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TETRAZOLES. 42.* 2-4(NITROPHENYL)-5-FUNCTIONALLY-SUBSTITUTED TETRAZOLES*[2]

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We have studied the reactions of 5-methylsulfonyl-2-(4-nitrophenyl)tetrazole with N- and O-nucleophiles. For the first time we show that in 2-(4-nitrophenyl)-5-phenoxytetrazole, the tetrazole ring is substituted when treated with phenoxide ion, 4-nitrodiphenyl ether being formed.

Keywords: 2,5-disubstituted tetrazoles, 5-methylsulfonyl-2-(4-nitrophenyl)tetrazole, nucleophilic substitution.

The choice of methods for obtaining 2,5-disubstituted tetrazoles is quite limited [2-4]. Nevertheless, despite significant interest in these compounds, no new theoretical approaches have been proposed in recent years indicating that a tetrazole ring might be formed with substituents in the 2 and 5 position of the heterocycle. Obviously, one way to solve this problem may be to develop a simple method for functionalization of 2-substituted tetrazoles as a result of reactions at a ring carbon atom. The effectiveness of such an approach has been recently demonstrated for the example of 1-aryltetrazoles. It was shown that 1-aryl-5-functionally substituted tetrazoles are formed in high yield upon reaction of 1-aryl-5-methylsulfonyltetrazoles with C-, N-, and O-nucleophiles [5-7].

Continuing the study of derivatives of tetrazole-5-thiones as convenient synthons in the synthesis of functionally substituted tetrazoles, we have studied the reactivity of 5-methylsulfonyl-2-(4-nitrophenyl)tetrazole relative to N- and O-nucleophiles. 5-Methylsulfonyl-2-(4-nitrophenyl)tetrazole was selected as the object of investigation because of the following considerations. This substrate is an easily accessible reagent [8] and, very importantly, may be used as a model in comparing the reactivity of 1-aryl- and 2-aryl-5-methylsulfonyltetrazoles in nucleophilic substitution reactions.

We note that the problem of the reactivity of isomeric 1- and 2-substituted 5-R-tetrazoles in nucleophilic substitution reactions has practically not been discussed previously. We know that substitution of bromine in 5-bromo-1-methyltetrazole when treated with hydroxide ion occurs significantly more easily than in the isomeric 5-bromo-2-methyltetrazole [9].

Analogous data were obtained in studying the reaction kinetics of the same substrates with piperidine [10]. These results agree well with a MNDO assessment of the electronic structure of tetrazoles [11]. Thus in 1-substituted tetrazoles, the carbon atom of the heterocycle is more electronegative than in 2-substituted

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*[2] Dedicated to Professor E. Lukevics on his 65th birthday.

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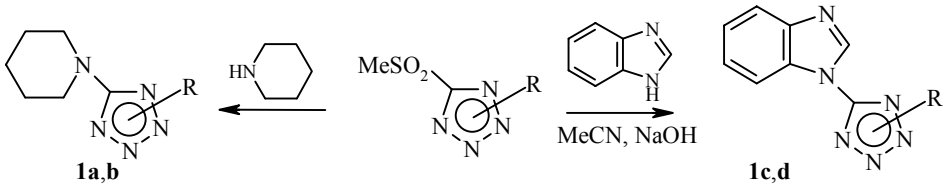
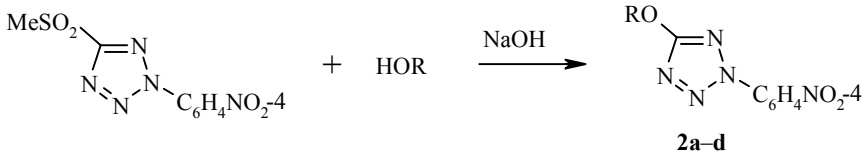
tetrazoles. This to a significant degree determines the higher reactivity of 5-bromo-1-methyltetrazole compared with the 2-methyl-substituted isomer in nucleophilic substitution reactions.

Thus we might expect that analogous behavior may be preserved on going from 5-methylsulfonyl-1-(4-nitrophenyl)tetrazole to the isomeric 5-methylsulfonyl-2-(4-nitrophenyl)tetrazole. In fact, when the indicated substrates react with piperidine and benzimidazole, the corresponding derivatives **1a-d** are formed (Tables 1 and 2). However, as hypothesized, substitution of the methylsulfonyl group in 5-methylsulfonyl-2-(4-nitrophenyl)tetrazole occurs at a much slower rate.



1 a, **c** R = 1-(4-nitrophenyl); **b**, **d** R = 2-(4-nitrophenyl)

The analogous dependence is preserved in reactions of 5-methylsulfonyl-1-(4-nitrophenyl)- and 5-methylsulfonyl-2-(4-nitrophenyl)tetrazoles with O-nucleophiles. In the first case, substitution occurs at 20°C [7], while on going to the 2-substituted isomer, heating at higher temperature is required.



2 a R = CH_3, **b** R = C_2H_5, **c** R = Me_2CH, **d** R = *n*-C_4H_9

TABLE 1. Characteristics of Tetrazoles **1-3**

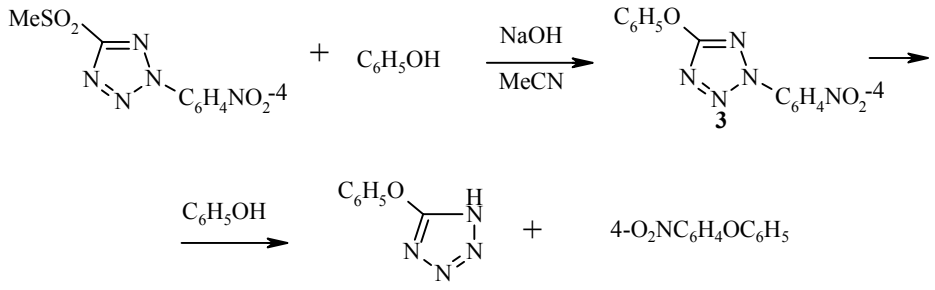
Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Yield, %
		C	H	N		
1a	$C_{12}H_{14}N_6O_2$	52.59 / 52.54	5.29 / 5.15	30.65 / 30.64	91-92	78
1b	$C_{12}H_{14}N_6O_2$	52.32 / 52.54	5.15 / 5.15	30.71 / 30.64	65-166	63
1c	$C_{14}H_9N_7O_2$	54.71 / 54.72	3.00 / 2.93	31.69 / 31.92	227-229	51
1d	$C_{14}H_9N_7O_2$	54.75 / 54.72	2.98 / 2.93	31.86 / 31.92	210-211	45
2a	$C_8H_7N_5O_3$	43.43 / 43.44	3.41 / 3.17	31.60 / 31.67	158-159	92
2b	$C_9H_9N_5O_3$	45.84 / 45.96	3.76 / 3.83	29.87 / 29.79	142	82
2c	$C_{10}H_{11}N_5O_3$	48.08 / 48.19	4.30 / 4.42	28.29 / 28.11	112-113	95
2d	$C_{11}H_{13}N_5O_3$	50.96 / 50.12	5.27 / 4.92	26.88 / 26.61	86-87	51
3	$C_{13}H_9N_5O_3$	55.32 / 55.12	3.41 / 3.18	24.66 / 24.73	138-139	33

* Compounds **1a,b, 2a-d**, and **3** were recrystallized from ethanol; compound **1c** was recrystallized from a DMF–ethanol mixture, 1:1; **1d** was recrystallized from toluene.

TABLE 2. IR Spectra and ^{1}H NMR Spectra of Tetrazoles **1-3**

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm
1a	3000, 2960, 2940, 2870, 1620, 1600, 1560, 1535, 1505, 1475, 1455, 1450, 1420, 1380, 1350, 1340, 1305, 1300, 1290, 1265, 1215, 1160, 1115, 1085, 1055, 1040, 1025, 1015, 990, 965, 925	1.65 (6H, s, 3CH_2); 3.14 [4H, s, N(CH_2)]; 8.00 (2H, d, C_6H_4); 8.48 (2H, d, C_6H_4)
1b	3130, 3105, 2955, 2935, 2865, 1585, 1525, 1500, 1470, 1450, 1385, 1340, 1320, 1300, 1270, 1225, 1205, 1170, 1135, 1110, 1020, 985, 930	1.65 (6H, s, 3CH_2); 3.55 [4H, s, N(CH_2)]; 8.20 (2H, d, C_6H_4); 8.40 (2H, d, C_6H_4)
1c	3110, 3090, 1570, 1545, 1510, 1480, 1455, 1445, 1360, 1330, 1310, 1285, 1270, 1250, 1180, 1055, 1035, 1015, 1000, 975, 950, 905	7.33-7.38 (2H, m, C_6H_4); 7.72-7.76 (2H, m, C_6H_4); 7.86-8.48 (4H, m, $C_6H_4NO_2$); 8.63 (1H, s, NCHN)
1d	3140, 3100, 2940, 2870, 1620, 1580, 1540, 1510, 1460, 1440, 1410, 1370, 1350, 1301, 1203, 1107, 1102, 1001, 980, 860	7.39-7.55 (2H, m, C_6H_4); 7.83 (1H, d, C_6H_4); 8.29 (1H, d, C_6H_4); 8.48-8.58 (4H, m, $C_6H_4NO_2$); 8.97 (1H, s, NCHN)
2a	3140, 3100, 3070, 3030, 2970, 2940, 2870, 1600, 1570, 1520-1500, 1460, 1425, 1390, 1380, 1360, 1320, 1210, 1180, 1120, 1060, 990	4.20 (3H, s, CH_3); 8.27 (2H, d, C_6H_4); 8.47 (2H, d, C_6H_4)
2b	3100, 3020, 3000, 2940, 2860, 1600, 1575, 1540, 1500, 1440, 1400, 1350, 1315, 1210, 1180, 1110, 1060, 1030, 1015, 995, 910	1.50 (3H, t, CH_3); 4.60 (2H, m, CH_2); 8.25 (2H, d, C_6H_4); 8.45 (2H, d, C_6H_4)
2c	3140, 3110, 3000, 2950, 2870, 1620, 1600, 1560, 1540, 1500, 1470, 1440, 1390, 1370, 1350, 1320, 1300, 1220, 1190, 1150, 1120, 1100, 1060, 1010, 990	1.50 (6H, m, 2CH_3); 5.10 (1H, m, CH); 8.30 (2H, d, C_6H_4); 8.45 (2H, d, C_6H_4)
2d	3130, 3110, 2980, 2950, 2890, 1620, 1600, 1560, 1550, 1540, 1500, 1470, 1440, 1400, 1370, 1350, 1320, 1210, 1180, 1120, 1070, 1060, 1020, 1000, 970	1.00 (3H, t, CH_3); 1.50 (2H, m, CH_2); 1.82 (2H, m, CH_2); 4.50 (2H, t, CH_2); 8.30 (2H, d, C_6H_4); 8.50 (2H, d, C_6H_4)
3	3135, 3105, 3030, 2935, 2870, 1735, 1625, 1605, 1590, 1530, 1490, 1470, 1440, 1390, 1375, 1350, 1320, 1270, 1200, 1180, 1165, 1080, 1060, 1030, 1000, 910	7.40 (5H, m, C_6H_5); 8.25 (2H, d, C_6H_4); 8.45 (2H, d, C_6H_4)

Quite unexpected results were obtained in studying substitution of the methylsulfonyl group in 5-methylsulfonyl-2-(4-nitrophenyl)tetrazole when treated with phenoxide ion. It was shown that when 5-methylsulfonyl-1-(4-nitrophenyl)tetrazole reacts with phenol in the presence of sodium hydroxide, 1-(4-nitrophenyl)-5-phenoxytetrazole is formed in 82% yield [7]. 2-(4-Nitrophenyl)-5-phenoxytetrazole (**3**) and 4-nitrodiphenyl ether are formed in ~1:1 ratio from 5-methylsulfonyl-2-(4-nitrophenyl)tetrazole in an analogous process. The reaction obviously occurs according to the following scheme:



The validity of such a hypothesis is confirmed by formation of 5-phenoxytetrazole and 4-nitrodiphenyl ether from known prepared 2-(4-nitrophenyl)-5-phenoxytetrazole and phenol upon heating the latter in acetonitrile in the presence of sodium hydroxide.

In conclusion, we note that nucleophilic substitution of the tetrazole ring in 2-aryl-5-R-tetrazoles has not been previously known. Such conversions have been described only for 5-aryl-2-benzoyltetrazoles, which are widely used as mild and effective acylating reagents in reactions with primary and secondary alcohols, phenols, amines, and NH-heterocycles [12, 13].

Thus the nucleophilic substitution of the tetrazole ring to 2-(4-nitrophenyl)-5-phenoxytetrazole when treated with phenoxide ion observed here for the first time may be considered as one more important piece of evidence for the fundamental differences in reactivity of 1,5- and 2,5-diaza-substituted tetrazoles.

EXPERIMENTAL

The IR spectra were obtained on a UR-20 spectrometer in KBr pellets; the ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer (working frequency 200 MHz) in DMSO-d_6. The purity and homogeneity of the compounds obtained were monitored by TLC on Silufol UV-254 plates. 5-Methylsulfonyl-1-(4-nitrophenyl)- and 5-methylsulfonyl-2-(4-nitrophenyl)tetrazoles were obtained as described in [7, 8].

The characteristics of the tetrazoles **1-3** obtained are presented in Tables 1 and 2.

1-(4-Nitrophenyl)-5-(piperidino)tetrazole (1a). A mixture of 5-methylsulfonyl-1-(4-nitrophenyl)-tetrazole (0.80 g, 3.0 mmol) and piperidine (15 ml) was stirred for 1.5 h at 100-105°C, cooled down to 5°C, and then water (50 ml) was added. The precipitate was filtered off, washed with water (15 ml), and dried in air. Obtained 0.58 g of tetrazole **1a**.

2-(4-Nitrophenyl)-5-(piperidino)tetrazole (1b) was obtained similarly; reaction time 10 h.

5-(Benzimidazol-1-yl)-1-(4-nitrophenyl)tetrazole (1c). Sodium hydroxide (0.12 g, 2.9 mmol) was added to a solution of 5-methylsulfonyl-1-(4-nitrophenyl)tetrazole (0.70 g, 2.6 mmol) and benzimidazole (0.34 g, 2.2 mmol) in acetonitrile (20 ml); this was stirred for 5.5 h at 20°C and then water (100 ml) was added. The aqueous solution was cooled down to 0-5°C. The precipitate was filtered off, washed with water (2 × 15 ml), and dried in air. Obtained 0.41 g of compound **1c**, which was recrystallized from a mixture of DMF–ethanol, 1:1.

5-(Benzimidazol-1-yl)-2-(4-nitrophenyl)tetrazole (1d) was obtained similarly. Reaction time 10h; temperature 80°C.

5-Methoxy-2-(4-nitrophenyl)tetrazole (2a). 5-Methylsulfonyl-2-(4-nitrophenyl)tetrazole (0.46 g, 1.7 mmol) was added to a solution of sodium hydroxide (0.085 g, 2.1 mmol) in methanol (15 ml). This was stirred for 30 min at 50°C and water (45 ml) was added. The precipitate was filtered off, washed with water (3 × 10 ml), and dried at 50°C. Obtained 0.35 g of compound **2a**, which was recrystallized from ethanol.

Tetrazoles **2b-d** were obtained similarly.

Reaction of 5-Methylsulfonyl-2-(4-nitrophenyl)tetrazole with Phenol. Sodium hydroxide (0.09 g, 2.2 mmol) was added to a solution of 5-methylsulfonyl-2-(4-nitrophenyl)tetrazole (0.48 g, 1.8 mmol) and phenol (0.21 g, 2.2 mmol) in acetonitrile (15 ml). The reaction mixture was stirred at 80°C for 10 h. This was cooled down to 15°C and water (100 ml) was added. The precipitate was filtered off, washed with water (3 × 10 ml), dried at 50°C and chromatographed on silica gel (chloroform as eluent). Obtained 0.17 g of 2-(4-nitrophenyl)-5-phenoxytetrazole (**3**), which was recrystallized from ethanol, and 0.14 g (36%) of 4-nitrodiphenyl ether with mp 54-56°C [14]. IR spectrum, ν, cm^{-1}: 2940, 1620, 1610, 1515, 1490, 1460, 1350, 1300, 1255, 1200, 1160, 1120, 1080, 1030, 930, 875, 850. Found, %: C 66.93; H 4.10; N 6.50. $C_{12}H_9NO_2$. Calculated, %: C 66.97; H 4.18; N 6.51.

Reaction of 2-(4-Nitrophenyl)-5-phenoxytetrazole (3) with Phenol. Sodium hydroxide (0.06 g, 1.54 mmol) was added to a solution of compound **3** (0.4 g, 1.4 mmol) and phenol (0.14 g, 1.54 mmol) in

acetonitrile (15 ml). The reaction mixture was stirred at 80°C for 20 h. This was cooled down to 15°C and then water (75 ml) was added. The precipitate was filtered off, washed with water (3 × 15 ml), dried at room temperature, and chromatographed on silica gel (chloroform as eluent). Obtained 0.14 g (58%) 4-nitrodiphenyl ether; mp 54-56°C, and 0.04 g of compound **3**. The combined aqueous filtrate was acidified with concentrated HCl to pH 1 and extracted with chloroform (3 × 20 ml), the extract was dried with magnesium sulfate and the solvent was distilled off. Obtained 0.1 g (43%) of 5-phenoxytetrazole; mp 136-138°C [15]. IR spectrum, ν, cm^{-1}: 3075, 2930, 2865, 2750, 1625, 1575, 1490, 1460, 1440, 1420, 1350, 1290, 1270, 1250, 1220, 1195, 1165, 1130, 1060, 1030, 985, 930, 885, 860. Found, %: C 51.84; H 3.87; N 34.24. $C_7H_6N_4O$. Calculated, %: C 51.85; H 3.70; N 34.57.

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