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LETTERS TO THE EDITOR

ALKYLATION OF 5-BENZYL-TETRAZOLE UNDER MICROWAVE ACTIVATION CONDITIONS

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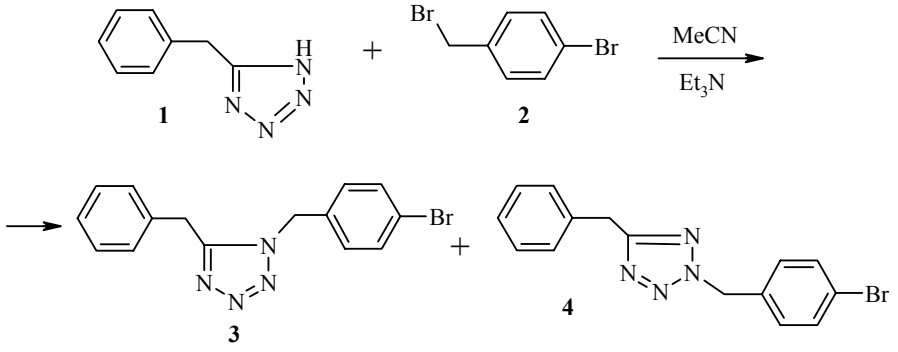
The alkylation of 5-substituted tetrazoles is a common method for obtaining 1,5- and 2,5-disubstituted tetrazoles [1]. An important feature of this reaction is that the alkylation leads most often to a mixture of isomeric disubstituted tetrazoles, whose separation is quite difficult.

In a continuation of a study of the methods for the preparation of functionally-substituted tetrazoles, we studied the alkylation of 5-benzyltetrazole **1** using 4-bromobenzyl bromide **2** in acetonitrile and chloroform under thermal and microwave activation conditions, assuming that the use of microwave activation would give different regioselectivity for this reaction [2].



However, regardless of the nature of the solvent and reaction conditions, the ratio of the isomeric tetrazole products **3** and **4** remained 1:1. On the other hand, the total yield of the isomeric tetrazoles and reaction rate under microwave activation conditions proved much higher than upon thermal heating.

Upon thermal heating, the reaction requires 3 h at 75°C in acetonitrile to give a yield of 50% and 3 h at 60°C in chloroform to give a yield of 59%. Under microwave activation conditions, the reaction requires only 1 h at 75°C in acetonitrile with 74% yield and 1 h at 60°C in chloroform with 96% yield.

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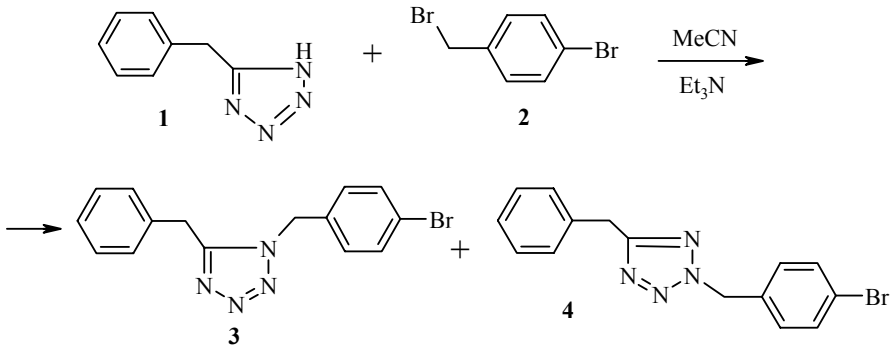

The ratio of isomeric tetrazoles **3** and **4** was determined by ^{1}H NMR spectroscopy by analyzing aliquots taken from the reaction solution at the end of the alkylation. The ratios of the isomeric tetrazoles were obtained as the arithmetic mean of three parallel measurements. The IR spectra were taken on a Shimadzu FTIR-8400S spectrometer for KBr pellets. The ^{1}H NMR spectra were taken on a Bruker WM-400 spectrometer at 400 MHz in acetone-d_6. The signal of the residual protons of the deuterated solvent at δ 2.00 ppm served as the internal standard. The elemental analysis was carried out on a LECO CHNS(O)-932 analyzer. The reactions under microwave activation conditions were carried out in a Milestone P/N 44072 reactor. The purity of the products obtained was monitored by thin-layer chromatography on Silufol UV-254 plates using 2:3 ethyl acetate–carbon tetrachloride as the eluent.

5-Benzyl-1-(4-bromobenzyl)tetrazole (3) and 5-benzyl-2-(4-bromobenzyl)tetrazole (4). 4-Bromobenzyl bromide (0.78 g, 3.1 mmol) and triethylamine (0.49 g, 4.1 mmol) were added to a solution of 5-benzyltetrazole (0.5 g, 3.1 mmol) in acetonitrile (20 ml). The reaction mixture was stirred for 1 h at 75°C under microwave activation conditions (90 W) and cooled to 10-15°C. Then, 50 ml water was added. The crystalline precipitate was filtered off, washed with water, and dried in the air. The total yield of isomeric tetrazoles **3** and **4** was 0.76 g (74%). The mixture of isomers was separated by fractional crystallization from carbon tetrachloride.

5-Benzyl-1-(4-bromobenzyl)tetrazole (3). Mp 90°C (carbon tetrachloride). IR spectrum, ν, cm^{-1}: 807, 852, 1013, 1071, 1120, 1197, 1229, 1277, 1411, 1454, 1503, 1593, 2851, 2924, 3034, 3064, 3090. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.35 (2H, s, C–CH_2); 5.60 (2H, s, N–CH_2); 7.06 (2H, d, *J* = 8.8, ArH); 7.16-7.27 (5H, m, ArH); 7.45 (2H, d, *J* = 9.2, ArH). Found, %: C 54.72; H 3.99; N 17.06. $C_{15}H_{13}BrN_4$. Calculated, %: C 54.71; H 3.95; N 17.02.

5-benzyl-2-(4-bromobenzyl)tetrazole (4). mp 49°C (1:3 water–ethanol). IR spectrum, ν, cm^{-1}: 799, 825, 1014, 1069, 1137, 1197, 1260, 1345, 1427, 1457, 1488, 1593, 2925, 2958, 2998, 3033, 3086. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.19 (2H, s, C–CH_2); 5.83 (2H, s, N–CH_2); 7.21-7.28 (5H, m, ArH); 7.31 (2H, d, *J* = 7.6, ArH); 7.56 (2H, d, *J* = 9.2, ArH). Found, %: C 54.88; H 3.99; N, 17.00. $C_{15}H_{13}BrN_4$. Calculated, %: C 54.71; H, 3.95; N 17.02.

In the alkylation in chloroform, the solvent was removed in vacuum prior to separation of the products.

The alkylation of 5-benzyltetrazole **1** under thermal heating conditions was carried out analogously.

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