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SHORT COMMUNICATIONS

Preparation of 1,5-Functionally Disubstituted Tetrazoles

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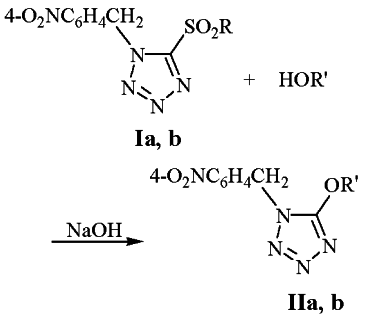
The extensive application of tetrazoles to the synthesis of pharmaceuticals of high efficiency [1, 2] significantly stimulated the search for new and easy methods for preparation of functionally substituted tetrazoles.

We established that replacement of methyl- and phenylsulfonyl groups in 5-mesyl-1-(4-nitrobenzyl)- and 1-(4-nitrobenzyl)-5-phenylsulfonyltetrazoles effected by O-nucleophiles may be considered among methods of this sort.

For instance, reactions of the mentioned substrates with methanol, ethanol, and also with phenol in the presence of sodium hydroxide afforded the corresponding 5-alkoxy(phenoxy) tetrazoles in high yields. The reaction occurs under mild conditions in solution in the corresponding alcohol or in acetonitrile at the use of phenol as nucleophile.

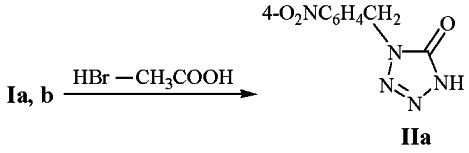


I, R = Me (**a**), Ph (**b**); **II**, R' = Me (**a**), Et (**b**), Ph (**c**).

Interestingly, the preparative nucleophilic substitution of methylsulfonyl and phenylsulfonyl groups in tetrazoles **Ia, b** proceeded with almost the same rate.

This fact suggests that the reaction occurs along the S_NAr mechanism. The same conclusion made Demko and Sharpless in the study of substitution of the phenylsulfonyl group in 1-benzyl-5-phenylsulfonyltetrazole by thiophenol [3].

It should be added to the above that the treatment of tetrazoles **Ia, b** with a mixture of hydrobromic and acetic acids cleanly provided hydrolysis product 1-(4-nitrobenzyl)-4,5-dihydro-1*H*-tetrazol-5-one.



1- and 2-(Nitrobenzyl)-5-phenylmercaptotetrazoles. To a solution of 2.3 mmol of 5-phenylmercaptotetrazole in 10 ml of 10% water solution of NaOH was added 0.1 mmol of tetrabutylammonium bromide and 20 mmol of 4-nitrobenzyl bromide in 45 ml of chloroform. The reaction mixture was stirred for 10 h at 18–20°C, the organic layer was separated, washed with 10% water solution of NaOH (20 ml), then with water (2 × 20 ml), and dried with magnesium sulfate. The solvent was removed in a vacuum, the solid residue was subjected to column chromatography on silica gel. eluent toluene–chloroform, 1 : 1.

1-(4-Nitrobenzyl)-5-phenylmercaptotetrazole. Yield 3.23 g (57%), mp 116–118°C (from toluene). IR spectrum, cm^{-1}: 930, 965, 1020, 1100, 1110, 1190, 1210, 1250, 1290, 1360, 1390, 1450, 1485, 1530, 1615, 2865, 2940, 3090, 3130. ^1H NMR spectrum, δ, ppm: 5.80 s (2H, CH_2), 7.27–7.42 m (7H arom), 8.15 d (2H arom). Found, %: C 53.70; H 3.55; N 22.38. $C_{14}H_{11}N_5O_2S$. Calculated, %: C 53.67; H 3.51; N 22.36.

1-(4-Nitrobenzyl)-5-phenylmercaptotetrazole. Yield 2.34 g (34%), mp 91–92°C (from ethanol). IR spectrum, cm^{-1}: 885, 1020, 1055, 1140, 1180, 1275, 1305, 1315, 1350, 1395, 1450, 1485, 1535, 1620, 2865, 2930, 3095, 3120. ^1H NMR spectrum, δ, ppm: 6.05 s (2H), 7.32– 7.56 m (5H arom), 7.60 d (2H, C_6H_4), 8.20 d (2H, C_6H_4). Found, %: C 53.80;

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H 3.41; N 22.48. $C_{14}H_{11}N_5O_2S$. Calculated, %: C 53.67; H 3.51; N 22.36.

1-(4-Nitrobenzyl)-5-phenylsulfonyltetrazole (Ib). A mixture of 4 mmol of 1-(4-nitrobenzyl)-5-phenylmercaptotetrazole, 0.4 mmol of tetrabutylammonium bromide, 15 ml of 10% acetic acid, and 15 ml of chloroform was stirred to homogenization, and then 8 mmol of potassium permanganate was added. The reaction mixture was stirred for 10 h at 20°C, then 5 ml of ethanol was added, the manganese(IV) oxide was filtered off, washed with boiling chloroform (3×15 ml), and the organic layer was separated, washed with water (15 ml), and dried over magnesium sulfate. The solvent was removed in a vacuum. Yield 1.34 g (97%), mp 100–102°C (from ethanol). IR spectrum, cm^{-1}: 860, 940, 1090, 1120, 1160, 1200, 1360, 1455, 1540, 1620, 2870, 2935, 3100. ^1H NMR spectrum, δ, ppm: 6.12 s (2H, CH_2), 7.50–8.25 m (9H arom). Found, %: C 48.75; H 3.07; N 20.20. $C_{14}H_{11}N_5O_4S$. Calculated, %: C 48.69; H 3.19; N 20.29.

5-Methoxy-1-(4-nitrobenzyl)tetrazole (IIa). A solution of 1.8 mmol of compound **Ia** and 2.2 mmol of NaOH in 15 ml of methanol were stirred for 2 h at 18–20°C, then 20 ml of water was added, and the mixture was cooled to 5–10°C. The separated precipitate was filtered off, washed with water (15 ml), and dried in air. Yield 0.33 g (81%), mp 108–109°C (from 50% ethanol). IR spectrum, cm^{-1}: 980, 1015, 1110, 1130, 1190, 1260, 1310, 1350, 1430, 1485, 1530, 1595, 2870, 2980, 3020, 3095, 3140. ^1H NMR spectrum, δ, ppm: 4.20 s (3H, CH_3), 5.50 s (2H, CH_2), 7.50–7.57 d (2H, C_6H_4). Found, %: C 45.91; H 3.77; N 29.88. $C_9H_9N_5O_3$. Calculated, %: C 45.96; H 3.83; N 29.79.

Tetrasole **IIb** was prepared in a similar way.

1-(4-Nitrobenzyl)-5-ethoxytetrazole (IIb). Yield 77%, mp 109°C (from 50% ethanol). IR spectrum, cm^{-1}: 905, 935, 970, 990, 1030, 1105, 1120, 1165, 1185, 1210, 1255, 1305, 1350, 1400, 1435, 1450, 1480, 1540, 1600, 2870, 2935, 3000, 3080, 3130. ^1H NMR spectrum, δ, ppm: 1.30 s (3H, CH_3), 4.50 m (2H, CH_2), 5.50 s (2H, CH_2Ar), 7.50 d (2H, C_6H_4), 8.25 d (2H, C_6H_4). Found, %: C 48.10; H 4.38; N 28.07. $C_{10}H_{11}N_5O_3$. Calculated, %: C 48.19; H 4.42; N 28.11.

1-(4-Nitrobenzyl)-5-phenoxytetrazole (IIc). A solution of 1.4 mmol of 5-mesyl-1-(4-nitrobenzyl)-tetrazole (**Ia**), 1.9 mmol of phenol, 1.9 mmol of NaOH in 15 ml of acetonitrile was stirred for 1.5 h at 20°C, water was added, the separated precipitate was filtered off and dried in air. Yield 0.32 g (78%), mp 119°C (from ethanol). IR spectrum, cm^{-1}: 930, 970, 985, 1000, 1010, 1030, 1075, 1110, 1130, 1165, 1190, 1210, 1255, 1295, 1320, 1355, 1435, 1490, 1530, 1560, 1600, 1620, 2870, 2935, 3070, 3095, 3140. ^1H NMR spectrum, δ, ppm: 5.70 s (2H, CH_2), 7.30–7.60 m (5H, C_6H_5), 7.70 d (2H, C_6H_4), 8.30 d (2H, C_6H_4). Found, %: C 56.69; H 3.85; N 23.64. $C_{14}H_{11}N_5O_3$. Calculated, %: C 56.57; H 3.70; N 23.57.

1-(4-Nitrobenzyl)-4,5-dihydro-1*H*-tetrazol-5-one (III). A solution of 1.8 mmol of compound **Ia** in a mixture of 10 ml of HBr and 10 ml of AcOH was stirred for 5 h at 120°C, on cooling to 10°C 50 ml of water was added, the separated precipitate was filtered off and dried in air. Yield 0.30 g (74%), mp174°C (from a mixture petroleum ether–ethyl acetate, 1:1). IR spectrum, cm^{-1}: 870, 940, 1010, 1080, 1115, 1150, 1195, 1295, 1310, 1350, 1370, 1430, 1505, 1535, 1620, 1705, 1720, 2870, 2940, 3090, 3200. ^1H NMR spectrum, δ, ppm: 5.30 s (2H, CH_2), 7.50 d (2H, C_6H_4), 8.25 d (2H, C_6H_4), 13.70 s (1H, NH). Found, %: C 43.52; H 3.17; N 31.56. $C_8H_7N_5O_3$. Calculated, %: C 43.44; H 3.17; N 31.67.

Characteristics of tetrazoles **IIa–c** and **III** prepared from **Ia, b** were identical.

5-Mesyl-1-(4-nitrobenzyl)tetrazole (Ia) was prepared by procedure from [4].

IR spectra were recorded on spectrometer UR-20 from samples pelletized with KBr. ^1H NMR spectra were registered on spectrometer Bruker AC-200 from solutions in DMSO-d_6. For column chromatography was used a sorbent Silicagel L 100/200.

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