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SHORT COMMUNICATIONS

2-Substituted 5-Methylthio- and 5-Methylsulfonyltetrazoles*

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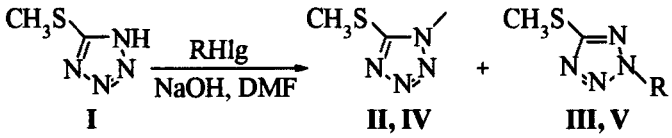
5-Methylthio- and 5-methylsulfonyl-1-aryltetrazoles show high bactericidal activity to Mycobacterium tuberculosis and they may be regarded as promising antitubercular preparations [1–3]. However there is no information on biological activity of the analogous 2-arylisomers. This is due first of all to inaccessibility of this kind compounds since the methods of their preparation are not virtually studied. Obviously the only plausible procedure for the synthesis of these compounds is alkylation (arylation) of the 5-methylthio- and 5-methylsulfonyltetrazoles.

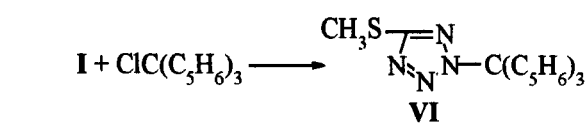
We actually found that in reaction of 5-methylthiotetrazole with 4-nitrobenzyl bromide and 4-nitrofluorobenzene in DMF in the presence of sodium hydroxide arose the corresponding isomeric 5-methylthiotetrazole. According to ^{1}H NMR spectra the ratio of isomers **II**:**III** and **IV**:**V** is 35:65 and 25:75 respectively.



I **II, IV** **III, V**

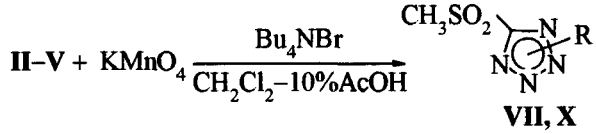
II, III, Hlg = Br, R = 4-$NO_2C_6H_4CH_2$; **IV, V**, Hlg = F, R = 4-$NO_2C_6H_4$.

The alkylation of 5-methylthiotetrazole with 4-nitrobenzyl bromide under phase transfer conditions also afforded a mixture of isomeric tetrazoles **II, III**. The changed conditions did not notably affect the isomers ratio that equaled to 45:55. To our regret under this conditions 5-methylthiotetrazole did not react with 4-nitrofluorobenzene. It is necessary to note that a significant change in regioselectivity occurred only at the use of triphenylmethyl chloride as alkylating agent. In this case forms a single isomer, 5-methylthio-2-triphenylmethyltetrazole.



VI

Apparently this course of reaction is due to the change in alkylation mechanism, where the reactive species is triphenylmethyl cation. Similar result was obtained formerly in tritylation of 5-methyltetrazole [4]. The substituted 5-methylsulfonyltetrazoles can be prepared by two procedures: by alkylation of 5-methylsulfonyltetrazole or by oxidation of the appropriate 5-methylthiotetrazoles. Taking into account the low reactivity of the 5-methyltetrazole toward alkylating agents we preferred the second way. Save 5-methylthio-2-triphenylmethyltetrazole all the other compounds obtained cleanly undergo oxidation by potassium permanganate in the two-phase system dichloromethane–aqueous acetic acid in the presence of tetrabutylammonium bromide.



VII, X

R = 1-(4-$NO_2C_6H_4CH_2$) (**VII**), 2-(4-$NO_2C_6H_4CH_2$) (**VIII**), 1-(4-$NO_2C_6H_4$) (**IX**), 2-(4-$NO_2C_6H_4$) (**X**).

Reaction of 5-methylthiotetrazole with 4-nitrobenzyl bromide. (a) A mixture of 0.011 mol of 5-methylthiotetrazole, 0.01 mol of 4-nitrobenzyl bromide, 0.011 mol of sodium hydroxide, and 40 ml of DMF was stirred at 90°C for 2 h, then the reaction mixture was evaporated on a water bath till 1/3 of its volume and poured into 50 ml of water. The separated precipitate was filtered off, washed with water (3×20 ml), and dried at 50°C. The precipitate was subjected to chromatography on a column packed with silica gel, eluent chloroform. We obtained

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0.65 g (26%) of tetrazole **II** and 1.20 g (48%) of tetrazole **III**.

5-Methylthio-1-(4-nitrobenzyl)tetrazole (II), mp 103–104°C (from ethanol). IR spectrum (ν, cm^{-1}): 930, 970, 1020, 1100, 1115, 1190, 1200, 1220, 1265, 1280, 1310, 1320, 1350, 1400, 1430, 1500, 1530, 1610, 2860, 2950, 2990, 3090, 3120. ^1H NMR spectrum (δ, ppm): 2.75 s (3H, CH_3), 5.70 s (2H, CH2), 7.50 d (2H, C_6H_4), 8.20 d (2H, C_6H_4). Found, %: C 43.10; H 3.42; N 27.78. $C_9H_9N_5O_2S$. Calculated, %: C 43.03; H 3.58; N 27.89.

5-Methylthio-2-(4-nitrobenzyl)tetrazole (III), mp 70–71°C (from heptane–chloroform mixture, 3:1). IR spectrum (ν, cm^{-1}): 980, 1020, 1060, 1115, 1140, 1190, 1275, 1300, 1320, 1350, 1400, 1420, 1430, 1445, 1530, 1610, 2870, 2945, 3025, 3090, 3120. ^1H NMR spectrum (δ, ppm): 2.63 s (3H, CH_3), 6.00 s (2H, CH_2), 7.63 d (2H, C_6H_4), 8.20 d (2H, C_6H_4). Found, %: C 43.28; H 3.50; N 27.80. $C_9H_9N_5O_2S$. Calculated, %: C 43.03; H 3.58; N 27.89.

(b) To a mixture of 0.01 mol of 5-methylthiotetrazole, 0.0004 mol of tetrabutylammonium bromide, 25 ml of aqueous 10 wt% sodium hydroxide, and 10 ml of chloroform was added at 20°C a solution of 0.075 mol of 4-nitrobenzyl bromide in 15 ml of chloroform. The reaction mixture was stirred for 3 h at 20°C, the phases were separated, the organic layer was washed with water (3 × 15 ml0 and evaporated till dryness. The residue was subjected to chromatography on a column with silica gel, eluent chloroform. We obtained 0.66 g (35%) of tetrazole **II**, mp 103–104°C (from ethanol) and 0.85 g (45%) of tetrazole **III**, mp 70–71°C (from heptane–chloroform mixture, 3:1). Tetrazoles **IV** and **V** were similarly obtained along procedure a, tetrazole **VI** was obtained by procedure b. The characteristics of compounds **IV–VI** are given below.

5-Methylthio-1-(4-nitrophenyl)tetrazole (IV). Yield 12%, mp 147–148°C (from DMF–ethanol mixture, 3:1) [5]. ^1H NMR spectrum (δ, ppm): 2.82 s (3H, CH_3), 8.02 d (2H, C_6H_4), 8.50 d (2H, C_6H_4).

5-Methylthio-2-(4-nitrophenyl)tetrazole (V). Yield 38%, mp 117–118°C (from cyclohexane). IR spectrum (ν, cm^{-1}): 990, 1015, 1040, 1090, 1110, 1170, 1180, 1195, 1280, 1310, 1320, 1350, 1400, 1410, 1430, 1500, 1530, 1600, 2865, 2930, 3100, 3130. ^1H NMR spectrum (δ, ppm): 2.78 s (3H, CH_3), 8.34 d (2H, C_6H_4), 8.48 d (2H, C_6H_4). Found, %: C 40.67; H 2.83; N 29.50. $C_8H_9N_5O_2S$. Calculated, %: C 40.50; H 2.95; N 29.53.

5-Methylthio-2-(triphenylmethyl)tetrazole (VI). Yield 86%, mp 134–135°C (from butyl acetate IR spectrum (ν, cm^{-1}): 910, 940, 1005, 1030, 1040, 1060, 1090, 1150, 1170, 1190, 1220, 1285, 1300, 1390, 1450, 1500, 1590, 1605, 2860, 2940, 3040, 3070. ^1H NMR spectrum (δ, ppm): 2.64 s (3H, CH_3), 6.95–7.13 m (6H, $3C_6H_5$), 7.28–7.46 m (9H, $3C_6H_5$). Found, %: C 70.56; H 5.00; N 15.73. $C_{21}H_{18}N_4S$. Calculated, %: C 70.39; H 5.03; N 15.64.

5-Methylsulfonyl-1-(4-nitrobenzyl)tetrazole (VII). To a mixture of 0.04 mol of 5-methylthio-1-(4-nitrobenzyl)tetrazole, 0.0008 mol of tetrabutylammonium bromide, 15 ml of 10% acetic acid, and 15 ml of chloroform at 20°C was added 0.012 mol of potassium permanganate. The reaction mixture was stirred at 20°C for 14 h, then the phases were separated, the organic layer was washed with water (3 × 10 ml) and evaporated till dryness. We obtained 0.8 g (72%) of 5-methylsulfonyl-1-(4-nitrobenzyl)-tetrazole. mp 134–135°C (from toluene). IR spectrum (ν, cm^{-1}): 960, 990, 1025, 1060, 1110, 1120, 1150, 1200, 1210,1290, 1315, 1325,1350, 1360, 1405, 1430, 1475, 1500, 1540, 1620, 2870, 2940, 3035, 3100, 3130. ^1H NMR spectrum(δ, ppm): 3.65 s (3H, CH_3), 6.05 s (2H, CH_2), 7.62 d (2H, C_6H_4), 8.13 d (2H, C_6H_4). Found, %: C 38.38; H 3.43; N 24.85. $C_9H_9N_5O_4S$. Calculated, %: C 38.16; H 3.18; N 24.73.

The other 5-methylsulfonyltetrazoles are prepared similarly; their characteristics are given below.

5-Methylsulfonyl-2-(4-nitrobenzyl)tetrazole (VIII). Yield 78%, mp 132–133°C (from ethanol). IR spectrum (ν, cm^{-1}): 970, 980, 1020, 1030, 1070, 1110, 1125, 1160, 1200, 1310, 1340, 1350, 1410, 1430, 1450, 1525, 1620, 2865, 2940, 2990, 3025, 3090, 3140. ^1H NMR spectrum (δ, ppm): 3.45 s (3H, CH_3), 6.25 s (2H, CH_2), 7.12 d (2H, C_6H_4), 8.25 d (2H, C_6H_4). Found, %: C 38.38; H 3.43; N 24.85. $C_9H_9N_5O_4S$. Calculated, %: C 38.16; H 3.18; N 24.73.

5-Methylsulfonyl-1-(4-nitrophenyl)tetrazole (IX). Yield 85%, mp 149–150°C (from DMF–ethanol mixture, 2:1) [6]. ^1H NMR spectrum (δ, ppm): 3.68 s (3H, CH_3), 8.07 d (2H, C_6H_4), 8.48 d (2H, C_6H_4).

5-Methylsulfonyl-2-(4-nitrophenyl)tetrazole (X). Yield 88%, mp 161–162°C (from ethanol–DMF mixture, 5:1). IR spectrum (ν, cm^{-1}): 970, 1010, 1045, 1080, 1120, 1150, 1170, 1225, 1300, 1310, 1330, 1350, 1375, 1420, 1500, 1560, 1605,1620, 2850, 2940, 3020, 3035, 3080, 3100, 3130. ^1H NMR

spectrum (δ, ppm): 3.55 s (3H, CH_3), 8.40–8.60 m (4H, C_6H_4). Found, %: C 35.70; H 2.52; N 26.11. $C_8H_7N_5O_4S$. Calculated, %: C 35.69; H 2.60; N 26.02.

IR spectra were recorded on spectrometer UR-20 from KBr pellets. ^1H NMR spectra were registered on spectrometer Bruker AC-200 in DMSO-d_6. The sorbent used for column chromatography was silica gel of Silpearl brand.

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