Facile synthesis of bis(azolyl) derivatives in a superbasic meduim

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Abstract

Reaction of azoles (1,2,4-triazole, benzimidazole, bezotriazole) and dihalogenoderivatives of alkanes and oligoethyleneglycols in a superbasic KOH-dimethylsulfoxide medium was used for the synthesis of bis(azolyl)alkanes and related compounds. The new method does not involve the use of toxic solvents and catalysts, does not require column chromatography for product separation and gives the target compounds in high yields.

Keywords: 1,2,4-triazole, benzimidazole, bezotriazole, alkylation, superbasic medium

Introduction

Organic compounds, containing several azole cycles – poly(azol-1-yl)alkanes (scorpionates) are chelating ligands forming complexes with most transition metals and some main group elements. Complexes with more than seventy elements are reported so far [1, 2].

The chemistry of polydentate azole-containing ligands is still at the stage of a rapid development, which is clearly seen from a large number of reviews [3-12] and two separate books [13, 14], published in recent years. The development of scorpionate chemistry is somewhat limited by the complex experimental procedures for their preparation, involving use of dry solvents, alkaline metals and their hydrides, expensive catalysts.

Previously we reported facile synthesis of bis(pyrazol-1-yl)alkanes by double alkylation of pyrazoles with dihalogenoderivatives in a superbasic KOH-dimethylsulfoxide medium [15-19]. The versatility of double alkylation of azoles is demonstrated here on the examples of 1,2,3-benzotriazole, benzimidazole and 1,2,4-triazole.

Experimental

NMR spectra were recorded on Bruker AV300 instrument operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. IR spectra were recorded on Nikolet 5700 (400-4000 cm^{-1} range) as KBr pellets.

Bis(benzotrizol-1-yl)methane (**1**). To a solution of 5.00 g (42.0 mmol) of benzotriazole in 40 мл of DMSO, 3.53 g (63.0 mmol) of powdered KOH were added. The suspension was agitated for 1 hour at 60 °C, then 3.66 g (1.5 ml, 21.0 mmol) of CH_2Br_2 in 10 ml of DMSO were added dropwise during 50 minutes. The reaction mixture was stirred for 2 h at 60 °C and then poured into 400 ml of water. The resulting precipitate was filtered, washed with water and dried. The product (4.67 g, 89 %), based on GC/MS analysis, contains 71.7, 28.1 and 0.27 % mol. of compounds **1a**, **1b** and **1c**. Crystallization from toluene gave pure compound **1a** as colorless crystals in 25 % yield, m.p. 191-192 °C (lit. m.p. 192-193 °C [20]). IR spectra, cm^{-1}:

2880 (C-H), 1600 (C=C), 1160 (C-N), 950 (δ_{C-H}), 740 (δ_{C-H}). NMR ^{1}H ($CDCl_3$), δ, ppm: 7.36 t (2H, H^6-bta, *J* 7.5 Hz), 7.42 s (CH_2), 7.51 t (2H, H^5-bta, *J* 7.5 HZ), 7.86 d (2H, H^7-bta, *J* 8 Hz), 8.00 d (2H, H^4-bta, *J* 8 Hz). NMR ^{13}C ($CDCl_3$), δ, ppm: 58.08 (CH_2), 109.94 (C^4-bta), 120.22 (C^5-bta), 124.93 (C^6-bta), 128.84 (C^7-bta), 132.32 (C^8-bta), 146.42 (C^9-bta). Found, %: C 63.03; H 4.38; N 33.77. $C_{13}H_{10}N_6$. Calculated, %: C 62.39; H 4.03; N 33.58.

Isolation of compound 1a from the isomer mixture. To the solution of 1.07 g (4.28 mmol) of the isomer mixture **1a-1c** in 15 ml of acetone the solution of 0.366 g (2.14 mmol) of $CuCl_2 \cdot 2H_2O$ in 10 ml of acetone was added. The resulting microcrystalline light-green precipitate was filtered, washed with acetone and dried. Complex yield $[Cu(L)Cl_2]$ (L – compound **1a**) 0.717 g (87 %), m.p. 263-264 °C (decomposed). Found, %: Cu 16.29. Calculated, %: Cu 16.52.

The complex obtained (0.70 g) was dissolved in 10 ml of DMSO, the resulting solvent was poured into 100 ml of water, the precipitate was washed with 10 % aqueous ammonia and water. Compound **1a** (0.36 g, 80 %) was obtained as colorless crystals, m.p. 187-188 °C. The yield based on the starting isomer mixture is 34 %.

1,3-Bis(benzotriazol-1-yl)propane (**2a**) was prepared and isolated similarly to compound **1a**. Yield of isomer mixture **2a-2c** 82 %, colorless crystals, m.p. 71-87 °C. Yield of isomer **2a** 24 %, m.p. 139-140 °C (*i*-PrOH). NMR ^{1}H ($CDCl_3$) of compound **2a**, δ, ppm: 2.85 q (2H, $CH_2C\underline{\mathbf{H}}_2CH_2$, *J* 6 Hz), 4.68 t (4H, $BtaCH_2$, *J* 6 Hz), 7.43, 8.06 (8H, Ar). NMR ^{13}C ($CDCl_3$) of compound **2a**, δ, ppm: 29.1 ($CH_2\underline{\mathbf{C}}H_2CH_2$), 44.7 ($BtaCH_2$), 109.1 ($C^7$ (Bta)), 119.9 (C^4 (Bta)), 124.1 (C^5 (Bta)), 127.6 (C^6 (Bta)), 132.9 (C^8 (Bta)), 145.8 (C^9 (Bta)).

Bis(benzimidazol-1-yl)methane (**3**). Yield 70 %, colorless crystals, m.p. 245-246 °C (*i*-PrOH), lit. m.p. 246-247 °C [21]. NMR ^{1}H (DMSO-d_6), δ, ppm: 6.43 s (2H, CH_2), 7.05 (4H, H^5-Bim, H^6-BIm), 7.34 d (2H, H^4-BIm, *J* 6 Hz), 7.51 d (2H, H^7-BIm, *J* 6 Hz), 8.15 s (2H, H^2-BIm). NMR ^{13}C (DMSO-d_6), δ, ppm: 52.8 (CH_2), 109.3 (C^7-BIm), 119.9 (C^4-BIm), 122.3 (C^5-BIm), 123.2 (C^6-BIm), 132.1 (C^8-BIm), 143.1 (C^9-BIm, C^2-BIm).

1,3-Bis(benzimidazol-1-yl)propane (**4**). Yield 98 %, colorless crystals, m.p. 82-84 °C (EtOH-H_2O, 2:1), lit. m.p. 120-121 °C [22]. NMR ^1H ($CDCl_3$), δ, ppm: 2.46 t (2H, $CH_2C\underline{\mathbf{H}}_2CH_2$, *J* 7 Hz), 4.12 t (4H, $BImCH_2$, *J* 7 Hz), 7.28 m (8H, Ar), 7.81 s (2H, H^2-BIm). NMR ^{13}C ($CDCl_3$), δ, ppm: 41.5 (CH_2), 108.8 (C^7-BIm), 119.9 (C^4-BIm), 121.9 (C^5-BIm), 122.7 (C^6-BIm), 132.6 (C^8-BIm), 142.3 (C^2-BIm), 143.1 (C^9-BIm). The NMR spectra fully correspond to literature data [22].

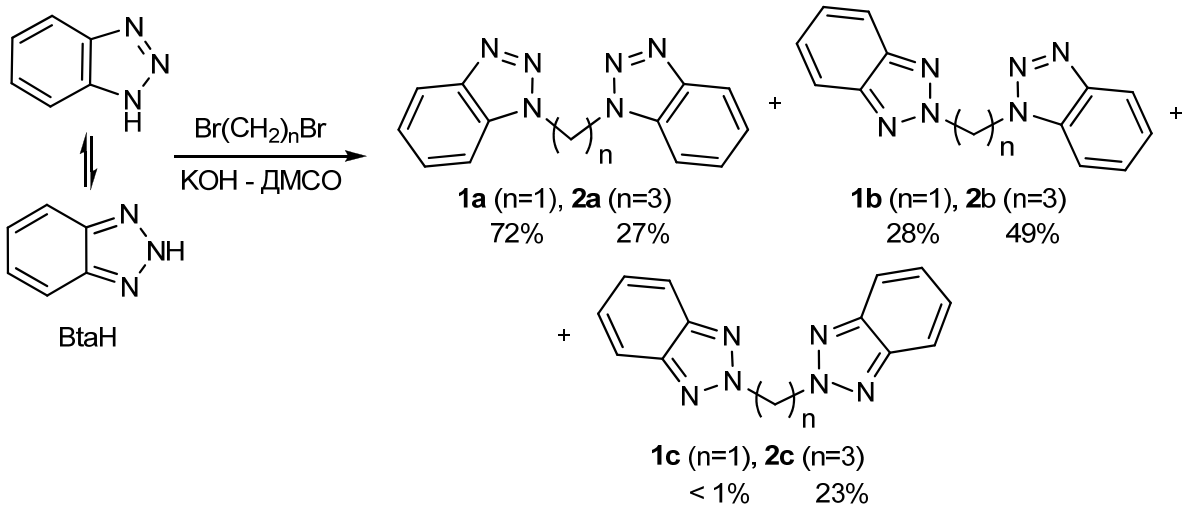
1,5-Bis(benzimidazol-1-yl)-3-oxapentane (**5**). Yield 83 %, colorless crystals, m.p. 83-84 °C. NMR ^1H ($CDCl_3$), δ, ppm: 3.54 t (4H, CH_2O, *J* 5 Hz), 4.08 t (4H, $BImCH_2$, *J* 5 Hz), 7.23 m (8H, Ar), 7.72 s (2H, H^2-BIm). NMR ^{13}C ($CDCl_3$), δ, ppm: 44.4 (OCH_2), 69.0 (CH_2BIm), 109.3 (C^7-BIm), 119.7 (C^4-BIm), 121.9 (C^5-BIm), 122.7 (C^6-BIm), 133.2 (C^8-BIm), 142.9 (C^2-BIm), 143.0 (C^9-BIm).

Bis(1,2,4-triazol-1-yl)methane (**6**). Yield 55 %, colorless crystals, m.p. 135-137 °C, lit. m.p. 127 °C [23], 142-143 °C [24]. NMR ^1H (DMSO-d_6), δ, ppm: 6.72 s (2H, CH_2), 8.03 s (2H, H^3-Tz), 8.92 s (2H, H^5-Tz). NMR ^{13}C (DMSO-d_6), δ, ppm: 59.1 (CH_2), 145.2 (C^5-Tz), 152.3 (C^3-Tz).

Results and discussion

In case of benzotriazole alkylation it was found that the amount of potassium hydroxide greatly affects the product yield. Thus, decreasing the relative amount of KOH from 2 to 1.5 mole on one mole of starting benzotriazole results in product yield increase from 17 to 88-89 % at the same temperature (Table 1). Benzotriazole is more reactive in alkylation compared to pyrazole, which is probably explained by its greater acidity (ionization constants of benzotriazole and pyrazole in DMSO are pK_a = 11.9 and pK_a = 19.8 correspondingly [25]), leading to more effective heterocycle anion generation in the reaction mixture.

Since benzotriazole exists in two tautomeric forms, double alkylation reaction of benzotriazole gave three isomers with heterocycles substituted at nitrogen atoms *1* of *2* (Scheme 1, relative amounts of isomers are given, % mol.).



Scheme 1

Таблица 1 – Conditions of double alkylation of azoles and product yields

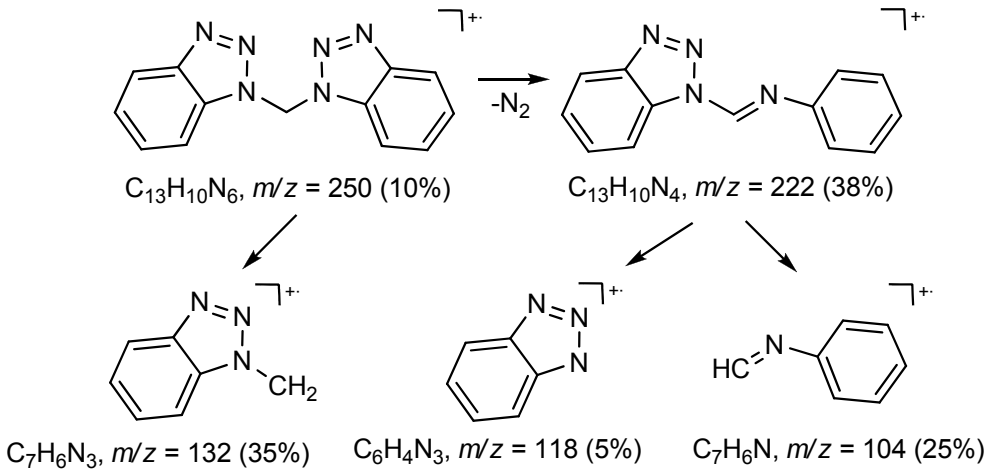
Starting azole	Alkylating agent	$n_{rel.}$(KOH) [1]	t, °C	τ, h [2]	Yield, %
BtaH	$BrCH_2Br$	2	20	2	14 [3]
BtaH	$BrCH_2Br$	2	60	1.5	17 [3]
BtaH	$BrCH_2Br$	2	80	1	17 [3]
BtaH	$BrCH_2Br$	1.5	60	2	89 [3]
BtaH	$BrCH_2Br$	1.5	80	2	88 [3]
BtaH	$Br(CH_2)_3Br$	1	80	3	91 [3]
BImH	$BrCH_2Br$	2	80	4	65
BImH	$Br(CH_2)_3Br$	2	80	4	81
BImH	$Cl(CH_2)_2O(CH_2)_2Cl$	2	80	3	83
TzH	$ClCH_2Cl$	3	40	24	53
TzH	$BrCH_2Br$	2	80	6	41

Notes: [1] Amount of KOH on one mole of azole; [2] Reaction duration, based on TLC; [3] Yield of isomer mixture.

The signals in NMR 1H spectrum of product mixture **1a-1c** overlap, so it was not possible to determine the product composition by NMR. Therefore, GC/MC method was used for the determination of relative amounts of isomers.

The mass-chromatogram of product mixture shows three peaks, molecular ion $[M]^+$ *m/z* = 250 corresponding to each of them (Figure 1). For compound with the

smallest retention time, peak at *m/z* = 222, corresponding to nitrogen loss $[M\text{-}N_2]^+$, is absent, and the molecular ion is fairly stable. In the mass-spectrum of the next compound (by retention time) peak with *m/z* = 222 appears and the intensity of molecular ion peak decreases. In the mass-spectrum of compound with the greatest retention time the peak of molecular ion decreases even more and the intensity of $[M\text{-}N_2]^+$ peak is about twice as much as in the spectrum of a previous product. The tentative fragmentation path of the molecular ion **1a** is shown on scheme 2. Similar fragmentation pathway of 1-substituted benzotriazoles was proposed in paper [26]. The results obtained suggest that the first compound, incapable of nitrogen loss fragmentation, is bis(benzotriazol-2-yl)methane **1c** (0.27 % mol. based on GC/MS), the following by retention time compound is unsymmetrical 1,2′-substituted isomer **1b** (28.1 % mol.), while the last, most easily loosing nitrogen, is product **1a** (71.7 % mol.). In mass-spectra of compounds 1a and 1b peaks with *m/z* = 104 ($[C_6H_5N{=}CH]^{+\cdot}$), 118 ($[C_6H_4N_3]^{+\cdot}$) are also present. Intensive peaks with *m/z* = 132 ($[C_6H_4N_3{-}CH_2]^{+\cdot}$) and *m/z* = 77 ($[C_6H_5]^{+\cdot}$) were detected in the spectra of all three compounds, the last peak is characteristic for all aromatic compounds.



Scheme 2

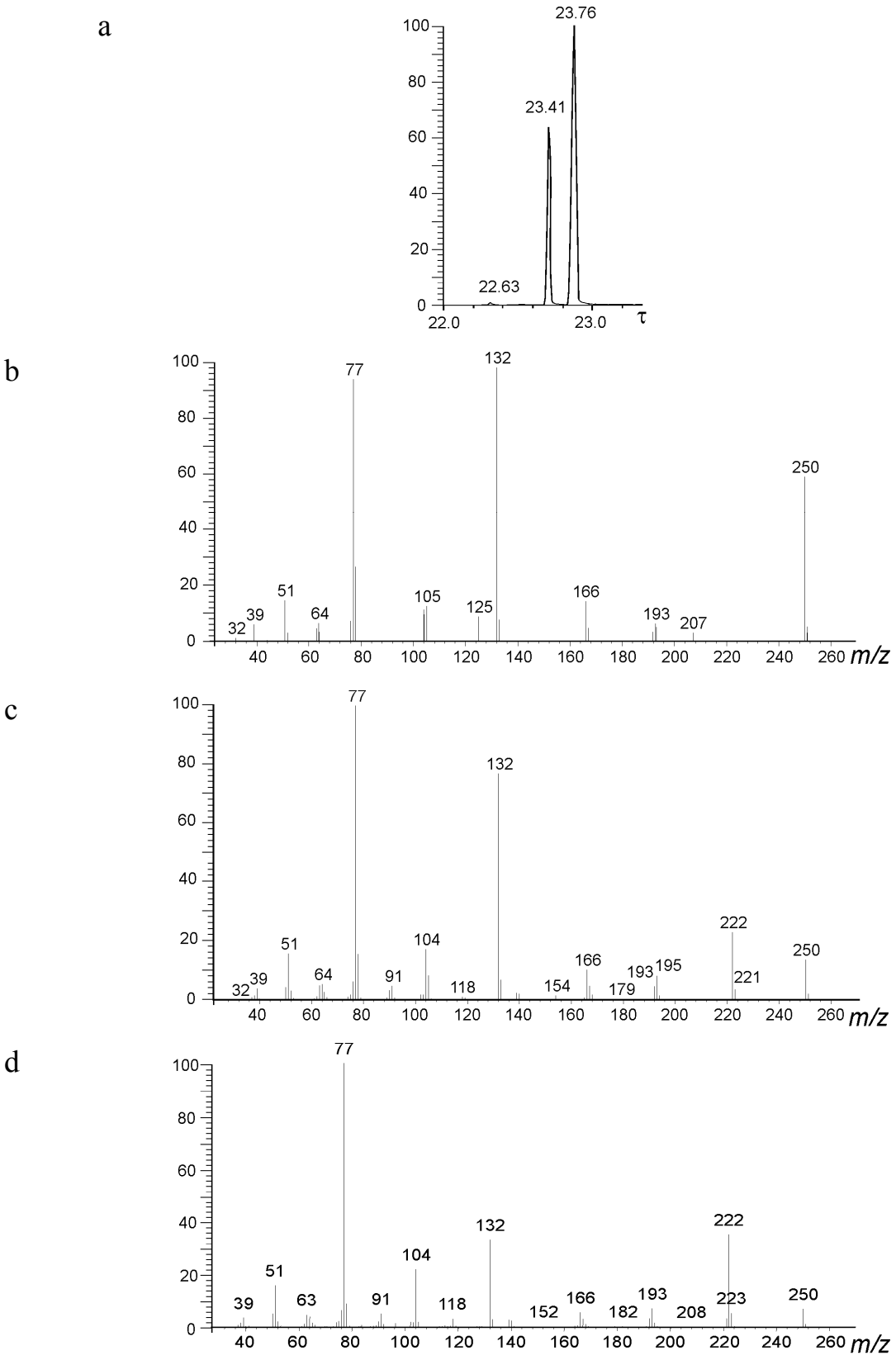


Figure 1 – Results of GC/MS study of benzotriazole – dibromomethane reaction products. Mass-spectra (b, c, d) correspond to peaks of compounds **1c**, **1b**, **1a** with retention times 22.63, 23.41 and 23.76 min on chromatogram (a).

The composition of isomer mixture **2a-2c** was easily determined by NMR using the integral intensities of methylene group linked to benzotriazole ring triplets, which did not overlap.

The ^{1}H NMR spectrum of the isolated isomer mixture contains four triplets of approximately equal intensity in the interval of 4.6-4.9 ppm. After a single crystallization the intensity of two triplets at 4.71 и 4.78 ppm considerably diminishes, and after a subsequent crystallization the triplet at 4.85 ppm also disappears. After three crystallizations of the isomer mixture **2a-2c** from *i*-PrOH pure isomer with a triplet of CH_2 group linked to benzotriazole cycle at 4.65 pm was obtained. NMR ^{1}H and ^{13}C of this product fully correspond to 1-substituted derivative **2a**. Two triplets (4.71 and 4.78 ppm) of the product removed by the first crystallization correspond to the unsymmetrical compound **2b**, and a triplet at 4.85 ppm – to the isomer **2c**. Relative amounts of the isomers calculated from the signal integral intensities are shown on Scheme 1. As one can see, the ratio is close to statistical, therefore, alkylation of benzotriazole cycle by 1,3-dibromopropane at positions *1* and *2* proceeds with approximately equal probability.

Publication [27] reports the following composition of isomer mixture obtained in phase transfer conditions: 50.8 % **1a**, 40.8 % **1b**, 8.4 % **1c**, and the ratio of the isomers corresponded to the equation $(a+b)^2=a^2+2ab+b^2$ with a=71 and b=29. The proposed approach was employed here for the analysis of the regioselectivity of benzotriazole alkylation by dibromomethane in a superbasic medium.

The members of $a^2+2ab+b^2$ sum are proportional to parts of the isomers A, B and C in product mixture. The sum of squared deviations of these parts form sum members is:

$$\Sigma = \left(a^2 - A\right)^2 + \left(2ab - B\right)^2 + \left(b^2 - C\right)^2$$

Taking into account that a+b=1, we get a one-argument function, minimization of which gives coefficients a and b, characterizing the relative activity of two nucleophilic centers in benzotriazolate-anion.

$$f(a) = \left(a^2 - A\right)^2 + \left(2a(1-a) - B\right)^2 + \left((1-a)^2 - C\right)^2 \quad \rightarrow \quad \min$$

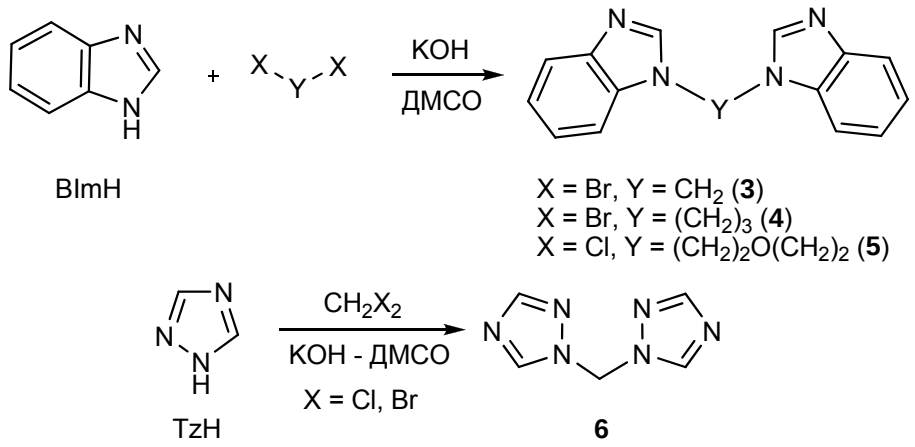
When a∈[0;1] this function has only one minimum at a=0.842, which gives the relative activity of two nucleophilic centers of 84:16. It should be noted that this ratio characterizes the average reactivity of benzotriazolate anion in two stages, since this reactivity is influenced not only by the electronic factors, but also by steric factors which are different for the substitution of the first and the second halogen atoms, as well for different linker length.

It can be assumed that the coordination compounds of ligands **1a-1c** demonstrate different stability. This would allow to isolate the isomer forming the most stable complexes. It was found, that when the mixture of isomers **1a-1c** is treated with copper(II) chloride in acetone green crystals of complex with melting point 252-253 °C (decomposed) were formed. Narrow melting point range suggest the formation of an individual compound. The determination of copper(II) content gave the formula $[Cu(C_{13}H_{10}N_6)Cl_2]$. It is evident, that complex with metal to ligand ratio 1:1 was formed, in spite of reagents ratio of 1:2. Complex yield was 87 % based on $CuCl_2$. The ligand was displaced from the complex by the action of dimethylsulfoxide and isolated by precipitation into the water. The colorless crystals obtained had a melting point of 187-189 °C and NMR spectra corresponding to individual bis(benzotriazol-1-yl)methane **1a**. Apparently, when excess of ligand is used, only the most stable complex is formed, which allows to isolate the ligand **1a** from the isomer mixture with high yield.

Similarly, when the mixture of isomers with trimethylene linker **2a-2c** was treated with copper(II) chloride in acetone complex with $CuCl_2$:L ratio of 2:1 was formed (yield 92 %). Decomposition of this complex by DMSO gave pure **2a** in high yield (88 %).

The structure of bis(benzotriazol-1-yl)methane isomers was additionally studied by X-Ray diffraction, the results are reported elsewhere [28].

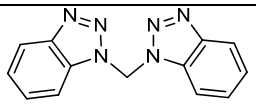
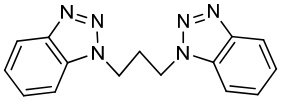
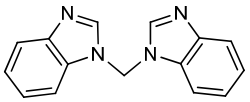
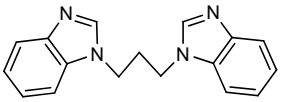
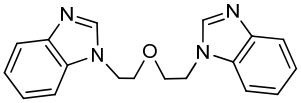
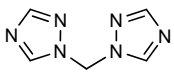
Alkylation of benzimidazole and 1,2,4-triazole proceeds smoothly at 80 °C and double excess of KOH (Scheme 3). Table 2 lists the formulas, yields and melting points of synthesized products together with literature data.



Scheme 3

Table 2

Yields and melting points of bis(azolyl)alkanes

Compound	Structure	Yield, %	m.p., °C	Lit. yield, %	Lit. m.p., °C
1a		89	191-192	88 [20]	192-193 [20]
2a		82	139-140	48 [29]	119-121 [29] 138 [30]
3		70	245-246	83 [21]	246-247 [21]
4		98	82-84	85 [31]	120-121 [22]
5		83	83-84	67 [32] 72 [33]	73 [32] 96-98 [33]
6		55	135-137	62 [23]	127 [23] 142-143 [24]

Conclusion

In summary, the method proposed here for the synthesis of bis(azolyl)alkanes and related compounds has several advantages compared to the methods described in literature – only non-toxic DMSO is used as solvent, there is no need for the use of expensive phase transfer catalysts and other reagents requiring special handling, such as sodium hydride and alkaline metals. The methods are easily scalable to multigram quantities.

Acknowledgements

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