

Synthesis of 5-phenyltetrazole and its N-methyl Derivatives in a Microreactor

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Azidation of benzonitrile with dimethylammonium azide yielding 5-phenyltetrazole dimethylammonium salt was performed under microreactor conditions. The kinetics of azidation of benzonitrile in DMF was investigated at the range 80–95 °C. The reaction rate constants were determined: $k^{\text{II}} \cdot 10^4$ (L mol⁻¹ s⁻¹): 0.79, 0.97, 1.19, 1.51, at 80, 85, 90, and 95 °C, respectively. It was found that the reaction rate constants obtained in a microreactor are comparable to ones for a batch-type reactor. The thermodynamic parameters of azidation under the microreactor conditions correspond to the mechanism of the 1,3-dipolar cycloaddition of azides to nitriles. It was established that the excessive pressure in the microreactor notably accelerates the process. The alkylation of 5-phenyltetrazole with methyl iodide in microreactor was performed in dichloromethane-aqueous sodium hydroxide system. The accumulation of regioisomers of N1- and N2-methyl-5-phenyltetrazole in the microreactor under the conditions of slug flow of the reaction mixture occurs considerably faster than in the batch-type reactor in the conditions of phase-transfer catalysis.

Key words:

azidation of nitriles, tetrazoles, synthesis, alkylation, rate constants, microreactor

Introduction

The properties of tetrazoles are extreme among other azoles. They possess the highest acidity, the least basicity, the maximum dipole moment, high enthalpy of formation, the highest content of nitrogen at sufficiently high stability of the ring system. The tetrazole derivatives possess a number of valuable properties and are interesting objects for the fundamental research. Tetrazoles have applications in medical chemistry, organic and organometallic synthesis, chemistry of energetic compounds and materials, etc.¹ At the same time, in certain cases the methods of tetrazole synthesis are insufficiently safe and selective. For instance, the traditional procedure of preparation of NH-unsubstituted 5R-tetrazoles, the reaction of hydrazoic acid salts with nitriles, is extremely hazardous and is unsuitable for large-scale synthesis since it requires the use of a large amount of toxic, explosive, expensive reagents and promoters. In this regard, a search for new effective and safe ways for production of tetrazoles is relevant. It has been shown that one of the effective and safe ways to 5R-tetrazoles is the azidation of nitriles under microreactor conditions.² The essential advantages of the microreactors are as follows: compactness; high factors of heat and mass transfer;

developed specific surfaces of phase contact and heat exchange; narrow distribution of the dwell time of the phases in the apparatus and the high selectivity of reactions originating from this fact; easy control of the temperature conditions in the reaction due to the small thermal inertness of the apparatus; high quality of liquid mixing. An important feature of these devices is the exclusively high safety of handling explosive materials due to the small cross-diameter of the micro(milli)channels not exceeding 2–3 mm (and in some cases reaching 10–20 μm), essentially decreasing the hazard of detonation spreading in the reaction volume.³

To the disadvantages of microreactors belong: 1) smaller productivity compared with the usual macro scaled reactors used in bulk chemistry; 2) some problems with clogging; 3) microreactors are hardly ever applicable for the processing of suspensions; 4) high pressure drop for very viscous liquid flows; 5) the proper distribution of fluid is complicated for microstructured (multi-channel) microreactors; 6) there are some restrictions for the planar technologies of microreactor plates fabrication.

Nevertheless, microreactors are quite attractive technology, especially for production of small amounts, where the safety and high precision of reaction conditions (pressure, temperature) are necessary.

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Materials and methods

Azidation of benzonitrile in microreactor conditions

Palde *et al.* described the synthesis of a series of 5R-tetrazoles in a flow microreactor.² The azidation of nitriles was performed with NaN_3 in the presence of ZnBr_2 in the system N-methylpyrrolidone – water at 190 °C. It was demonstrated that under the conditions of the continuous-flow microreactor, the 5R-tetrazoles could be obtained in high yields at the materially equimolar ratio of the reagents nitrile – azide (1.0:1.05). The advantage of this method was its safety due to the insignificant accumulation in the system of the hydrazoic acid and the rapid course of the reaction (20–30 min).² Yet it should be noted that no quantitative study of the kinetics of nitriles azidation under microreactor conditions was carried out. However, such data would give an objective evaluation of the effect on the reaction rate produced by the construction features of the reactor, as well as allow a conclusion on the mechanism of the studied processes. In this connection, we investigated the azidation kinetics in the microreactor and compared the reaction rate constants obtained with the known data derived from the azidation in the batch reactor. We have chosen benzonitrile as the model compound, whose azidation kinetics with dimethylammonium azide in the batch reactor have been thoroughly investigated earlier.⁴

The azidation of benzonitrile affording 5-phenyltetrazolate occurs in conformity to scheme (Fig. 1).

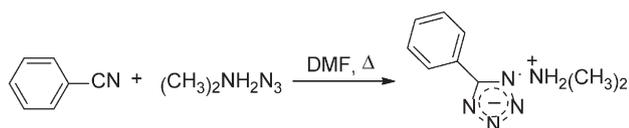


Fig. 1 – Scheme of benzonitrile azidation

The experimental microreactor installation (Fig. 2) is a pipe **1** of polytetrafluorethylene with internal diameter 1000 μm , and 13 m long immersed into a thermostat **2** at controlled temperature and pressure. The temperature was controlled in the thermostat assuming that the mixing within of the microreactor tube was high enough to provide an even temperature distribution. The pressure in the microreactor for the benzonitrile azidation was set at 3 barg and was controlled by means of piezoelectric pressure gauge AIR-20 M/2 (Russia). The flow of the reaction mixture in the channel was performed using a peristaltic pump **3** of 3 mL min^{-1} output. The sampling was carried out through the T-shaped element **4**.

The kinetics of this reaction in the microreactor was investigated under conditions of the pseu-

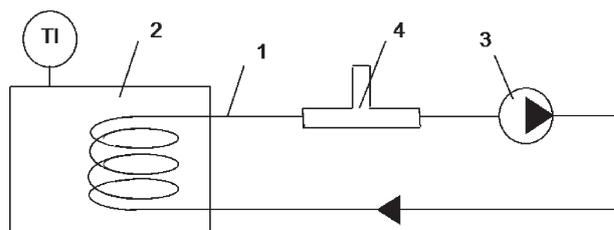


Fig. 2 – Scheme of microreactor: 1 – PTFE tube; 2 – thermostat; 3 – peristaltic pump; 4 – T-shaped element

do-first-order with respect to the substrate in DMF at 80–95 °C. The azidating agent, dimethylammonium azide, was taken in a ten-fold excess with respect to the substrate. It was shown formerly that the dimethylammonium azide at the concentration in the solution of 0.1 mol L^{-1} entered the reaction with nitriles in the form of a complex with a hydrogen bond $(\text{CH}_2)_2\text{NH}_2^+\cdots\text{N}_3^-$ capable to behave as a 1,3-dipole.⁵

The reaction progress was monitored by gas-liquid chromatography following the consumption of the initial reagent, benzonitrile. Chromatographic studies in the course of benzonitrile azidation were carried out on a gas chromatograph Shimadzu GC – 17A equipped with a flame-ionization detector and a capillary column Phenomenex Zebron ZB-5 (30 m · 0.25 mm · 0.5 μm). Chromatography parameters were as follows: carrier gas helium (1.5–1.8 $\text{cm}^3 \text{min}^{-1}$), split ratio at the input of the column 1:5, the probe volume 1 μL , vaporizer temperature 200 °C, detector temperature 200 °C, oven temperature 100 °C, analysis duration 5 minutes. The HPLC analyses were performed on a chromatograph Shimadzu LC10-AVP, chromatographic column Waters C-18 (4.6 × 250 mm, 5 μm). The measurements were carried out at 30 °C. The UV spectra were recorded on a spectrophotometer Shimadzu UV 2401-PC.

A sample of precise weight of the substrate (benzonitrile) was placed in a volumetric flask (10 mL) and into the flask was added a solution of a known concentration of dimethylammonium azide in DMF. Then the solution was charged into the reactor preheated to the temperature of the experiment. As the starting point of the reaction, the time was regarded when the installation reached the stationary temperature regime. At definite intervals (15–30 minutes) sampling of the reaction mixture was performed with a syringe. The sample of a precise volume was placed into a volumetric flask and diluted with ethanol to quench the reaction. The obtained ethanol solution was introduced by a micro-syringe into the injector of the gas chromatograph. The nitrile concentration was calculated from the chromatographic peak area by the method of absolute calibration.

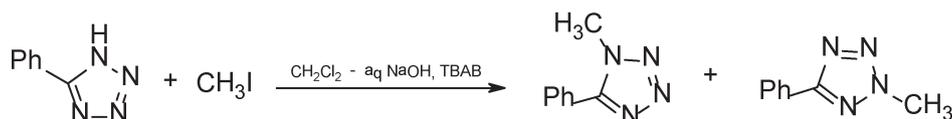


Fig. 3 – Scheme of 5-phenyltetrazole methylation

Alkylation of 5-phenyltetrazole under the microreactor conditions

Versatile N-substituted tetrazoles, in particular, a number of practically important compounds, can be obtained by alkylation of NH-unsubstituted tetrazoles.⁶ The alkylation of NH-5R-tetrazoles is usually carried out in water or organic solvents in the presence of a base and phase-transfer catalysts. Haloalkanes, esters of sulfuric acid, aromatic sulfonic acids, acetates of nitroaminoalcohols or compounds containing activated multiple bonds are used as alkylating agents.¹ It should be noted that these reactions require the use of expensive reagents and toxic solvents. In this regard, the search for a new effective and safe way for production of tetrazoles is relevant. In our opinion, one of the solutions to the problem is to produce N-substituted tetrazoles in microreactors.

In this work, alkylation of 5-phenyltetrazole was carried out by methyl iodide in a heterophase system: dichloromethane – NaOH (aq.). Alkylation of 5-phenyltetrazole by methyl iodide proceeds according to scheme (Fig. 3). Concentration of phase transfer catalyst (where it has been used) was 0.02 mol L⁻¹.

Experimental procedure used in this work was according to experimental technique described in the paper⁶ and not presented here in details due to paper's size limitation.

The alkylation of 5-phenyltetrazole with methyl iodide was carried out in a glass microreactor ($d = 1500 \mu\text{m}$, $L = 2 \text{ m}$) at 24 °C without adding of TBAB. Charged into the reactor through a mixer was a solution of 5-phenyltetrazole in NaOH (aq.) (0.14 mol L⁻¹) and a solution of methyl iodide in dichloromethane (0.154 mol L⁻¹). In the microreactor, the slug flow was operated for improved mixing of the two-phase system. The pressure in the microreactor was nearly atmospheric for the alkylation's process because the inner volume of microreactor was connected with the environmental air and the pressure drop according to our theoretical estimation was not higher than 0.2 barg. After desired time intervals (15–120 minutes) the reaction mixture was poured into a special vessel, after the separation of layers a precise weight of the organic phase (0.5 g) was placed into a volumetric flask of 5 mL, and the content of the flask was diluted with acetonitrile. From the volumetric flask with the working solution the sample was injected into the chromatograph

injection system with a micro-syringe of 50 μL (the volume of the dosing loop of the probe admission was 20 μL).

The benzonitrile was purified by double distillation in a vacuum. Dimethylammonium azide was prepared from dimethylamine hydrochloride and sodium azide in DMF by a known procedure.⁵ 5-Phenyltetrazole was obtained from benzonitrile and dimethylammonium azide in DMF by a known method and possessed the characteristics consistent with the published data.^{5,14}

Results and discussion

Azidation of benzonitrile in microreactor conditions

The plots of benzonitrile concentration in time are curves characteristic of the features of first-order reactions (Fig. 4).

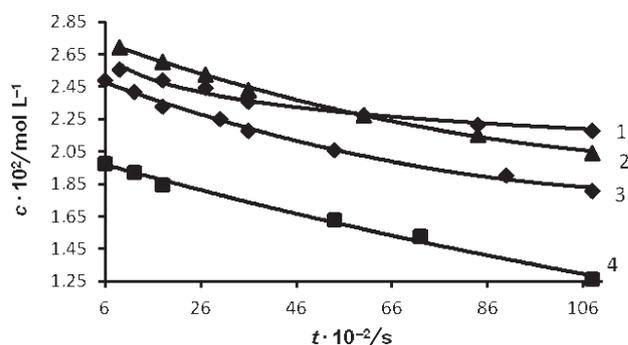


Fig. 4 – Time dependence of the benzonitrile concentration in the reaction mixture at temperature, °C: 1 – 80, 2 – 85, 3 – 90, 4 – 95

The experimental kinetic data are presented as straight lines in semi-log coordinates (Fig. 5). The rate constants of the pseudo-first-order reactions (k^I) were calculated by an integral method utilizing the semi-log plots of the kinetic data.⁷ From the slope of the linear dependences of k^I on the concentration of dimethylammonium azide we evaluated the rate constants of the second-order reaction $k^{II} \cdot 10^4$, which attained (L mol⁻¹ s⁻¹): 0.79, 0.97, 1.19, 1.51, at 80, 85, 90, and 95 °C, respectively. Comparing the obtained values of the rate constants of the second-order reaction with the known data on benzonitrile azidation in conditions of a batch chemical reactor ($k^{II} \cdot 10^4$ (L mol⁻¹ s⁻¹): 0.3, 0.8, 1.5,

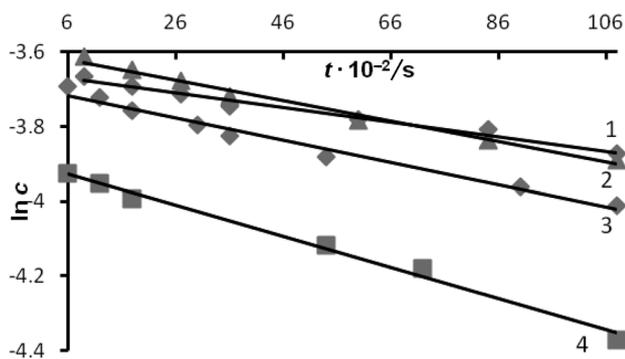


Fig. 5 – Semi-log plots of kinetic data at temperature, °C: 1 – 80, 2 – 85, 3 – 90, 4 – 95

3.5, at 70, 80, 90, and 100 °C, respectively}, it was possible to conclude that for this reaction in the batch reactor and microreactor, the reaction rates were nearly the same.⁴

Based on the data obtained, the activation parameters of benzonitrile azidation were calculated according to Arrhenius-Eyring (Table 1).⁸

Table 1 – Activation parameters of azidation of benzonitrile with dimethylammonium azide in DMF

| Activation parameter | Microreactor | Batch reactor |
|---|--------------|---------------|
| $\Delta H_{298}^{\ddagger}$, kJ mol ⁻¹ | 44 | 80 |
| $\Delta S_{298}^{\ddagger}$, J mol ⁻¹ K ⁻¹ | -201 | -101 |

The low enthalpy value and low negative value of the activation entropy indicate that the limiting stage of the reaction is bimolecular. The obtained values of the activation parameters are characteristic of reactions proceeding along 1,3-dipolar addition mechanism, same as the azidation under common conditions.⁴ Therefore, it is possible to conclude that the reaction mechanism in the batch reactor and microreactor has not fundamentally changed.

It should be noted, however, that the activation entropy of the processes proceeding in the microreactor is somewhat smaller than this activation parameter of the azidation under conditions of batch reactor (Table 1). This apparently indicates the lower accuracy in the measuring rate constants in the microreactor. The results obtained here (Table 1) does not contradict to the values typical for the 1,3-dipolar addition mechanism [1].

For the batch reactor there has been a huge amount experiments performed allowing us to minimize the data scattering. For the microreactor setup we have just 3 experimental points for each temperature, and therefore the spreading was higher. Besides, sampling for the microreactor conditions is not so easy due to smaller size of the capillary

(compared to the sizes of the batch reactor flask), locally nonstationary flow (the concentration of product varies slightly during sampling process).

In this paper we would like to demonstrate the opportunity and the preferences of processing the highly-explosive reagents by means of microreactors. We intend to refine the experimental data and publish them in the next contribution.

The next stage of the investigation consisted of the study of the pressure effect on the rate of benzonitrile azidation. In the microreactor contour, the temperature was set at 85 °C and pressure at 3 barg. Evaluation of the rate constant of the second order along the procedure described above gave the value $k'' 2.11 \cdot 10^4 \text{ L mol}^{-1} \text{ s}^{-1}$ indicating a significant acceleration of the azidation under the elevated pressure. This fact requires additional interpretation which will be performed within our next paper.

Alkylation of 5-phenyltetrazole under the microreactor conditions

The reaction was carried out in the batch reactor at different modes of mixing in the presence of a phase transfer catalyst, tetrabutylammonium bromide (TBAB, 0.02 mol L⁻¹), or without it, and in the custom-made glass microreactor under slug (Taylor) flow. The developed interface was reached in the batch reactor by means of high shear stresses generated by high-speed stator-rotor type emulsifier (atomizer) IKA ULTRA-TURRAX Package T18. Monitoring of reagents conversion and determination of selectivity were carried out by HPLC with UV detection.

It was found that in the batch reactor the formation of regioisomeric 1-methyl- and 2-methyl-5-phenyltetrazoles occurs both in the presence or absence of a phase transfer catalyst. However, in the presence of TBAB, the accumulation of alkylation products is much faster (20 times) than in its absence.

It is known that the rate of diffusion-controlled processes is greatly affected by mixing. In the next step, we carried out the alkylation of 5-phenyltetrazole in microreactor under slug flow.

In the case of using a heterophase liquid-liquid system, the slug flow is a flow where one liquid phase is moving in the form of elongated slugs separated by the liquid droplets of another phase. The special feature of this mode is an efficient mixing within the slug owing to Taylor vortices (Fig. 6).

We compared the data obtained in the alkylation of 5-phenyltetrazole in batch reactor in the presence of a phase transfer catalyst and the same data obtained in the microreactor in a slug flow regime (at flow rate of 11.5 mL min⁻¹) of the reaction liquid without phase transfer catalyst.¹⁰ The accu-

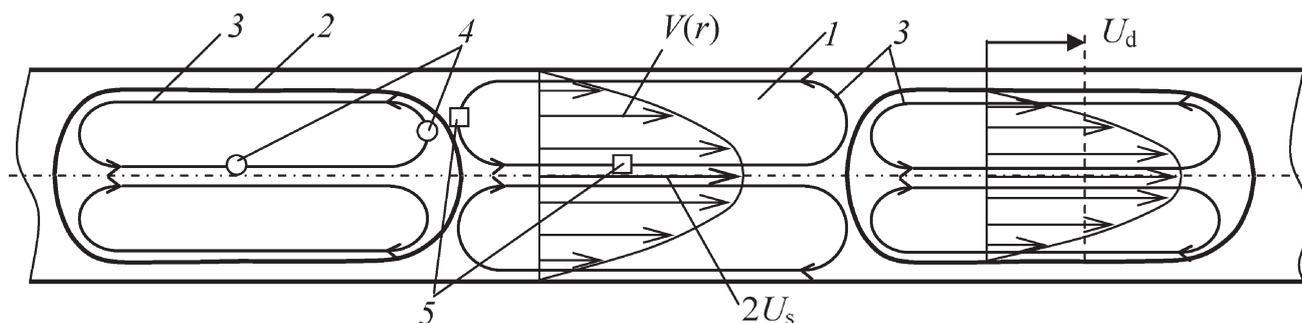


Fig. 6 – Schematic of mass transfer intensification of Taylor flow in microreactor: 1 – slug of continuous phase; 2 – droplet of dispersed phase; 3 – Taylor vortices; 4, 5 – reacting volumes involved in convectational mass transfer. U_d , U_s – average velocities of droplet and liquid slug; $V(r)$ – velocity profile in liquid slug of continuous phase.

mulation of alkylation products of 5-phenyltetrazole by methyl iodide under the Taylor regime in a microreactor is much faster than in a batch reactor even in the presence of a phase transfer catalyst in the latter case (Fig. 7).

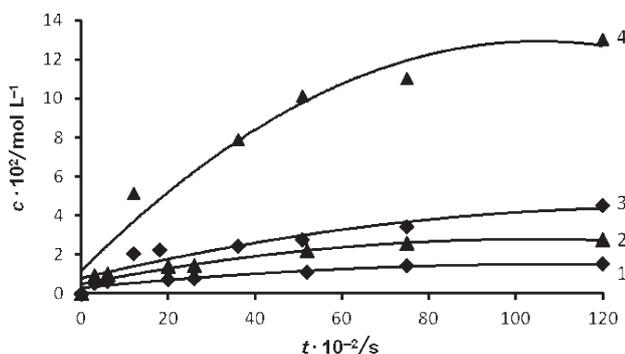


Fig. 7 – Dependence of the concentration of 2-methyl-5-phenyltetrazole (1, 3) and 1-methyl-5-phenyltetrazole (2, 4) on time: 1, 2 – in a batch reactor with TBAB; 3, 4 – in a microreactor without TBAB

The reason for the increase in alkylation products accumulation is toroidal streamlines of Taylor vortices, the shape of which is depicted in Fig. 6. The circles and squares in Fig. 6 correspond to the micro-volumes of liquid (containing molecules of methyl iodide and 5-phenyltetrazole) moving with velocities up to 0.2 m s^{-1} along closed streamlines. Due to frequent contacting of reacting mediums on the phase interface and frequent renovation of the latter apparent reaction rate limited with mass transfer is intensified in microreactor. The role of convectational mass transfer is also well pronounced by Peclet number, which value has an order of $3 \cdot 10^5$.

For realization of mass transfer intensification by use of Taylor vortices it is necessary (1) to build up the droplets with appropriate length (from one side the droplets with length less than double diameter of capillary are unstable, and from the other side the longer the droplets the lower the frequency of contacting reacting mediums and therefore the

slower the circulation time);¹¹ (2) to guarantee the reverse flow within both droplets of dispersed phase and liquid slugs of continuous phase (see Fig. 6). The latter condition is feasible for horizontal micro-channels at capillary number $Ca < 0.7$ and for vertical micro-channels or with an arbitrary angle to the horizon the more general criterion was found.^{12,13} Hence, organizing of proper flow conditions is a very important part of microreactor technologies, especially for two or more phase reactions.

For embodiment of all conditions described above, an experimental setup was constructed which contained two peristaltic pumps (Heidolph), a home-made glass Y-shaped micro dispergator-mixer, connected directly with loop-type microreactor. At the other end of microreactor, a double-step phase separator was mounted in order to separate both liquid phases, and occasionally involved in the process, air/vapor bubbles whose presence might disturb hydrodynamic behavior of the two-phase system.

Conclusion

The data obtained leads us to conclude that microreactors could be used for the safe synthesis of NH-unsubstituted and N-substituted 5R-tetrazoles. However, this method requires further optimization. Taking into account the fast development of the microreactor methods in chemical engineering, this approach may become an alternative to the traditional methods of tetrazole synthesis both in the laboratory and in small-scale production.⁹

Future perspectives of this research work are as follows: 1) other diffusion limited reactions with either explosive reagents or products will be tested in the microreactor conditions; 2) we intend to find a theoretical approach which allows explaining more precisely the mechanism of reaction rate acceleration even without phase transfer catalyst.

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