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Tetrazoles: XLVI.* Alkylation of 5-Substituted Tetrazoles with Methyl Chloromethyl Ether and α-Methylstyrene

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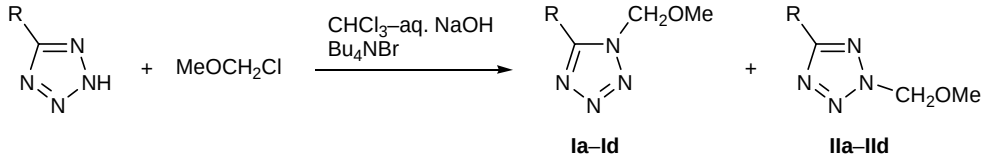
Abstract—Alkylation of 5-aryl(hetaryl)tetrazoles with methyl chloromethyl ether under conditions of phase-transfer catalysis leads to formation of isomeric 1- and 2-methoxymethyltetrazoles at a ratio of ~1:2. The reaction of 5-substituted tetrazoles with α-methylstyrene in the presence of trichloroacetic acid gives the corresponding 2-(α,α-dimethylbenzyl)tetrazoles in high yield and with high regioselectivity.

In continuation of our studies on the synthesis of 1,5- and 2,5-disubstituted tetrazoles, we examined alkylation of a series of 5-substituted tetrazoles with methyl chloromethyl ether and α-methylstyrene. It was shown previously that analogous reaction between tetrazole and benzyl chloromethyl ether gives a mixture of isomeric 1- and 2-benzyloxymethyltetrazoles at a ratio of ~1:1 [2–4]. On the other hand, the alkylation of 5-(4-methoxyphenyl)tetrazoles and 5-(2,3-dimethoxyphenyl)tetrazole with α-methylstyrene occurs exclusively at the 2-position of the heteroring [5]. In the present work we found that the use of methyl chloromethyl ether as alkylating agent instead of benzyl chloromethyl ether considerably increases the selectivity of the process: according to the NMR data, regardless of the substituent in the 5-position, isomeric 1- and 2-methoxymethyltetrazoles are formed at a ratio of ~1:2. The reactions were carried out in the two-phase system chloroform–10% aqueous NaOH in the presence of tetrabutylammonium bromide at 20°C. Under these conditions, the reaction occurred at a high rate, and the overall yield of isomeric 1- and 2-methoxymethyltetrazoles was 79–93% (Scheme 1).

We also found that heating of 1-methoxymethyltetrazoles in methyl chloromethyl ether for 8–10 h at 85–90°C results in their isomerization into the more stable 2-substituted isomer. Obviously, the isomerization follows a scheme proposed in [6] (Scheme 2). This mechanism is supported by the fact that the isomerization of 1-methoxymethyltetrazoles into 2-methoxymethyltetrazoles occurs only in the presence of methyl chloromethyl ether.

The isomerization can also be effected in one step without preliminary isolation of 1-substituted isomer. For this purpose, a mixture of isomeric 1- and 2-methoxymethyltetrazoles obtained by alkylation of the corresponding 5-substituted tetrazole under conditions of phase-transfer catalysis, should be heated in methyl chloromethyl ether for 10 h at 90°C. In all

Scheme 1.



Ia–Id **IIa–IId**

R = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 4-ClC_6H_4 (**c**), 2-pyridyl (**d**).

* For communication XLV, see [1].

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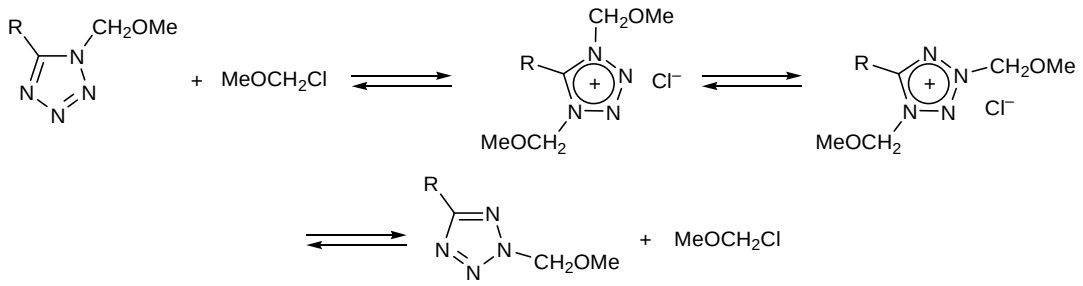
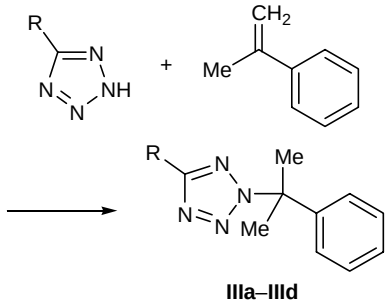
Scheme 2.



cases, even on prolonged heating of isomeric *N*-methoxymethyltetrazoles, an equilibrium establishes. This follows from the presence of a small amount (~10%) of the 1-isomer.

The alkylation of 5-substituted tetrazoles with α-methylstyrene in the presence of trichloroacetic acid occurred strictly regioselectively, and the corresponding 2-(α,α-dimethylbenzyl)tetrazoles were formed in 71–93% yield (Scheme 3).

Scheme 3.



IIIa–IIId

R = Me (**a**), Ph (**b**), 4-ClC_6H_4 (**c**), 2-pyridyl (**d**).

These results, as well as the previously obtained data [5, 7, 8], indicate that alkylation of tetrazoles with unsaturated compounds in the presence of acid catalysts provides a universal method of synthesis of 2-mono- and 2,5-disubstituted tetrazoles.

EXPERIMENTAL

The IR spectra were recorded in KBr on a UR-20 spectrometer. The ^{1}H NMR spectra were measured on a Bruker AC-200 spectrometer in acetone-d_6.

1- and 2-Methoxymethyl-5-phenyltetrazoles Ia–Id and IIa–IId (*general procedure***).** A mixture of 14 mmol of 5-substituted tetrazole, 2 mmol of tetrabutylammonium bromide, 10 ml of 10% aqueous NaOH, and 10 ml of chloroform was stirred for 5 h at 20°C, 20 mmol of methyl chloromethyl ether in 20 ml of chloroform was added, and the mixture was stirred for 1 h at 20°C. The organic phase was separated, washed with 10% aqueous sodium hydroxide (5 ml) and water (2×10 ml), and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography on silica gel using petroleum ether–ethyl acetate (5:1) as eluent. The product was additionally purified by recrystallization from petroleum ether–ethyl acetate (10:1).

1-Methoxymethyl-5-phenyltetrazole (Ia). Yield 0.7 g (26%), mp 42°C. IR spectrum, ν, cm $^{-1}$: 920, 940, 980, 1030, 1050, 1100, 1185, 1215, 1340, 1385, 1410, 1470, 1550, 2860, 2955, 3010. ^{1}H NMR spectrum, δ, ppm: 3.49 s (3H, CH_3), 5.65 s (2H, CH_2), 7.4–7.6 m (3H, H_{arom}), 7.85–7.9 m (2H, H_{arom}). Found, %: C 56.83; H 5.45; N 29.38. $C_9H_{10}N_4O$. Calculated, %: C 56.84; H 5.26; N 29.47.

2-Methoxymethyl-5-phenyltetrazol (IIa). Yield 1.4 g (53%), colorless oily substance. IR spectrum, ν, cm^{-1}: 930, 1030, 1050, 1070, 1120, 1140, 1180, 1195, 1340, 1390, 1470, 1540, 2860, 2950. ^{1}H NMR spectrum, δ, ppm: 3.46 s (3H, CH_3), 5.84 s (2H, CH_2), 7.4–7.5 m (3H, H_{arom}), 8.1–8.2 m (2H, H_{arom}). Found, %: C 56.93; H 5.21; N 29.34. $C_9H_{10}N_4O$. Calculated, %: C 56.84; H 5.26; N 29.47.

1-Methoxymethyl-5-(4-methoxyphenyl)tetrazole (Ib). Yield 0.82 g (31%), mp 89–90°C. IR spectrum, ν, cm^{-1}: 850, 920, 1030, 1100, 1190, 1220, 1260, 1310, 1340, 1390, 1450, 1485, 1620, 2860, 2960, 3450. ^{1}H NMR spectrum, δ, ppm: 3.54 s (3H, CH_3), 3.87 s (3H, CH_3), 5.67 s (2H, CH_2), 7.02–7.07 m (2H, H_{arom}), 7.88–7.93 m (2H, H_{arom}). Found, %: C 54.65; H 5.39; N 25.49. $C_{10}H_{12}N_4O_2$. Calculated, %: C 54.55; H 5.45; N 25.45.

2-Methoxymethyl-5-(4-methoxyphenyl)tetrazole (IIb). Yield 1.67 g (63%), mp 45-47°C. IR spectrum, ν, cm^{-1}: 850, 920, 1040, 1110, 1190, 1260, 1300, 1310, 1340, 1400, 1470, 1620, 2850, 2970, 3440. ^{1}H NMR

spectrum, δ, ppm: 3.49 s (3H, CH_3), 3.87 s (3H, CH_3), 5.86 s (2H, CH_2), 6.9–7.03 m (2H, H_{arom}), 8.09–814 m (2H, H_{arom}). Found, %: C 54.71; H 5.41; N 25.42. $C_{10}H_{12}N_4O_2$. Calculated, %: C 54.55; H 5.45; N 25.45.

5-(4-Chlorophenyl)-1-methoxymethyltetrazole (Ic). Yield 0.84 g (27%), mp 83°C. IR spectrum, ν, cm^{-1}: 920, 1005, 1020, 1330, 1420, 1470, 1610, 2850, 2970. ^1H NMR spectrum, δ, ppm: 3.51 s (3H, CH_3), 5.84 s (2H, CH_2), 7.4–7.5 m (3H, H_{arom}), 8.1–8.2 m (2H, H_{arom}). Found, %: C 48.31; H 4.07; N 25.10. $C_9H_9ClN_4O$. Calculated, %: C 48.11; H 4.01; N 24.94.

5-(4-Chlorophenyl)-2-methoxymethyltetrazole (IIc). Yield 1.68 g (54%), mp 63°C. IR spectrum, ν, cm^{-1}: 915, 1015, 1095, 1180, 1210, 1280, 1330, 1370, 1440, 1470, 1610, 2860, 2960. ^1H NMR spectrum, δ, ppm: 3.50 s (3H, CH_3), 6.01 s (2H, CH_2), 7.60–7.65 d (2H, H_{arom}), 8.15–8.20 d (2H, H_{arom}). Found, %: C 48.35; H 4.11; N 24.98. $C_9H_{10}N_4O$. Calculated, %: C 48.11; H 4.01; N 24.94.

1-Methoxymethyl-5-(2-pyridyl)tetrazole (Id). Yield 0.83 g (31%), mp 93°C. IR spectrum, ν, cm^{-1}: 920, 1020, 1050, 1120, 1190, 1200, 1250, 1330, 1450, 1540, 1580, 1600, 2850, 2950, 3050. ^1H NMR spectrum, δ, ppm: 3.50 s (3H, CH_3), 6.05 s (2H, CH_2), 7.50–7.65 m (1H, H_{arom}), 7.97–8.06 m (1H, H_{arom}), 8.21–8.25 d (1H, H_{arom}), 8.75–8.79 d (1H, H_{arom}). Found, %: C 50.45; H 4.89; N 36.58. $C_8H_9N_5O$. Calculated, %: C 50.26; H 4.71; N 36.65.

2-Methoxymethyl-5-(2-pyridyl)tetrazole (IId). Yield 1.66 g (62%), mp 72°C. IR spectrum, ν, cm^{-1}: 920, 990, 1000, 1030, 1050, 1070, 1100, 1190, 1210, 1260, 1310, 1440, 1480, 1540, 1595, 2850, 2950. ^1H NMR spectrum, δ, ppm: 3.40 s (3H, CH_3), 6.37 s (2H, CH_2), 7.60–7.69 m (1H, H_{arom}), 8.11–8.16 m (1H, H_{arom}), 8.32–8.36 d (1H, H_{arom}), 8.82–8.85 d (1H, H_{arom}). Found, %: C 50.39; H 4.88; N 36.77. $C_8H_9N_5O$. Calculated, %: C 50.26; H 4.71; N 36.65.

Isomerization of 1-methoxymethyl-5-phenyltetrazole (Ia). A solution of 1 mmol of 1-methoxymethyl-5-phenyltetrazole in 3 ml of methyl chloromethyl ether was heated for 10 h at 85–90°C in a sealed ampule. Methyl chloromethyl ether was removed under reduced pressure, the residue was dissolved in 10 ml of chloroform, and the solution was washed with 10% aqueuos NaOH (2×10 ml) and water (2×10 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the residue was 2-methoxymethyl-5-phenyltetrazole (**IIa**). Yield 0.072 g (72%), colorless oily substance.

Isomerization of tetrazoles **Ib** and **Ic** was performed in a similar way.

2-(α,α-Dimethylbenzyl)-5-methyltetrazole (IIIa). A mixture of 12 mmol of 5-methyltetrazole and 35 mmol of trichloroacetic acid in 20 ml of chloroform was stirred for 5 min at 20°C. A solution of 12 mmol of α-methylstyrene in 10 ml of chloroform was added over a period of 20 min to the resulting suspension, and the mixture was stirred for 6 h at 20°C. It was then cooled to 10°C, 20 ml of 10% aqueous sodium hydroxide and 30 ml of ethyl acetate were added, the mixture was stirred for 0.5 h, and the organic phase was separated, washed with water (2×30 ml), and dried over magnesium sulfate. The solvent was removed under reduced pressure to obtain compound **IIIa** as a colorless oily substance. Yield 1.99 g (82%). IR spectrum, ν, cm^{-1}: 1040, 1085, 1110, 1170, 1195, 1260, 1310, 1380, 1400, 1450, 1510, 2870, 2950, 3000. ^1H NMR spectrum, δ, ppm: 2.14 s (6H, $2CH_3$), 2.46 s (3H, CH_3), 7.10–7.15 m (2H, H_{arom}), 7.30–7.35 m (3H, H_{arom}). Found, %: C 65.41; H 7.05; N 27.65. $C_{11}H_{14}N_4$. Calculated, %: C 65.35; H 6.93; N 27.72.

Tetrazoles **IIIb**–**IIId** were synthesized in a similar way.

2-(α,α-Dimethylbenzyl)-5-phenyltetrazole (IIIb). Yield 2.94 g (93%), mp 51°C (from petroleum ether). IR spectrum, ν, cm^{-1}: 1010, 1030, 1050, 1080, 1180, 1180, 1200, 1265, 1310, 1380, 1460, 1480, 1500, 1540, 2860, 2940, 3010. ^1H NMR spectrum, δ, ppm: 2.24 s (6H, $2CH_3$), 7.10–7.55 m (8H, H_{arom}), 8.11–8.16 m (2H, H_{arom}). Found, %: C 72.80; H 6.15; N 21.29. $C_{16}H_{16}N_4$. Calculated, %: C 72.73; H 6.06; N 21.21.

5-(4-Chlorophenyl)-2-(α,α-dimethylbenzyl)tetrazole (IIIc). Yield 2.55 g (71%), colorless oily substance. IR spectrum, ν, cm^{-1}: 850, 1010, 1020, 1040, 1170, 1200, 1260, 1330, 1390, 1430, 1480, 1610, 2850, 2960. ^1H NMR spectrum, δ, ppm: 2.24 s (6H, $2CH_3$), 7.20–7.60 m (7H, H_{arom}), 8.11–8.16 m (2H, H_{arom}). Found, %: C 64.40; H 5.09; N 18.85. $C_{16}H_{15}ClN_4$. Calculated, %: C 64.32; H 5.03; N 18.76.

2-(α,α-Dimethylbenzyl)-5-(2-pyridyl)tetrazole (IIId). Yield 2.60 g (85%), mp 68°C (from petroleum ether). IR spectrum, ν, cm^{-1}: 930, 1000, 1050, 1100, 1160, 1180, 1200, 1260, 1310, 1380, 1400, 1420, 1460, 1500, 1600, 2860, 2940, 3000, 3020, 3080. ^1H NMR spectrum, δ, ppm: 2.26 s (6H, $2CH_3$), 7.20–7.38 m

(5H, H_{arom}), 7.45–7.52 m (1H, H_{arom}), 7.90–8.05 m (1H, H_{arom}), 8.18–8.23 d (1H, H_{arom}), 8.70–8.75 d (1H, H_{arom}). Found, %: C 67.70; H 5.57; N 26.49. $C_{15}H_{15}N_5$. Calculated, %: C 67.92; H 5.66; N 26.41.

Acid hydrolysis of 2-methoxymethyl-5-phenyltetrazole (IIa). A solution of 0.01 mol of tetrazole **IIa** in 10 ml of 10% hydrochloric acid was stirred for 1.5–2 h at 70°C. The mixture was cooled to 5°C, and the precipitate was filtered off and dried in air. Yield of 5-phenyltetrazole 1.39 g (95%), mp 218°C [9].

Acid hydrolysis of tetrazoles **Ia**–**Ic**, **IIb**, and **IIc** was performed in a similar way; the hydrolysis of tetrazoles **IIIa**–**IIId** took 6–8 h.

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