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Dedicated to Full Member of the Russian Academy of Sciences O.N. Chupakhin on his 80th anniversary

Vinyltetrazoles: IV.* Microwave Activation of Metal-Catalyzed Arylation of *C*- and *N*-Vinyltetrazoles

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Abstract—Microwave-assisted Heck arylation of *C*- and *N*-vinyltetrazoles has been accomplished for the first time. Microwave irradiation has been shown to considerably promote the arylation of tetrazoles.

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Tetrazole (a five-membered aromatic nitrogen-containing heterocycle) and its derivatives are used in various fields of human activities, including defense and space engineering, fire-fighting systems, medicine, electronics, etc. [2]. A specific place in this series of heterocyclic compounds is occupied by vinyltetrazoles. The presence in their molecules of a vinyl group activated by the heterocycle underlies their use as monomers for the preparation of high-molecular-weight polynitrogen compounds, poly(vinyltetrazoles). Poly(vinyltetrazoles) are promising as components of actuating media of highly efficient gas generators, polymer base of binders for fuels, blasting powders, and energy-rich composite materials, flocculants, ion-exchange resins, catalysts, super moisture adsorbents, and immobilizers for various media. Vinyltetrazoles are also important as intermediate products in total syntheses of biologically active compounds [2, 3].

In recent time, much attention has been given to styryltetrazoles [1–3]. It is known that styryl derivatives of tetrazole exhibit antibacterial and antiallergic properties [4]. Styryltetrazoles constitute a series of promising monomers whose polymerization could give rise to unique high-molecular-weight products and materials.

However, particular practical applications of styryltetrazoles are restrained due to their relatively low accessibility. General disadvantages of the existing methods for the synthesis of vinyl-substituted tetrazoles include the use of toxic and explosive reagents, low yields of intermediate and target products, low concentration of the main substance in the products, side polymerization processes, and hence unsatisfactory reproducibility of the results [1–3]. In view of the above stated, development of efficient procedures for the synthesis of styryltetrazoles is a topical problem.

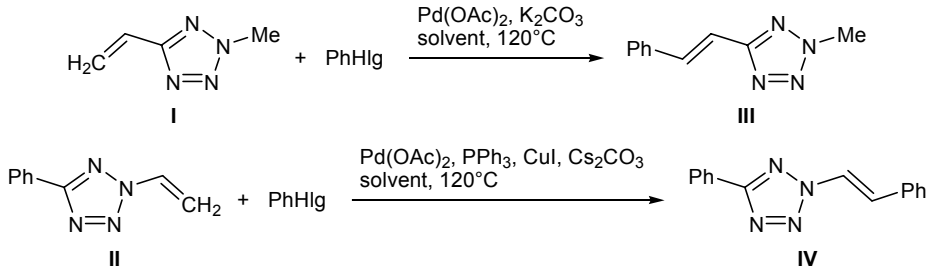
We previously reported on the synthesis of *C*- and *N*-styryltetrazoles via metal-catalyzed arylation of *C*- and *N*-vinyltetrazoles according to Heck [1]. Despite essential advantages of the proposed procedure, the complete conversion of initial vinyltetrazoles required a fairly long reaction time, up to 20 h. Obviously, an important problem in the chemistry of styryltetrazoles is minimization of time consumption for the Heck arylation of vinyltetrazoles. Successful solution of this problem should reduce the probability of spontaneous uncontrolled polymerization of styryltetrazoles.

In recent time, microwave (MW) activation has been widely used to accelerate various chemical processes [5–7]. Examples of tetrazole synthesis under microwave irradiation have also been reported [8–10]. There are published data on pronounced promoting effect of MW radiation on reactions catalyzed by palladium and other metal salts, including Heck arylation of alkenes [11–13]. We anticipated that microwave activation should considerably reduce the reaction time in the synthesis of *C*- and *N*-styryltetrazoles.

For this purpose, we tried to obtain *C*- and *N*-styryltetrazoles by Heck arylation under conditions

* For communication III, see [1].

Scheme 1.



of microwave irradiation. As substrates we selected 2-methyl-5-vinyltetrazole (**I**) and 5-phenyl-2-vinyltetrazole (**II**). As arylating agents we used aryl halides: iodobenzene, bromobenzene, and chlorobenzene (Scheme 1). In order to estimate the effect of MW radiation on the Heck arylation of vinyltetrazoles **I** and **II**, we used the same reagents as those indicated in [1]. In particular, the arylation of 2-methyl-5-vinyltetrazole (**I**) was carried out in the presence of $Pd(OAc)_2$ as catalyst and K_2CO_3 as base. In the arylation of 5-phenyl-2-vinyltetrazole (**II**), the combination of the catalyst, ligand, and base was more complex: $Pd(OAc)_2$, CuI, PPh_3, and Cs_2SO_3. In both cases, the choice of catalyst and reactants was substantiated in [1].

An important factor in experiments with MW radiation is proper choice of the solvent [13]. For the MW-assisted Heck arylation of vinyltetrazoles **I** and **II** we selected DMSO, DMF, and 1,4-dioxane. These solvents are frequently used in cross coupling reactions [12, 14] and are characterized by different abilities to absorb MW radiation [15]. The results are presented in Tables 1 and 2. The obtained data show that the strongest promoting effect of MW radiation is observed in the metal-catalyzed arylation of *C*-vinyltetrazole **I**. Analogous effect in the reaction with *N*-vinyltetrazole **II** is appreciably weaker, which may be rationalized by possible coordination of the tetrazole ring to the catalyst [1].

We can conclude that the use of MW activation in the synthesis of styryltetrazoles **III** and **IV** may be regarded as advisable due to considerable shortening of the reaction time as compared to traditional conditions and high yields and acceptable purity of the target products. The MW-assisted arylation of vinyltetrazoles with iodobenzene in DMSO at 120°C ensures preparation of styryltetrazoles **III** and **IV** with the best yields in a few minutes.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer at 300.1 and 75.5 MHz, respectively, using $CDCl_3$ as solvent and reference ($CHCl_3$, δ 7.26 ppm; $CDCl_3$, δ_C 77.16 ppm). The mass spectra were obtained on a Waters LCT Premier LC/MS system (ESI, TOF) with positive ion detection. The melting points were measured on a PTP melting point apparatus at a heating rate of 1 deg/min near the melting point. The properties of tetrazoles **I**–**IV** were in agreement with published data [1, 16].

All reactions were carried out under argon. The conversion of vinyltetrazoles and accumulation of the

Table 1. Heck arylation of 2-methyl-5-vinyltetrazole (**I**) under convection heating and microwave irradiation

Solvent	PhHlg	Convection heating		Microwave irradiation		
		time, h	yield, %	time, min	power, W	yield, %
DMF	PhI	40 min	80	5	60	77
	PhBr	1.5	80	10	75	82
	PhCl	10	–	60	72	–
DMSO	PhI	30 min	85	2	55	81
	PhBr	1	81	2	55	82
	PhCl	10	–	60	60	–
1,4-Dioxane	PhI	15	–	60	62	–
	PhBr	15	–	60	63	–
	PhCl	15	–	60	62	–

Table 2. Heck arylation of 5-phenyl-2-vinyltetrazole **II** under convection heating and microwave irradiation

Solvent	PhHlg	Convection heating		Microwave irradiation		
		time, h	yield, %	time, min	power, W	yield, %
DMF	PhI	2.5	80	7	70	79
	PhBr	9	82	20	74	80
	PhCl	10	–	60	72	–
DMSO	PhI	2	78	5	60	75
	PhBr	4.5	80	10	61	78
	PhCl	10	–	60	60	–
1,4-Dioxane	PhI	15	–	60	62	–
	PhBr	15	–	60	59	–
	PhCl	15	–	60	62	–

arylation products were monitored by TLC on Kieselgel $60F_{245}$ plates (Merck); spots were visualized under UV light (λ 254 nm). Microwave-assisted reactions were performed in an MLS ETHOS Milestone laboratory oven under continuous irradiation at a frequency of 2450 MHz (maximum power 1000 W) and continuous monitoring of the reaction temperature. The products were isolated by column chromatography on Silica Gel 60 (0.063–0.200 μm, Merck).

2-Methyl-5-[2-(*E*)-phenylethenyl]tetrazole (III). Phenyl halide, 9.0 mmol, was dissolved in 2 mL of appropriate solvent, 0.072 mmol of $Pd(OAc)_2$ was added, and the mixture was heated under stirring to 50°C and kept for 20 min at that temperature. Vinyltetrazole **I**, 1.8 mmol, and potassium carbonate, 3.6 mmol, were added to the solution, and the mixture was heated in two ways.

a. *Convection heating*. The mixture was heated under stirring to 120°C.

b. *Microwave heating*. The mixture was placed into the microwave furnace and was heated under stirring to 120°C.

The mixture was heated for a time necessary to complete the reaction.

In all cases, the mixture was then cooled to 20°C and poured into 20 mL of water under vigorous stirring, the resulting suspension was filtered through celite, the precipitate was washed with water (2× 5 mL), and the filtrate was combined with the washings and extracted with ethyl acetate (3×10 mL). The combined extracts were dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel, followed by recrystallization from ethanol. Colorless crystals, mp 87–88°C, R_f 0.4 (hexane–CH_2Cl_2–EtOAc, 7:2.5:0.5). ^{1}H NMR spectrum, δ, ppm: 4.36 s (3H, CH_3), 7.14 d (1H, C**H**=CHPh, J = 16.5 Hz), 7.34–7.42 m (3H, Ph), 7.54–7.58 m (2H, Ph), 7.73 d (1H, CH=C**H**Ph, J = 16.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 39.48 (CH_3), 113.46 (**C**H=CHPh); 127.23, 128.93, 129.14, 135.75 (Ph); 136.37 (CH=**C**HPh), 164.46 (C^5). Found: m/z 187.0921 [M + H]$^+$. $C_{10}H_{10}N_4$. Calculated: M 186.2132.

2-[2-(*E*)-Phenylethenyl]-5-phenyltetrazole (IV). Copper(I) iodide, 1.8 mmol, and vinyltetrazole **II**, 1.8 mmol, were dispersed in 2 mL of appropriate solvent, 0.072 mmol of $Pd(OAc)_2$, 0.21 mmol of PPh_3, 9.0 mmol of PhHlg, and 2.7 mmol of Cs_2CO_3 were added, and the subsequent procedure was the same as above. Colorless crystals, mp 113–114°C, R_f 0.2 (hexane–EtOAc, 8:2). ^{1}H NMR spectrum, δ, ppm: 7.26–7.56 m (8H, C_6H_5), 7.69 d (1H, C**H**=CHN, J = 14.5 Hz), 7.99 d (1H, CH=C**H**N, J = 14.5 Hz), 8.21–8.23 m (2H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 122.53 (**C**H=CHN), 124.95 (CH=**C**HN); 127.13, 127.23, 127.33, 129.10, 129.24, 129.31, 130.77, 133.20 (C_6H_5); 164.96 (C^5). Found: m/z 249.2121 [M + H]$^+$. $C_{15}H_{12}N_4$. Calculated: M 248.2825.

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