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METHOD OF THE SYNTHESIS OF 1,2,4,5-TETRAKIS(BENZAZOL)BENZOLES

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We developed the simple method of obtaining of 1,2,4,5-tetrakis(benzimidazolyl)benzene and 1,2,4,5-tetrakis(1H-benzotriazol-1-yl)benzene based on the substitution of all functional groups in 1,3-dichloro-4,6-dinitrobenzene under S_NAr reaction conditions.

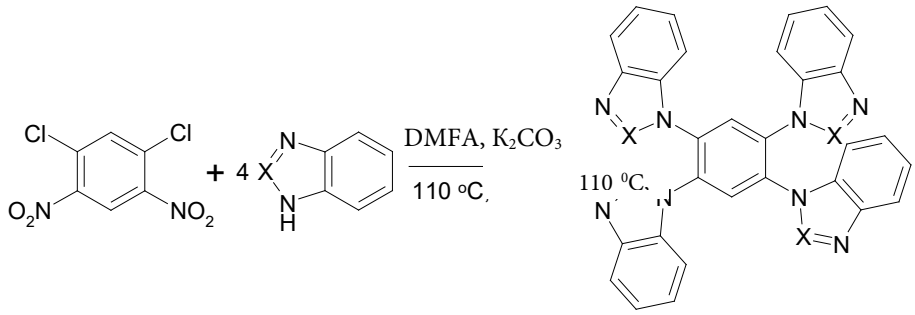
Introduction

Symmetrical polysubstituted benzene derivatives are widely used compounds. This is especially true for arenas containing primary or cyclic amines of the same structure. The functional groups of 1,2,4,5-substituted benzene can act as coordination centres [1-5] form complexes with various compounds. Therefore, such structures are used as ligands to produce catalysts [6]. Also, they form light-absorbing complexes that can be used in optoelectronics [7], etc. The cyclic amines in the ligand molecules provide the possibility of their use in drug development. Thus, complexes of 1,2,4,5-tetrakis(benzimidazolyl)benzene with zinc are promising anticancer agents. Their action is based on the ability to overcome carcinoma resistance by inducing mitochondria-mediated apoptosis or triggering mitochondrial fragmentation (8). However, there are few studies on their biological activity. This is due to a lack of easy, environmentally friendly methods for the synthesis of symmetrical arenes containing several cyclic amines as substituents. For example, the heating of 1,2,4,5-tetracyanobenzene [9] or 1,2,4,5-benzoltetracarboxylic acid [8] with 1,2-phenylenediamine in polyphosphoric acid at 190 °C for 4 h was used to obtain tetrakis(benzimidazolyl)benzenes.

Therefore, the aim of this work was to develop an efficient method for the synthesis of 1,2,4,5-tetrakis(benzazol)benzoles.

We consider [10] the substitution of all functional groups in 1,3-dichloro-4,6-dinitrobenzene (1) in reaction of S_NAr with thiophenols at 140 °C for 4 h. At the same time, there were no tetrasubstituted products with phenol, aniline and morpholine. Thus, the possibility of using heterocyclic amines, benzimidazole (2a) and benzotriazole (2b), as nucleophiles was investigated. The reaction proceeds in dimethyl formamide (DMFA) with the presence of potassium

carbonate (K_2CO_3) Both halogen atoms and two nitro groups were successfully substituted for the reagents used at 110 °C according to the scheme:



1 **2a,b** **3a 91%**
b 93%

X = a) CH, b) N

For the substances obtained, ^{1}H NMR- (Fig. 1 and 2) and IR spectra as well as low- and high-resolution mass spectra were recorded.

The ^{1}H NMR spectrum of product 3a (see Fig. 1) contains 5 signals from 22 protons of 1,2,4,5-tetrakis(benzimidazolyl)benzene. In the weakest field (8.53 m.d.) a singlet from H^3 and H^6 of the central benzene ring, strongly descreened by 4 electron acceptor azaheterocyclic fragments, emerged. At 8.38 m.d. there was a singlet from 4 benzimidazole protons in position 2 of the heterocycle. The remaining proton signals appeared in a stronger field and had the form of two doublets and two triplet doublets.

In the low resolution mass spectrum of 1,2,4,5-tetrakis(benzimidazolyl)benzene there was only one signal from a molecular ion with high intensity and *m/z* 541. There was also a number of isotopic peaks. All the fragment ions appeared were unstable and had very low intensity.

There were five signals in the ^{1}H NMR spectrum of 1,2,4,5-tetrakis(1H-benzotriazol-1-yl)benzene (see Fig. 2). Four from protons of benzotriazole fragments (integral area 16) and one singlet from two protons of the central benzene ring (integral area 2). The protons H^3 and H^6 were both equivalent, so they appeared as a singlet at 8.94 m.d. This strong shift to the high frequency region was caused by the presence of four electron acceptor heterocyclic fragments, two in the *ortho*-position and two in the *meta*-position to each of the benzene hydrogen atoms. The protons of the benzotriazole rings were two doublets and two triplets.

The ease of obtaining N-substituted 1,2,4,5-tetraaminobenzenes in comparison with the previously described results with thiophenols [10] may be explained in terms of many heterocyclic fragments possess of activating effect comparable with that of CN and CF_3 groups [11]. Thus, our results are the new example of nitrogen-activated S_NAr reactions.

The synthesised products are interesting as ligands for organometallic polymers and for π-complexation in supramolecular systems.

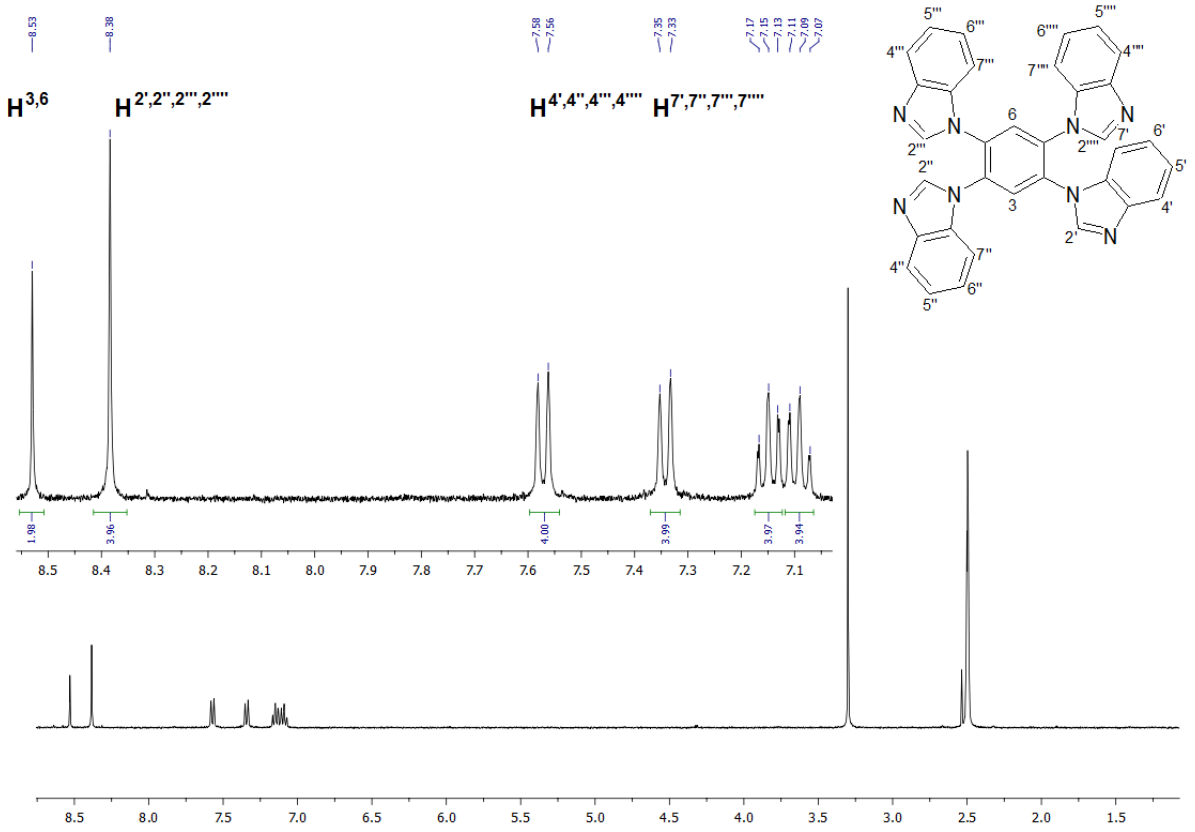


Fig. 1. [1]-N NMR spectrum of1,2,4,5-tetrakis(benzimidazolyl)benzene (Bruker DRX400, 400 MHz, DMSO-d_6, 303 K)

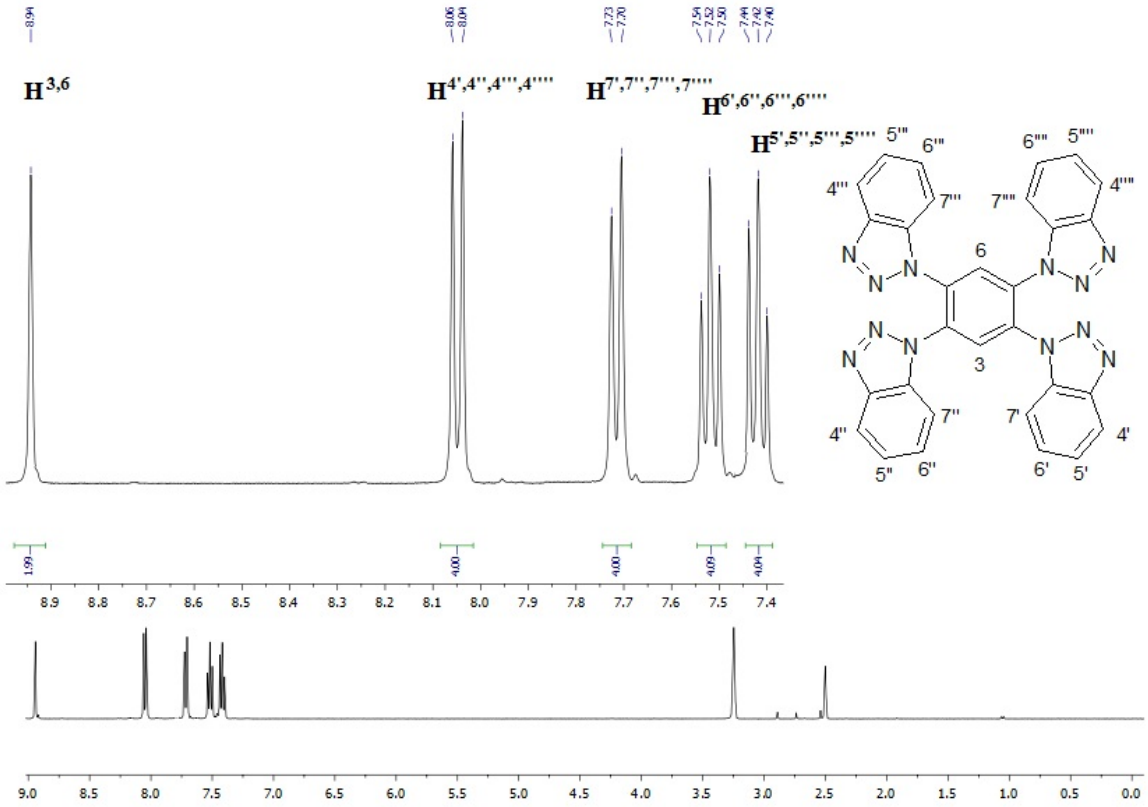


Fig. 2. [1]H NMR spectrum of 1,2,4,5-tetrakis(1H-benzotriazol-1-yl)benzene(BrukerDRX400, 400 MHz, DMSO-d_6, 303 K)

Experimental part

We determine the melting temperatures by apparatus PolyTherm A with a heating rate of 3 °C/min and do not correct the temperature values. We recorded IR spectra by apparatus «Perkin Elmer Spectrum 65 FT-IR Spectrometer» on a Universal ATR Sampling Accessory using Attenuation Total Reflection method (ATRM). Spectrum recording conditions: Band 4000-600 cm^{-1}, resolution 4 cm^{-1}, 32 scans. We recorded NMR spectra by «Bruker DRX-400» for DMSO-d_6 solutions at 30 °C. The signals of the residual solvent protons in ^1H NMR (δ_H 2.50 m.p.) were used as a reference for the chemical shift readout. Mass spectra were recorded by «FINNIGAN MAT.INCOS 50» chromato-mass spectrometer at an ionisation voltage of 70 eV and an ionisation chamber temperature of 100–220 °C. The authors obtained the high resolution mass spectra by «Bruker micrOTOF II» (Bruker Daltonics), Electrospray Ionisation (ESI), mass scanning range (*m/z* 50) 3000 Da, syringe injection. Solvent MeCN or MeOH, solution flow rate 3 μl/min. Interface temperature 180 °C, atomiser gas is nitrogen (4.0 l/min).

Methodology for the synthesis of compounds 3 a,b. The researchers added solution of 2.09 g (17.7 mmol) benzimidazole or 2.11 g (17.7 mmol) benzotriazole in 20 mL DMFA to 2.93 g (21.2 mmol) anhydrous K_2CO_3 and 1.00 g (4.22 mmol) of reagent 1, stirred 4 h at 110 °C, cooled and poured into water. After they filtered the precipitate off, washed several times with water, dried in the desiccator and recrystallised from 2-propanol-DMFA.

1,2,4,5-tetrakis(benzimidazolyl)benzene (3a). Yield: 91%. m.p. = 350–353 °C. Spectrum ^1H NMR (DMSO-d_6, δ, m.d., *J*/Hz): 7.09 (*t*, 4H, H, *J* 7.6 Hz, $H^{5',5'',5''',5''''}$), 7.15 (*t*, 4H, H, *J* 7.0 Hz, $H^{6',6'',6''',6''''}$); 7.34 (d, 4H, $H^{7',7'',7''',7''''}$, *J* 8.0 Hz); 7.57 (d, 4H, $H^{4',4'',4''',4''''}$, *J* 7.7 Hz), 8.38 (s, 4H, $H^{2',2'',2''',2''''}$),. 8.53 (s, 2H, $H^{3,6}$), MS, *m/z* (I_{ratio}, %): 541 (100) [M^+]. IR (ATRM) ν/$см^{-1}$: 3029 (Ar), 1611 (Ar), 1529 (Ar), 1490 (Ar), 1464 (Ar), 1229 (Ar). HRMS: *m/z* calculated $C_{34}H_{23}N_8^+$ 543.2046 $[M+H]^+$, found: 543.2031.

1,2,4,5-tetrakis(1H-benzotriazol-1-yl)benzene (3b). Yield: 93%. m.p. = 309–313 °C. Spectrum ^1H NMR (DMSO-d_6, δ, m.d., *J*/Hz): 7.42 (*t*, 4H, *J* 7.5 Hz); 7.52 (*t*, 4H, *J* 7.6 Hz); 7.72 (d, 4H, *J* 8.3 Hz); 8.05 (d, 4H, *J* 8.3 Hz); 8.94 (s, 2H, $H^{3,6}$). IR (ATRM) ν/$см^{-1}$: 3091, 3058, 1606, 1493, 1450, 1282, 999, 768, 748. HRMS: *m/z* calculated $C_{30}H_{19}N_{12}^+$ 547.1856 $[M+H]^+$, found: 547.1839.

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