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SHORT COMMUNICATIONS

Dedicated to Full Member of the Russian Academy of Sciences N.S. Zefirov on His 70th Anniversary

Reactions of 5-Methylsulfinyl-1-(4-nitrophenyl)tetrazole with N-Nucleophiles

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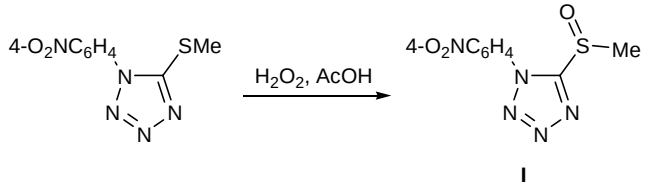
Wide application of tetrazoles in the synthesis of new medical agents for various purposes [1–7] stimulated extensive search for simple and effective procedures for functionalization of these compounds. While continuing our studies on 1-aryltetrazole-5-thiones as readily accessible synthons for the preparation of functionally substituted tetrazoles, we examined the reactivity of 5-methylsulfinyl-1-(4-nitrophenyl)tetrazole with respect to various nitrogen-centered nucleophiles. Initial 5-methylsulfinyl-1-(4-nitrophenyl)tetrazole (**I**) was synthesized by oxidation of 5-methylsulfanyl-1-(4-nitrophenyl)tetrazole with 35% hydrogen peroxide in acetic acid at 70°C (Scheme 1). Under these conditions, compound **I** was formed in almost quantitative yield. The rate of oxidation considerably increases under microwave irradiation, while the yield of tetrazole **I** remains almost unchanged.

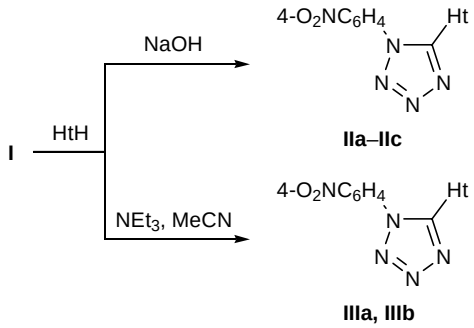
Scheme 1.



I

We found that 5-methylsulfinyl-1-(4-nitrophenyl)-tetrazole (**I**) reacts with pyrrolidine, piperidine, morpholine, imidazole, and benzimidazole to give the corresponding 5-substituted tetrazoles in high yield (Scheme 2). The reactions with pyrrolidine, piperidine, and morpholine were performed at room temperature in the presence of sodium hydroxide using the corresponding nucleophile as reaction medium. The reactions of **I** with imidazole and benzimidazole were carried out in acetonitrile.

Scheme 2.



IIa–IIc

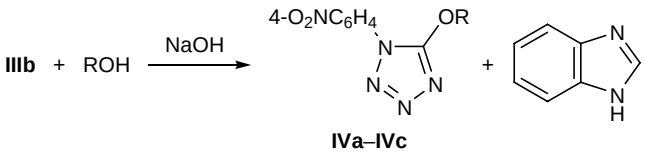
IIIa, IIIb

II, Ht = 1-pyrrolidinyl (**a**), piperidino (**b**), morpholino (**c**);
III, Ht = 1-imidazolyl (**a**), 1-benzimidazolyl (**b**).

We examined chemical properties of some products thus obtained and found that the benzimidazole fragment in compound **IIIb** is replaced by the action of oxygen-centered nucleophiles under mild conditions (Scheme 3).

To conclude, it should be noted that 5-methylsulfinyl-1-(4-nitrophenyl)tetrazole is more reactive

Scheme 3.



IVa–IVc

R = H (**a**), Me (**b**), Et (**c**).

toward N-nucleophiles than 5-methylsulfonyl-1-(4-nitrophenyl)tetrazole [8].

5-Methylsulfinyl-1-(4-nitrophenyl)tetrazole (I). *a.* To a solution of 2.3 g (10 mmol) of 5-methylsulfanyl-1-(4-nitrophenyl)tetrazole [9] in 25 ml of glacial acetic acid we added at 20°C 4 ml of 35% hydrogen peroxide. The mixture was stirred for 5 h at 70°C, cooled to 18°C, and diluted with 100 ml of ice water, and the precipitate was filtered off, washed with water (3×20 ml), and dried in air. Yield 2.34 g (95%), mp 155–156°C (from ethanol–acetonitrile, 2:1). IR spectrum, ν, cm^{-1}: 954, 1010, 1060, 1103, 1118, 1164, 1231, 1270, 1299, 1313, 1326, 1339, 1380, 1416, 1499, 1527, 1539, 1596, 1618, 2300, 2870, 2931, 3009, 3046, 3081, 3122. ^{1}H NMR spectrum, δ, ppm: 3.70 s (3H, CH_3), 8.04–8.68 d (2H, H_{arom}), 8.47–8.52 d (2H, H_{arom}). Found, %: C 37.74; H 2.70; N 27.70. $C_8H_7N_5O_3S$. Calculated, %: C 37.94; H 2.77; N 27.67.

b. A heat-resistant reactor was charged with a solution of 2.3 g (10 mmol) of 5-methylsulfanyl-1-(4-nitrophenyl)tetrazole in 25 ml of glacial acetic acid, 4 ml of 35% hydrogen peroxide was added at 20°C, and the mixture was stirred for 1 h at 70°C under microwave irradiation (65 W) and was treated as described above in *a*. Yield 2.25 g (91%), mp 155–156°C.

1-(4-Nitrophenyl)-5-(1-pyrrolidinyl)tetrazole (IIa). To a solution of 0.5 g (2 mmol) of tetrazole **I** in 10 ml of pyrrolidine we added 0.08 g (2 mmol) of sodium hydroxide. The mixture was stirred for 15 min at room temperature, diluted with 50 ml of ice water, and acidified with concentrated hydrochloric acid to pH 1. The precipitate was filtered off, washed with water (2×5 ml), and dried in air. Yield 0.42 g (82%), mp 145–146°C (from ethanol). IR spectrum, ν, cm^{-1}: 956, 1010, 1043, 1078, 1100, 1108, 1137, 1236, 1249, 1287, 1315, 1348, 1429, 1460, 1498, 1528, 1593, 1603, 2876, 2930, 2956, 2982, 3049, 3068, 3093, 3117. ^{1}H NMR spectrum, δ, ppm: 1.88–1.98 m (4H, CH_2), 3.28–3.53 m (4H, CH_2), 7.68–7.73 d (2H, H_{arom}), 8.38–8.42 d (2H, H_{arom}). Found, %: C 50.75; H 4.51; N 32.33. $C_{11}H_{12}N_6O_2$. Calculated, %: C 50.77; H 4.61; N 32.31.

Tetrazoles **IIb** and **IIc** were synthesized in a similar way (in the synthesis of compound **IIc**, the mixture was stirred for 2 h).

1-(4-Nitrophenyl)-5-piperidinotetrazole (IIb). Yield 78%, mp 89–90°C (from methanol) [10]. IR spectrum, ν, cm^{-1}: 909, 956, 982, 1007, 1019, 1035, 1066, 1108, 1120, 1149, 1261, 1286, 1331, 1346, 1382, 1412, 1422, 1452, 1499, 1520, 1541, 1596, 1612, 1755, 2848, 2861, 2926, 2947, 2980, 3089, 3119. ^{1}H NMR spectrum, δ, ppm: 1.66 s (6H, CH_2), 3.22 s (4H, CH_2), 7.90–7.94 d (2H, H_{arom}), 8.40–8.45 d (2H, H_{arom}).

5-Morpholino-1-(4-nitrophenyl)tetrazole (IIc). Yield 70%, mp 198–200°C (from ethanol–DMF, 3:1) [10]. IR spectrum, ν, cm^{-1}: 936, 988, 1010, 1049, 1071, 1079, 1106, 1116, 1174, 1253, 1274, 1294, 1314, 1336, 1352, 1366, 1378, 1427, 1453, 1500, 1530, 1566, 1600, 1615, 2857, 2899, 2931, 2973, 3010, 3055, 3073, 3087, 3119. ^{1}H NMR spectrum, δ, ppm: 3.25 t (4H, OCH_2), 3.75 t (4H, NCH_2), 7.92 d (2H, H_{arom}), 8.42 d (2H, H_{arom}).

5-(1-Imidazolyl)-1-(4-nitrophenyl)tetrazole (IIIa). To a solution of 0.5 g (2 mmol) of tetrazole **I** in 10 ml of acetonitrile we added 0.14 g (2 mmol) of imidazole and 0.22 g (2.2 mmol) of triethylamine. The mixture was stirred for 7 h at 50°C, diluted with 30 ml of ice water, and acidified with concentrated hydrochloric acid to pH 1. The precipitate was filtered off, washed with water (2×5 ml), and dried in air. Yield 0.35 g (67%), mp 158–159°C (from acetonitrile). IR spectrum, ν, cm^{-1}: 951, 991, 1016, 1033, 1053, 1087, 1106, 1170, 1246, 1256, 1288, 1307, 1348, 1377, 1452, 1500, 1525, 1540, 1574, 1596, 1614, 3092, 3119, 3156. ^{1}H NMR spectrum, δ, ppm: 7.16 s (1H, 4-H), 7.38 s (1H, 5-H), 8.02 s (1H, 2-H), 7.81–7.86 d (2H, H_{arom}), 8.44–8.48 d (2H, H_{arom}). Found, %: C 46.69; H 2.72; N 38.13. $C_{10}H_7N_7O_2$. Calculated, %: C 46.77; H 2.71; N 38.22.

Tetrazole **IIIb** was synthesized in a similar way (reaction time 1 h at 20°C).

5-(1-Benzimidazolyl)-1-(4-nitrophenyl)tetrazole (IIIb). Yield 83%, mp 183–184°C (from acetonitrile). IR spectrum, ν, cm^{-1}: 941, 969, 989, 1009, 1090, 1110, 1118, 1126, 1152, 1182, 1188, 1195, 1249, 1276, 1282, 1293, 1315, 1350, 1379, 1423, 1437, 1451, 1482, 1499, 1525, 1568, 1596, 1614, 3071, 3083. ^{1}H NMR spectrum, δ, ppm: 7.35–7.82 m (4H, H_{arom}), 8.20 s (1H, NH), 7.87–7.91 d (2H, H_{arom}), 8.40–8.45 d (2H, H_{arom}). Found, %: C 54.79; H 3.10; N 32.00. $C_{14}H_9N_7O_2$. Calculated, %: C 54.72; H 2.93; N 31.92.

1-(4-Nitrophenyl)tetrazol-5-one (IVa). To a suspension of 0.2 g (0.65 mmol) of tetrazole **IIIa** in 10 ml of water we added 0.03 g (0.65 mmol) of sodium hydroxide. The mixture was stirred for 2 h at room temperature, diluted with 30 ml of ice water, and acidified with concentrated hydrochloric acid to pH 1.

The precipitate was filtered off, washed with water (2 × 5 ml), and dried in air. Yield 0.13 g (98%), mp 216–217°C (from ethanol–water, 3:1) [9]. IR spectrum, ν, cm^{-1}: 959, 1030, 1054, 1112, 1149, 1305, 1336, 1373, 1502, 1513, 1595, 1632, 1738, 3085, 3120, 3216. ^1H NMR spectrum, δ, ppm: 8.02 d (2H, H_{arom}), 8.50 d (2H, H_{arom}), 14.85 s (1H, NH).

5-Methoxy-1-(4-nitrophenyl)tetrazole (IVb). To a solution of 0.35 g (1.15 mmol) of tetrazole **IIIb** in 10 ml of methanol we added 0.045 g (1.15 mmol) of sodium hydroxide. The mixture was stirred for 15–20 min at 20°C and diluted with 50 ml of ice water, and the precipitate was filtered off and dried in air. Yield 0.16 g (65%), mp 167–168°C (from ethanol–acetonitrile, 3:1) [9]. IR spectrum, ν, cm^{-1}: 962, 1000, 1039, 1092, 1109, 1132, 1190, 1291, 1313, 1338, 1353, 1411, 1442, 1503, 1514, 1525, 1577, 1584, 1595, 1614, 1725, 2850, 2919, 2950, 3104, 3124. ^1H NMR spectrum, δ, ppm: 4.40 s (3H, CH_3), 8.06 d (2H, H_{arom}), 8.56 d (2H, H_{arom}).

Tetrazole **IVc** was synthesized in a similar way.

5-Ethoxy-1-(4-nitrophenyl)tetrazole (IVc). Yield 58%, mp 155–156°C (from ethanol–acetonitrile, 3:1) [9]. IR spectrum, ν, cm^{-1}: 979, 1006, 1028, 1055, 1082, 1114, 1176, 1215, 1244, 1279, 1313, 1344, 1385, 1398, 1433, 1494, 1533, 1595, 1610, 3080. ^1H NMR spectrum, δ, ppm: 1.52 t (3H, CH_3), 4.66–4.75 m (2H, CH_2), 8.05 d (2H, H_{arom}), 8.40 d (2H, H_{arom}).

The IR spectra were recorded in KBr on a Shimadzu FTIR-8400S spectrometer. The ^1H NMR spectra were obtained on a Bruker AC-200 instrument from solutions in DMSO-d_6. Microwave-assisted reactions were performed in a Milestone P/N 44072 reactor (230 V, 50 Hz). The purity of the products was checked by TLC on Silufol plates using ethyl acetate–carbon tetrachloride (2:3) as eluent.

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