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Dedicated to the memory of Professor G.I. Koldobskii

Vinyltetrazoles: I. Synthesis of NH-Unsubstituted 5-Vinyltetrazole

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Abstract—The NH-unsubstituted 5-vinyltetrazole was obtained in 55% yield by exhaustive methylation of 5-(β-dimethylaminoethyl)tetrazole with dimethyl sulfate at the terminal dimethylamino group with the subsequent elimination of a proton from the α-CH_2 group and Hofmann β-cleavage of the intermediate 5-(β-trimethylammoniumethyl)tetrazolide methyl sulfate. The microwave irradiation was shown to reduce 5-fold the time of the synthesis of the initial substrate, 5-(β-dimethylaminoethyl)tetrazole.

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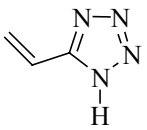
NH-Unsubstituted 5-vinyltetrazole (**I**) and its alkyl derivatives, e.g., **II** and **III**, have a considerable practical interest as substrates for preparation of polymers with a high nitrogen content, poly(vinyl-5-yltetrazoles) [1]. These polymers and materials based thereon are required by to-day medicine and engineering [2]. The poly(vinyl-5-yltetrazoles) can underlie the filter materials for the purification of the biological fluids from heavy metal ions and radionuclides [3], superabsorbents of moisture [4], efficient energy-rich materials [5].

Up till now only few chemical reactions of NH-unsubstituted 5-vinyltetrazole (**I**) are known at the endocyclic nitrogen atoms. Arnold and Thatcher showed that the acylation of 5-vinyltetrazole (**I**) with acetic anhydride followed by the thermolysis of the intermediate N-acyl derivative occurring with elimination of a nitrogen molecule led to the formation of 2-methyl-5-vinyl-1,3,4-oxadiazole [6]. The reaction of 5-vinyltetrazoles **I–III** with $PdCl_2$ resulted in the formation of coordination compounds of the general formula PdL_2Cl_2 [7]. On replacing in these processes palladium chloride with $CuCl_2$ or $NiCl_2$ the arising coordination compounds do not contain chlorine in their composition. Therefore Kizhnyaev and Kruglova [7] suggest that here the ligand is the corresponding anionic form 5-vinyltetrazolide. In [8] the rate constants were measured of tetrazole **I** alkylation with methyl iodide in acetonitrile in the presence of triethylamine, and the ratio was established of isomeric reaction products, 1- (**II**) and 2-methyl-5-vinyltetrazoles (**III**). The reactions involving the vinyl group of tetrazole **I** save the polymerization processes [1] are virtually unknown notwithstanding the obvious possibility to obtain in this way new promising compounds. The development of research in this field of the tetrazole chemistry is hampered by the limited availability of the initial compound, NH-unsubstituted 5-vinyltetrazole (**I**). Evidently the development of an efficient procedure of the synthesis of NH-unsubstituted 5-vinyltetrazole (**I**) is an urgent task.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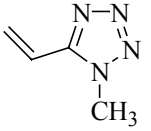
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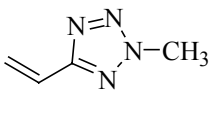

III

The most wide-spread preparation method for NH-unsubstituted 5-R-tetrazoles is the 1,3-dipolar cycloaddition of azides to nitriles. Recently versatile versions of this process were developed permitting the preparation of various 5-R-tetrazoles (R = Alk, Ar, Ht) in good yield and under relatively mild conditions [3]. However the only example of the synthesis of NH-unsubstituted 5-vinyltetrazole (**I**) directly from acrylonitrile was reported

in [6]. Arnold and Thatcher described the synthesis of NH-unsubstituted 5-vinyltetrazole (**I**) in 55% yield by the reaction of $Al(N_3)_3$ with acrylonitrile in dry THF under a nitrogen atmosphere. This method did not become extensively used for the sufficient conversion of reagents required a long (24 h) heating of the reagents in THF [6]. The use of the inert gas did not prevent the polymerization processes under the fairly severe conditions of the synthesis [9]. The potential hazards in the handling of aluminum azide, fairly sensitive to the mechanical action initiating explosive, should also be taken into consideration [10]. Our attempts at the preparation of NH-unsubstituted 5-vinyltetrazole (**I**) directly from acrylonitrile applying virtually all known now versions of the 1,3-dipolar cycloaddition of azides to nitriles, including the popular now method developed by Sharpless et al. [11] also were unsuccessful. The use of efficient polymerization inhibitors, like ionol, and the performance of the process in the atmosphere of an inert gas failed to prevent the formation of polymeric products. Therefore we focused on the alternative methode of introducing the vinyl substituent into the position *5* of the tetrazole ring.

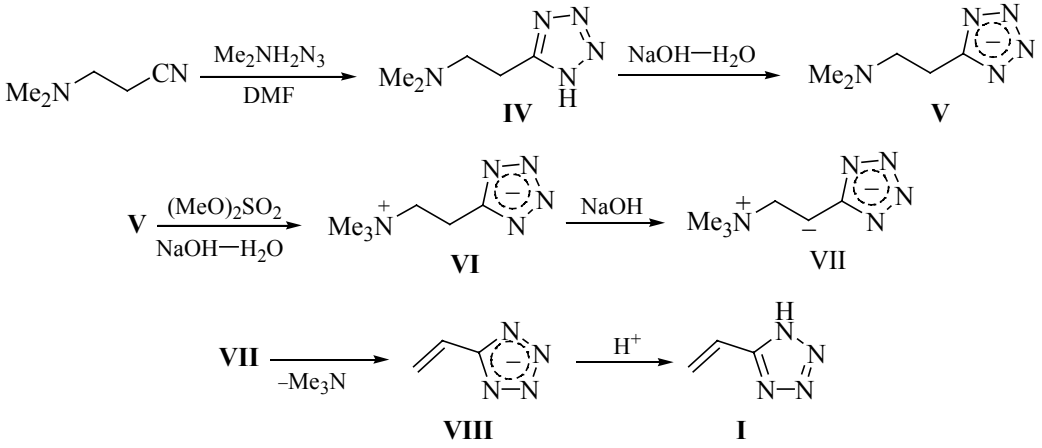
In the paper [6] of Arnold and Thatcher the "alternative " version of the preparation of 5-vinyltetrazole (**I**) was described involving the synthesis of an intermediate 5-(2-chloroethyl)tetrazole by the reaction of 3-chloropropionitrile with $Al(N_3)_3$ followed by the dehydrochlorination of the exocyclic substituent in the position *5* of the tetrazole ring. However the stage of the dehydrochlorination also proceeded with difficulties and resulted in a low yield of the target product. The later attempts at "simplifying" the dehydrochlorination of the 5-(2-chloroethyl)tetrazole by varying the temperature, solvent, adding the polymerization inhibitor [12] did not fundamentally improved the version reported in [6]. Another approach to the sysnthesis of derivatives of 5-vinyltetrazole (**I**) was developed in [13]. Here the results were presented on the study of the kinetics and mechanism of Hofmann deamination of isomeric *N*-methyl-5-(β-trimethylammoniumethyl) tetrazoles methylsulfates leading to the formation of the corresponding *N*-methyl-5-vinyltetrazoles **II** and **III**. Partially applying the method described in [13] we developed a new procedure of the synthesis of NH-unsubstituted 5-vinyltetrazole (**I**). This method is based on the synthesis of 5-(β-dimethyl-aminoethyl)tetrazole (**IV**) and its subsequent methylation at the terminal dimethylamino group. As a result of the selective alkylation 5-(β-trimethylammoniumethyl)-tetrazolide (**VI**) was formed which further suffered the β-elimination of trimethylamine (Hofmann deamination) to transform into NH-unsubstituted 5-vinyltetrazole (**I**). Note that in this reaction it is fundamentally important to carry out the alkylation of the initial tetrazole **IV** in such way as to exclude the formation of the side products of alkylation at the endocyclic nitrogen atoms (see the scheme).

5-(β-Dimethylaminoethyl)tetrazole (**IV**) was prepared as previously published in [14], by the 1,3-dipolar cycloaddition of dimethylammonium azide to β-dimethylaminopropionitrile. This method is simple in performing, relatively safe, and the necessary reagents are fairly available. However the overall time for the completion of the synthesis of 5-(β-dimethylaminoethyl)-tetrazole (**IV**) is long, 18 h. To reduce the reaction time we intensified the process by microwave irradiation. Note that the microwave activation is more and more used in the processes of 1,3-dipolar cycloaddition, in particular, in those resulting in the formation of NH-unsubstituted 5-R-tetrazoles [3, 15–17]. In this study we observed a significant promotion effect: The application of the microwave irradiation additionally to the common convection heating 5-fold reduced the reaction time (to 3 h).

According to the deamination mechanism [13] the conversion of 5-(β-trimethylammonium)tetrazolide (**VI**) into NH-unsubstituted 5-vinyltetrazole (**I**) requires a proton elimination from the methylene group in the α-position to the tetrazole ring of the bipolar ion **VI** (see the scheme). The formed anion **VII** suffers Hofmann β-elimination of trimethylamine and transforms into 5-vinyltetrazolide (**VIII**). The proton addition to the endocyclic nitrogen atom of tetrazolide **VIII** results in the formation of NH-unsubstituted 5-vinyltetrazole (**I**).

Evidently the fundamentally important condition for the successful proceeding of their reaction sequence is the correct choice of the pH of the reaction solution. We based on several considerations in selecting the pH. Firstly, during the methylation with dimethyl sulfate the terminal dimethylamino group should exist in a "free" state. Only under this condition the selective exhaustive alkylation should occur giving tetrazolide **VI**. In keeping with the known [14] indices of the acidity constants in water of the tetrazole ring of compound **IV** (pK_a 3.39) and the basicity constant of the terminal dimethylamino group (pK_{BH^+} 9.39) it is presumable that in the course of alkylation the pH >10.5 should be maintained. Secondly, the important condition of the selective exhaustive alkylation is the reagents ratio. We showed that for the selective alkylation the equimolar ratio of the reagents, tetrazole **IV**

Scheme.



and dimethyl sulfate, should be used. The exess alkylating agent (compared to the equimolar amount) resulted (according to HPLC) to the undesired formation of alkylation products at the endocyclic nireogen atoms, *N*-methyl-5-vinyltetrazoles **II** and **III**. Interestingly in this case, as show the HPLC data, first appears the chromatographic peak corresponding to 1-methyl-5-vinyltetrazole (**II**), and only after some time of the reaction, the peak corresponding to 2-methyl-5-vinyltetrazole (**III**). This fact does not contradict the mechanism discussed in [13]: According to the latter, the rate of the formation of tetrazole **II** from the 1-methyl-5-(β-trimethylammoniumethyl)tetrazole is significantly (21-fold) faster than the formation of tetrazole **III**. Finally, in keeping the suggestions of [13], for the elimination of the proton from the α-methylene group of the bipolar ion **VI** (see the scheme) in the reaction solution the pH ≥ 13 should be maintained.

Taking into account all the mentioned conditions we conserved the pH 13–14 throughout the total process of the synthesis up to the formation of tetrazolide **VII** (see the scheme). According to HPLC data, the conversion of tetrazole **IV** of 86% was reached already in 3 h after the start of the reaction.

Thus the method we developed makes it possible to obtain NH-unsubstituted 5-vinyltetrazole (**I**) in a plausible yield and a high content of the target substance from relatively available and safe in handling reagents.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker DPX-300 at operating frequencies 300.1 and 75.5 MHz respectively from solutions in DMSO-d_6 using as internal references the signals of the residual protons (δ 2.5 ppm) and carbon atoms (δ 39.5 ppm) of the solvent. The reactions were carried out with the microwave heating in a laboratory installation MLS ETHOS P/N 44072 at constant irradiation (60 W) and constant control of the internal temperature. The chromatographic analyses were carried out using a liquid chromatograph Shimadzu LC-10Avp equipped with a UV detector, column 250 × 4.6 mm with an inverse phase Supelko C^{18}, particles size 5 μm, temperature control of the column at 30°C, eluent acetonitrile–0.1% H_3PO_4, 1:9, analytical wavelengths 200 and 218 nm by the procedure described in [8]. The control of pH of water solutions was performed on a device Cyber-Scan pH-510/Ion-510. Mass spectra were measured on a liquid chromatograph-mass spectrometer Waters LCT Premier (ESI, TOF). IR spectra were recorded on a spectrophotometer Shimadzu FTIR 8400 from pellets with KBr. Elemental analysis was carried out on an analyzer LECO CHNS(O) 932. The homogeneity of compounds obtained was proved by TLC on Merck Kieselgel 60F245 plates, spots visualization under UV irradiation (λ 254 nm) or in iodine vapor.

5-(β-Dimethylaminoethyl)tetrazole (IV). To a solution of 12.6 g (154 mmol) of dimethylamine hydrochloride in 40 ml of DMF was added at stirring 10.0 g (154 mmol) of sodium azide. The dispersion obtained was heated at 40–50°C over 2 h. On cooling the precipitate of sodium chloride was filtered off. To the filtrate was added at stirring 15.1 ml (134 mmol) of β-dimethylaminopropionitrile. The heating of the reaction mixture was performed in two ways:

(a) Convection heating. The reaction mixture was

heated at 110°C while stirring and kept for 18 h.

(b) Microwave heating. The reaction mixture was placed into the reactor of the microwave installation and was heated at 110°C (60 W) while stirring over 3 h.

The reaction mixture was first cooled to the room temperature, then to 0°C. The precipitate was filtered off and washed with acetone (3×20 ml). Yield 12.7 g (67%), colorless crystals, mp 196°C (*a*), 197°C (*b*). IR spectrum, ν, cm^{-1}: 2900, 3030 (C–H, stretch.), 1340 m (C–H, bend.), 1510, 1380, 1250, 1110, 1080, 1060 (tetrazole ring). ^1H NMR spectrum (D_2O), δ, ppm: 2.86 s (6H, NMe_2), 3.23 t (2H, $C^{\beta}H_2$, *J* 7.3 Hz), 3.47 t (2H, $C^{\alpha}H_2$). ^{13}C NMR spectrum, δ, ppm: 20.33 ($C^{\alpha}H_2$), 42.78 (NMe_2), 55.96 ($C^{\beta}H_2$), 158.48 (CN_4). Mass spectrum: *m/z* 142.110 $[M + H]^+$. Found, %: C 42.4; H 7.67; N 49.93. $C_5H_{11}N_5$. Calculated, %: C 42.54; H 7.85; N 49.61. *M* 141.1743.

1*H*-5-Vinyltetrazole (I). To a solution of 10 g (70 mmol) of 5-(β-dimethylaminoethyl)tetrazole (**IV**) in 70 ml of water was added at stirring and cooling 5.7 g (141 mmol) of NaOH. The solution obtained (pH ≈ 14) was stirred for 15 min at 20°C, then was added dropwise 9.9 g (78 mmol) of freshly distilled dimethyl sulfate. The solution obtained was heated at 50–60°C and stirred for 3.5 h. On completion of the reaction the solution was cooled to 5°C and 0.1 g of ionol (polymerization inhibitor) was added, then dropwise was added 10% hydrochloric acid till pH ≈ 2. The solution obtained was extracted with ethyl acetate (7×30 ml), the combined extract was dried with anhydrous Na_2SO_4, the solvent was removed in a vacuum. The residue was crystallized from chloroform. Yield 3.7 g (55%) colorless crystals, mp 125°C. IR spectrum, ν, cm^{-1}: 2318–3116 (N–H), 1647 (C=C), 1558, 1458, 1372, 1296, 1122, 1053 (tetrazole ring). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 5.93 d (1H, CH_2=CH, *J* 10.8 Hz), 6.54 d (1H, CH_2=CH, *J* 17.7 Hz), 6.86 d.d (1H, CH_2=CH, *J* 10.8, *J* 17.7 Hz), 16.3 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 119.55 (CH_2), 125.7 (CH), 154.43 (CN_4),. Mass spectrum: *m/z* 97.0500 $[M + H]^+$. Found, %: C 37.59; H 4.21; N 58.20. $C_3H_4N_4$. Calculated, %: C 37.50; H 4.20; N 58.31. *M* 96.0907.

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