogously to compound **2a** from 6-(adamantyl)-1-dimethylaminomethyl-2-naphthol (**1b**) (0.5 g, 1.5 mmol), 3,4,5-tribromopyrazole (0.45 g, 1.5 mmol), and K_2CO_3 (0.41 g, 3 mmol) in DMF (5 ml). Yield 0.42 g (55%), colorless crystals; mp 210–211°C (a methanol–DMF mixture). IR spectrum, ν, cm^{-1}: 3090, 3040 (CH Ar), 2901, 2847 (CH Ad), 1612, 1562, 1551, 1528, 1508, 1474, 1450, 1404, 1292, 1207, 987, 968, 879, 810. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.77–1.85 (6H, m, CH_2 Ad); 2.01 (6H, br. s, CH_2 Ad); 2.15 (3H, br. s, CH Ad); 5.53 (2H, s, CH_2); 7.35 (1H, d, *J* = 8.7, H Ar); 7.61 (1H, d, *J* = 8.7, H Ar); 7.74 (1H, dd, *J* = 8.7, *J* = 1.8, H Ar); 7.77 (1H, s, H-4); 7.83 (1H, d, *J* = 8.7, H Ar). ^{13}C NMR spectrum, δ, ppm: 28.95 (CH); 36.42 (C); 36.81 (CH_2); 43.15 (CH_2); 45.19 (CH_2); 106.95 (C); 116.78 (CH); 121.33 (CH); 124.09 (CH); 126.34 (CH); 127.95 (C); 128.37 (C); 130.40 (CH); 130.73 (C); 144.62 (C); 145.19 (C); 149.07 (C). Found, %: C 56.09; H 4.26; N 5.50. $C_{24}H_{22}Br_2N_2O$. Calculated, %: C 56.05; H 4.31; N 5.45.

8,9-Dibromo-12-(4methoxyphenyl)-12H-naphtho[1,2-*e*]pyrazolo[5,1-*b*][1,3]oxazine (2c) was obtained analogously to compound **2a** from 1-dimethylamino-1-(4-methoxyphenyl)methyl-2-naphthol (**1c**) (1.54 g, 5 mmol), 3,4,5-tribromopyrazole (1.53 g, 5 mmol), and K_2CO_3 (1.38 g, 10 mmol) in DMF (15 ml). Yield 1.71 g (70%), colorless crystals; mp 234–235°C (a methanol–DMF mixture). IR spectrum, ν, cm^{-1}: 3040 (CH Ar), 2924, 2843 (CH), 1624, 1605, 1566, 1512, 1462, 1439, 1373, 1354, 1254, 1242, 1180, 1022, 968, 833,

810. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.72 (3H, s, OCH_3); 6.77 (2H, d, *J* = 8.3, H-3',5'); 6.86 (1H, s, CH); 7.24 (2H, d, *J* = 8.3, H-2',6'); 7.40–7.45 (2H, m, H Ar); 7.49 (1H, d, *J* = 9.2, H Ar); 7.60–7.65 and 85–7.90 (2H, m, H-2,3); 7.91 (1H, d, *J* = 8.7, H Ar). ^{13}C NMR spectrum, δ, ppm: 55.32 (CH_3); 59.19 (CH); 111.88 (C); 114.40 (CH); 116.99 (CH); 123.19 (CH); 125.59 (CH); 127.86 (CH); 128.37 (C); 128.92 (CH); 129.36 (CH); 129.81 (C); 131.00 (CH); 131.20 (C); 144.49 (C); 146.05 (C); 159.91 (C). Found, %: C 51.94; H 2.87; N 5.81. $C_{21}H_{14}Br_2N_2O_2$. Calculated, %: C 51.88; H 2.90; N 5.76.

9-Bromo-8-nitro-12H-naphtho[1,2-*e*]pyrazolo[5,1-*b*][1,3]oxazine (2d) was prepared analogously to compound **2a** from 1-dimethylaminomethyl-2-naphthol (**1a**) (1 g, 5 mmol) and 3,5-dibromo-4-nitropyrazole (1.35 g, 5 mmol) in DMF (10 ml). After purification by column chromatography (eluent chloroform) and recrystallization from a methanol–DMF mixture, compound **2d** was obtained as colorless crystals (1.12 g, 65%); mp 271–273°C. IR spectrum, ν, cm^{-1}: 2923, 2851 (CH_2), 1597, 1570, 1539, 1512 (NO_2), 1497, 1420, 1346 (NO_2), 1246, 1211, 1157, 976, 806. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.62 (2H, s, CH_2); 7.53 (1H, d, *J* = 9.2, H Ar); 7.61 (1H, ddd, *J* = 8.0, *J* = 6.0, *J* = 2.0, H Ar); 7.65–7.75 (2H, m, H Ar); 7.95 (2H, d, *J* = 8.7, H Ar). ^{13}C NMR spectrum, δ, ppm: 45.01 (CH_2); 106.91 (C); 116.98 (CH); 121.54 (CH); 123.94 (C); 126.61 (CH); 128.50 (CH); 129.15 (CH); 129.46 (C); 131.08 (CH); 131.20 (C); 144.38 (C). Found, %: C 48.63; H 2.30 N 12.19. $C_{14}H_8BrN_3O_3$. Calculated, %: C 48.58; H 2.33; N 12.14.

9-Bromo-12-(4-methoxyphenyl)-8-nitro-12H-naphtho[1,2-*e*]-pyrazolo[5,1-*b*][1,3]oxazine (2e) was obtained analogously to compound **2d** from 1-dimethylamino-1-(4-methoxyphenyl)methyl-2-naphthol (**1c**) (1.54 g, 5 mmol) and 3,5-dibromo-4-nitropyrazole (1.36 g, 5 mmol) in DMF (10 ml). Yield 1.2 g (53%) of colorless crystals; mp 266–268°C (chloroform). IR spectrum, ν, cm^{-1}: 3047 (CH Ar), 2966, 2935, 2839 (CH aliph.),1601, 1570, 1508 (NO_2), 1462, 1439, 1404, 1342 (NO_2), 1254, 1242, 1184, 1026, 976, 837, 806, 756. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.64 (3H, s, OCH_3); 6.82 (2H, d, *J* = 8.2, H-3',5'); 7.30 (1H, s, CH); 7.34 (2H, d, *J* = 8.2, H-2',6'); 7.45–7.50 (2H, m, H Ar); 7.68 (1H, d, *J* = 8.7, H Ar); 7.80–7.90 and 8.00–8.05 (2H, m, H-2,3); 8.12 (1H, d, *J* = 8.7, H Ar). ^{13}C NMR spectrum, δ, ppm: 55.48 (CH_3); 58.47 (CH); 112.36 (C); 114.68 (CH); 116.35 (C); 116.96 (CH); 123.44 (C); 124.07 (CH); 126.36 (CH); 128.16 (CH); 129.15 (CH); 129.39 (C); 129.81 (C); 129.96 (CH); 131.0 (C); 131.76 (CH); 143.82 (C); 144.92 (C); 160.06 (C). Found, %: C 55.81; H 3.16; N 9.32. $C_{21}H_{14}Br,N_3O_4$. Calculated, %: C 55.77; H 3.12; N 9.29.

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