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NEW APPROACH TO THE SYNTHESIS OF BENZO[*e*]PYRAZOLO[5,1-*b*][1,3]OXAZINES

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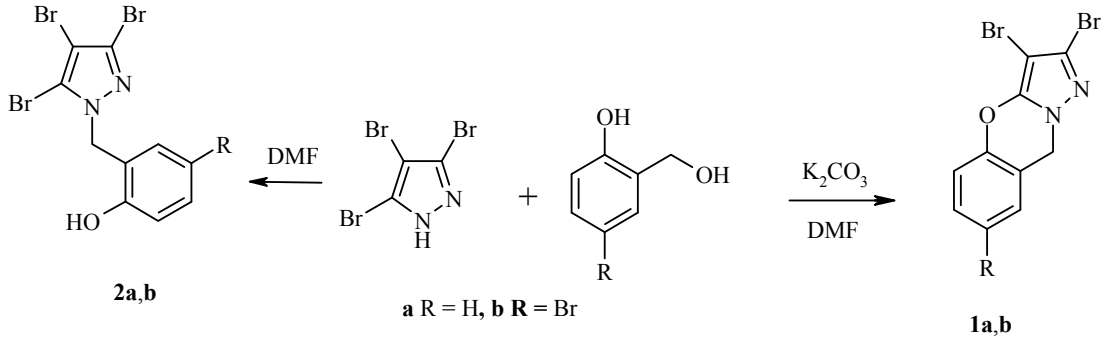
1,3-Benzoxazines fused to nitrogen heterocycles hold interest in light of their potential physiological activity. However, the number of available methods for the preparation of these compounds is very limited [1-3]. We propose a one-step method for the synthesis of pyrazolo[5,1-*b*][1,3]benzoxazines **1a**,**b** involving heating 3,4,5-tribromopyrazole with salicyl alcohols in DMF at reflux in the presence of K_2CO_3.



2a,**b**

a R = H, **b** R = Br

1a,**b**

Pyrazolylmethylphenols **2a**,**b** are formed selectively in the absence of potassium carbonate. The active alkylating agents in these reactions are probably *o*-methylenequinones formed upon the dehydration of the salicyl alcohols.

The IR spectra were taken on a Shimadzu FTIR-8400S spectrometer for KBr pellets. The ^{1}H NMR spectra were taken on a Bruker AM-400 spectrometer at 400 MHz in $CDCl_3$ (**1a**,**b**) and DMSO-d_6 (**2a**,**b**) with TMS as the internal standard. The mass spectra were taken on a Finnigan Trace DSQ mass spectrometer. The ionizing electron energy was 70 eV. The elemental analysis was carried out on a Eurovector EA-3000 automatic CHNS analyzer.

2,3-Dibromo-9H-pyrazolo[5,1-*b*][1,3]benzoxazine (1a). A mixture of 3,4,5-tribromopyrazole [4] (1 g, 3.3 mmol), salicyl alcohol (0.41 g, 3.3 mmol), and K_2CO_3 (1.38 g, 10 mmol) in DMF (10 ml) was heated at reflux for 6 h with stirring. The mixture was cooled and poured into 50 ml water. The precipitate formed was

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filtered off and recrystallized from ethanol–DMF to give 0.89 g (82%) compound **1a** as colorless crystals; mp 174-176°C. IR spectrum, ν, cm^{-1}: 2920, 1562, 1527, 1485, 1458, 1389, 1358, 1242, 1180, 1103, 1011, 899, 752. ^{1}H NMR spectrum, δ, ppm: 5.25 (2H, s, CH_2); 7.10-7.45 (4H, m, H arom). Mass spectrum for ^{79}Br isotope, *m/z* (I_{rel}, %): 328 $[M]^+$ (64), 327 $[M-H]^+$ (32), 248 $[M-HBr]^+$ (28), 169 $[M-Br-HBr]^+$ (9), 104 (35), 89 (20), 78 (50), 77 $[C_6H_5]^+$ (28), 63 (12), 52 (24), 51 (32). Found, %: C 36.48; H 1.79; N 8.55. $C_{10}H_6Br_2N_2O$. Calculated, %: C 36.40; H 1.83; N 8.49.

2,3,7-Tribromo-9H-pyrazolo[5,1-*b*][1,3]benzoxazine (1b) was obtained analogously to compound **1a** from 3,4,5-tribromopyrazole (1 g, 3.3 mmol), 4-bromo-2-hydroxymethylphenol (0.67 g, 3.3 mmol), and potassium carbonate (1.38 g, 10 mmol) in DMF (10 ml) as colorless crystals with mp 189-190°C (methanol–DMF). The yield of compound **1b** was 1.14 g (85%). IR spectrum, ν, cm^{-1}: 2928 (CH_2), 1562, 1528, 1477, 1416, 1385, 1358, 1265, 1246, 1177, 1115, 1014, 903, 872, 814, 644. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.24 (2H, s, CH_2); 7.16 (1H, d, *J* = 8.8, H-5); 7.40 (1H, s, H-8); 7.49 (1H, d, *J* = 8.8, H-6). Mass spectrum for ^{79}Br isotope, *m/z* (I_{rel}, %): 406 $[M]^+$ (56), 405 $[M-H]^+$ (16), 326 $[M-HBr]^+$ (16), 248 $[M-2Br]^+$ (21), 220 $[M-2Br-CO]^+$ (10), 182 $[C_2Br_2]^+$ (11), 156 $[C_6H_5Br]^+$ (21), 113 (26), 89 $[C_7H_5]^+$ (29), 77 $[C_6H_5]^+$ (79), 63 (41), 51 (45). Found, %: C 29.43; H 1.26; N 6.78. $C_{10}H_5Br_3N_2O$. Calculated, %: C 29.38; H 1.23; N 6.85.

2-(3,4,5-Tribromo-1H-1-pyrazolylmethyl)phenol (2a). A mixture of 3,4,5-tribromopyrazole (1 g, 3.3 mmol) and salicyl alcohol (0.41, g (3.3 mmol) in DMF (10 ml) was heated at reflux with stirring for 2 h. The mixture was cooled and poured into 50 ml water. The precipitate formed was filtered off and recrystallized from ethanol to give 0.85 g (63%) compound **2a** as colorless crystals with mp 145-146°C. IR spectrum, ν, cm^{-1}: 3400-3000 (OH), 1601, 1504, 1454, 1423, 1366, 1285, 1254, 1177, 1099, 1011, 849, 760. ^{1}H NMR spectrum, δ, ppm: 5.25 (2H, s, CH_2); 7.13-7.50 (4H, m, H arom); 9.41 (1H, s, OH). Mass spectrum for ^{79}Br isotope, *m/z* (I_{rel}, %): 408 $[M]^+$ (12), 391 $[M-OH]^+$ (1), 329 $[M-Br]^+$ (13), 302 $[C_3HBr_3N_2]^+$ (2), 250 $[M-2Br]^+$ (6), 249 $[M-2Br-H]^+$ (7), 107 $[C_7H_7O]^+$ (70), 106 $[C_7H_6O]^+$ (100), 79 (26), 78 (64), 77 $[C_6H_5]^+$ (67). Found, %: C 29.30; H 1.68; N 6.85. $C_{10}H_7Br_3N_2O$. Calculated, %: C 29.23; H 1.72; N 6.82.

4-Bromo-2-(3,4,5-tribromo-1H-1-pyrazolylmethyl)phenol (2b) was obtained analogously to compound **2a** from 3,4,5-tribromopyrazole (1 g, 3.3 mmol) and 4-bromo-2-hydroxymethylphenol (0.67 g, 3.3 mmol) in DMF (10 ml) as colorless crystals with mp 197-199°C (ethanol). The yield of compound **2b** was 1.19 g (74%). IR spectrum, ν, cm^{-1}: 3400-3000, 1593, 1493, 1416, 1362, 1342, 1308, 1281, 1254, 1173, 1119, 1053, 1011, 883, 818, 779, 629. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.43 (1H, s, H-3); 5.28 (2H, s, CH_2); 7.17 (1H, d, *J* = 8.8, H-6); 7.50 (1H, d, *J* = 8.8, H-5); 9.45 (1H, s, OH). Mass spectrum for ^{79}Br isotope, *m/z* (I_{rel}, %): 486 $[M]^+$ (8), 469 $[M-OH]^+$ (1), 407 $[M-Br]^+$ (9), 328 $[M-2Br]^+$ (4), 301 $[C_3Br_3N_2]^+$ (3), 185 $[C_7H_6BrO]^+$ (84), 184 $[C_7H_5BrO]^+$ (100), 156 $[C_6H_5Br]^+$ (35), 77 $[C_6H_5]^+$. Found, %: C 24.48; H 1.27; N 5.67. $C_{10}H_6Br_4N_2O$. Calculated, %: C 24.52; H 1.23; N 5.72.

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