Alternative pathways of the reaction between acetophenone and triethyl orthoformate

M. A. Kovaleva, A. I. Kovalev, and I. A. Khotina*

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28/1 ul. Vavilova, 119334 Moscow, Russian Federation. Fax: +7 (499) 135 6549. E-mail: alivkov7@yandex.ru

Using the condensation of acetophenone under the action of triethyl orthoformate as an example, the effect of ratios of solvents ($CH(OEt)_3$ and toluene) and the starting reactants on the composition and yields of aromatic products was studied. After treatment of reaction mixtures with ammonia, 1,3,5-triphenylbenzene, *m*-terphenyl, and 2,6-diphenylpyridine were isolated.

Key words: condensation, acetophenone, triethyl orthoformate, 1,3,5-triphenylbenzene, *m*-terphenyl, 2,6-diphenylpyridine.

The preparation of nitrogen-containing microporous polymers necessary for the manufacture of electrodes for electrochemical current sources is an urgent task at present.[1—5] Previously, we obtained microporous polyphenylenes by trimerization cyclocondensation of di- or triacetyl aromatic compounds.[6—13] The reaction was carried out in an aromatic solvent in the presence of triethyl orthoformate $CH(OEt)_3$ (TEOF) and gaseous hydrogen chloride. It is known[14] that the reactions of monoacetyl aromatic compounds with an excess of TEOF in the presence of an acid catalyst taken in molar amounts give pyrylium salts, which are easily converted under the action of ammonia into the corresponding pyridine derivatives.[15—16] In this regard, it was of interest to determine the optimal conditions for the synthesis of a polyphenylenepyrylium salt and its subsequent transformation into polyphenylenepyridine, a nitrogen-containing polymer.

In this work, using the example of a model condensation of monoacetyl arene, namely, acetophenone (**1**), in the presence of TEOF and gaseous hydrogen chloride, we studied the effect of reaction conditions on the composition and ratio of the resulting products containing aromatic polymer-forming fragments (Scheme 1). The variable parameter was the ratio of toluene and TEOF, with the latter in most cases acting both as a reagent and a solvent. The starting concentration of acetophenone (C = 0.4 mol L^{-1}) in the reaction solution was the same as the starting concentration of a diacetyl arene in the reaction of obtaining a highly porous polymer. To estimate, in the first approximation, the duration of polymer-forming reactions, the time of the synthesis was limited to 6 h, *i.e.*, the reactions were interrupted before they were completed. Then the reaction mixtures were treated with ammonia. As it turned out, along with the expected 1,3,5-triphenylbenzene (**2**) (see Scheme 1), *m*-terphenyl (**3**) was present among the reaction products. Diphenylpyrylium salt (**4**), which was formed during the reaction, was transformed into 2,6-diphenylpyridine (**5**) upon treatment of the reaction solution with ammonia.

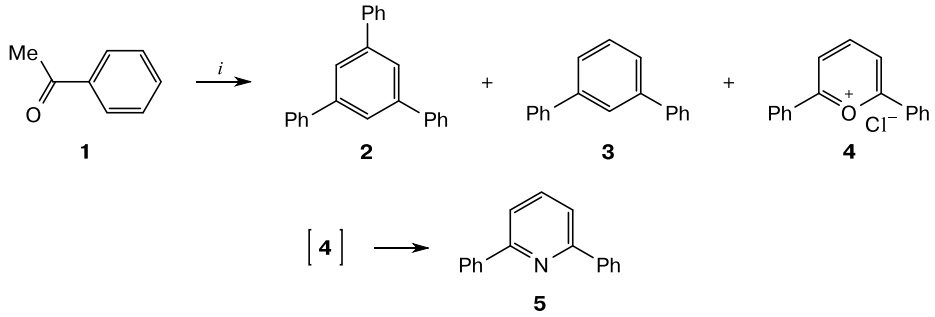
The synthesis conditions and the ratio and yields of the products are given in Table 1. When the reaction was carried out at low concentration of TEOF (runs *1* and *2*), the main product was compound **2**. In run *1*, its yield was very low, indicating the necessity of the use of TEOF at least in an equimolar ratio to acetophenone **1** (run *2*) to increase the yield of compound **2**.

With an increase in the proportion of TEOF in the solvent mixture, the proportion of hydrocarbon **2** among the reaction products decreased, whereas the proportion of pyridine derivative **5** sharply grew and reached to almost 90%. This happened when using a small amount of toluene or in the absence of toluene (runs *6* and *7*). The fact that different products are formed under seemingly similar conditions

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* Vol. 72, No. 5, pp. 1186—1191, May, 2023.

1066-5285/23/7205-1186 © 2023 Springer Science+Business Media LLC

Scheme 1



Reagents and conditions: *i*. 1) $HC(OEt)_3$, toluene, HCl, 20 °C, 6 h; 2) NH_3, $CHCl_3$, 20 °C, 65 h.

can be explained by proceeding of the reaction according to different mechanisms.

Initially, diethoxycarbonium cation (**A**) is formed under the action of an acid catalyst on TEOF (Scheme 2). In a non-polar solvent, ketone **1** predominantly exists in the keto form, which determines the following mechanism leading to the formation of compound **2**. Under these conditions, diethoxycarbonium cation **A**, which has strong alkylation ability, carries out *O*-ethylation of molecule **1**, converting it into carbocation **B**, which can reversibly be transformed into α-ethoxystyrene (**C**). Then, intermediate **B** is added to the methylene group of vinyl ether **C**, which is polarized due to the presence of the oxygen atom at the double bond. The ethanol elimination from the product results in the formation of a more stable carbocation stabilized by conjugation. The subsequent addition of another molecule **C** affords the trimeric carbocation, which forms an intermediate complex after the loss of an ethanol

Scheme 2

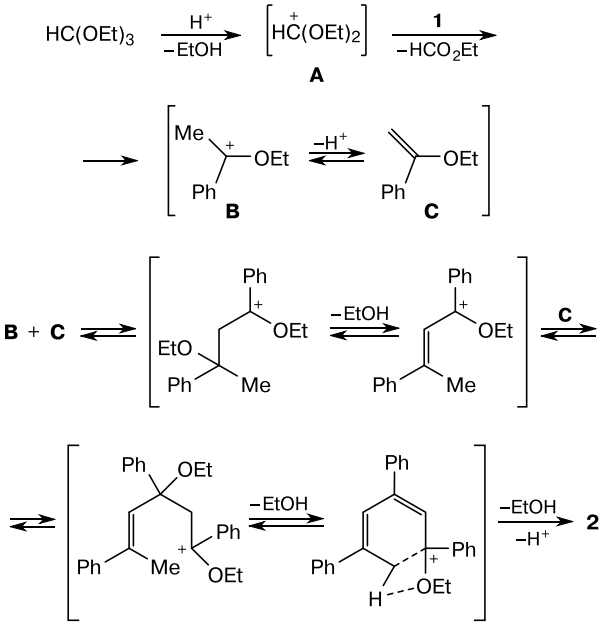


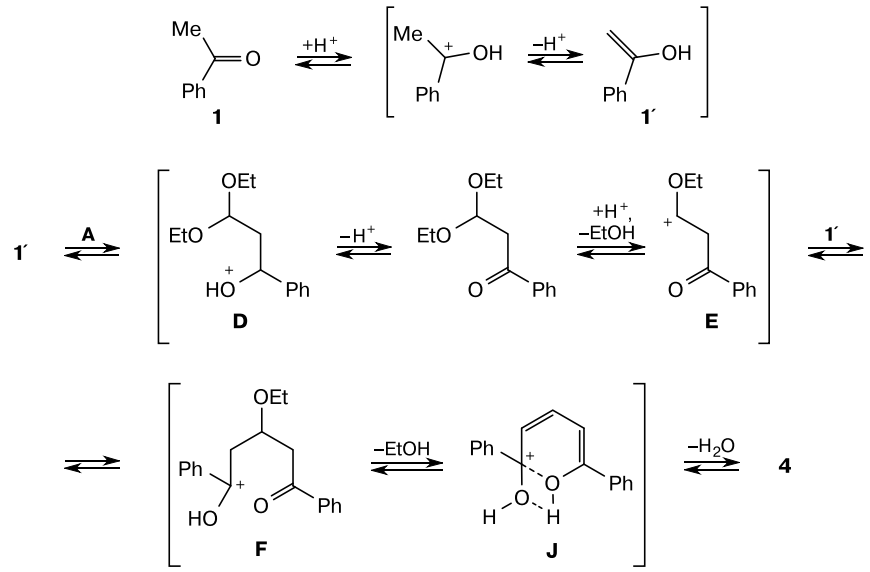
Table 1. Dependence of yield and molar ratio of reaction products on synthesis conditions[a]

Run	Molar ratio TEOF : **1**	TEOF content in initial mixture of solvents (TEOF—toluene) (%)	Yield of products Y (%)[b]			Mole fraction of products x (%)[b]		
			2	**3**	**5**	**2**	**3**	**5**
1	0.6 : 1	4	8.8	0	0	100	0	0
2	1.2 : 1	8	56.9	2.6	0	94.9	5.1	0
3	2.4 : 1	17	57.5	7.1	6.5	77.3	9.6	13.1
4	3.6 : 1	25	17.2	8.4	15.2	35.5	17.5	47.0
5	7.2 : 1	50	5.4	6.6	24.0	11.2	13.8	75.0
6	10.8 : 1	75	2.4	4.9	37.7	3.7	7.8	88.5
7	14.4 : 1	100	2.1	6.6	52.1	2.4	7.7	89.9

[a] Conditions: 1) Acetophenone (**1**) 1.2 mL (10 mmol), solvent (TEOF—toluene) 24 mL, HCl (gas), 6 h; 2) NH_3, 65 h.

[b] Calculated data, see Experimental.

Scheme 3



molecule. The latter is transformed into arene **2**, losing a proton and one more ethanol molecule.

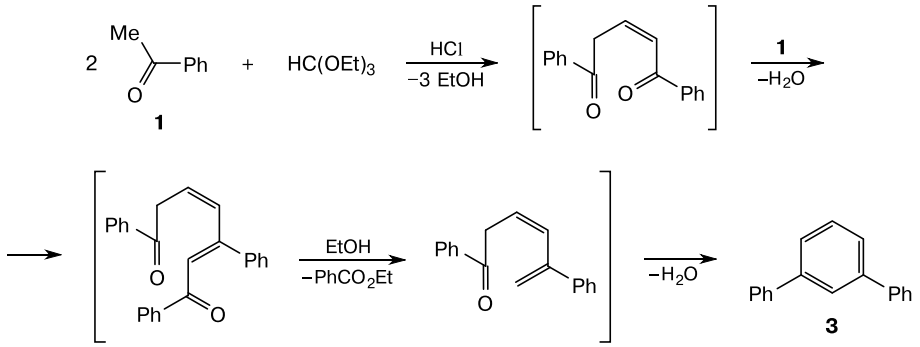
The presence of an acid catalyst, especially in molar amounts, intensifies the process of keto-enol tautomerism (Scheme 3). When the reaction is carried out in a medium consisting mainly or only of TEOF (see Table 1, runs *6* and *7*), the enol form (**1′**) of ketone is stabilized by hydrogen bonds with TEOF molecules. Therefore, under these conditions, TEOF reacts with the enol form **1′** of the ketone, which finally results in the formation of the pyrylium salt (see Scheme 3). Enol **1′** reacts with diethoxycarbonium cation **A**, producing carbocation **D**. The latter is transformed into another carbocation **E** in two steps. Carbocation **E** in its turn reacts with another molecule of enol **1′**. Resulting carbocation **F** eliminates an ethanol molecule with the formation of an intermediate complex (**J**), which eventually turns into pyrylium salt **4**.

The maximum proportion of terphenyl **3** among the reaction products was at a TEOF content of 25% in the initial mixture of solvents. The formation of compound **3** includes several steps in an arbitrary sequence. One of the possible pathways is represented in Scheme 4.

Triethyl orthoformate reacts with two molecules of ketone **1** with the formation of an unsaturated diketone, which reacts with one more molecule of ketone **1.** The resulting diketone dissociates to ethyl benzoate and dienone. The latter undergoes the cyclization to terphenyl **3**.

When the proportion of TEOF in the solvent mixture is 25% or more (see Table 1, runs *4*—*7*), compound **5** is the predominant reaction product.

Scheme 4



This fact makes it possible to expect that polyphenylenepyridines with a high nitrogen content can be obtained under similar conditions.

Experimental

Acetophenone (**1**) before use was purified by distillation in argon, collecting a fraction with b.p. 201—202 °C. Triethyl orthoformate, $CH(OEt)_3$, was distilled over potassium carbonate, collecting a fraction with b.p. 143—145 °C. Toluene was distilled in argon under sodium, collecting a fraction with b.p. 109—110 °C.

^{1}H NMR spectra were recorded on a Bruker Avance-400 spectrometer (400.13 MHz) in $CDCl_3$. Chemical shifts are given relative to the residual solvent signal. Preparative chromatographic separation of products was carried out on columns filled with Silica gel 70—230 mesh, 60 Å (Merck, Germany). Chloroform was used as an eluent.

1,3,5-Triphenylbenzene (2). ^{1}H NMR ($CDCl_3$), δ: 7.43 (t, 3 H, Ph, J = 7.2 Hz); 7.52 (t, 6 H, Ph, J = 7.4 Hz); 7.74 (d, 6 H, Ph, J = 7.6 Hz); 7.83 (s, 3 H, C_6H_3). These spectral data are close to the reported ones.[17]

2,6-Diphenylpyridine (5). ^{1}H NMR ($CDCl_3$), δ: 7.50—7.63 (m, 6 H, Ph); 7.74 (d, 2 H, C_5H_3N, J = 7.2 Hz); 7.83 (t, 1 H, C_5H_3N, J = 6.6 Hz); 8.27 (d, 4 H, Ph, J = 7.2 Hz).*

***m*-Terphenyl (3).** A comparison of the ^{1}H NMR spectrum of the corresponding fraction (Fig. 1) with literature data[11,18,19] made it possible to suppose that this fraction consisted of compounds **2** and **3**. The ^{1}H NMR spectrum of a mixture of triphenylbenzene **2** and commertially available *m*-terphenyl **3** in a ratio of 1 : 2.5 (by weight) was identical with the spectrum shown in Fig. 1.

Synthesis procedure. Hydrogen chloride was bubbled through a solution of acetophenone (1.2 mL, 0.01 mol) in a mixture of $CH(OEt)_3$ and toluene (see Table 1) under stirring at room temperature for 6 h. Then, the reaction mixture was added to a saturated ammonia solution in chloroform (200 mL) under stirring. Vapors over the resulting suspension showed an alkaline reaction in accordance with a test using indicator paper. The mixture was kept in a closed flask for 65 h. The precipitated salt was filtered off and washed with chloroform. The filtrate was evaporated under reduced pressure. Diphenylpyridine **5** (R_f –0.8) and a mixture of compounds **2** and **3** (R_f –0.9) were obtained by chromatographic separation of products. Since hydrocarbons **2** and **3** are difficult to separate chromatographically, the molar ratio and weights of the products were calculated using ^{1}H NMR spectra (see Fig. 1), based on the ratio of the integral intensities of the signals for the *ortho* protons of the phenyl groups with respect to those of the central benzene ring. Signals for other protons overlapped and thus were uninformative.

Calculation of the molar ratio and weights of products based on spectral data. The doublet for the *ortho* phenyl protons relative to the central benzene ring of arene **2** was observed at δ 7.74 (see Fig. 1). The number of these protons is 6; $p/6$ is the integral intensity per one proton for the signal at δ 7.74. The doublet for the *ortho* phenyl protons relative to the central benzene ring of arene **3** was observed at δ 7.69. The number of these protons is 4; $r/4$ is the integral intensity per one proton for the signal at δ 7.69. Therefore, $(p/6) : (r/4)$ is the molar ratio of arene **2** and terphenyl **3** in the mixture.

Mole fraction of compound **2** in the mixture (x):

$$x = (p/6)/(p/6 + r/4);$$

Mole fraction of compound **3** in the mixture (y):

$$y = (r/4)/(p/6 + r/4).$$

Calculations of weights of compounds **2** (m_2) and **3** (m_3) in the mixture were carried out by the following formulas:

$$m_2 = (m \cdot x \cdot M_2)/m_{av},\ m_3 = (m \cdot y \cdot M_3)/m_{av},$$

where m was the mixture weight (g), M_2 and M_3 were molecular weights of triphenylbenzene **2** and *m*-terphenyl **3**, respectively, m_{av} was an average molecular weight of the mixture obtained by the formula: $m_{av} = x \cdot M_2 + y \cdot M_3$.

Calculations of theoretical yields of the products with respect to acetophenone were carried out as follows. The number of millimoles of compounds **2** (μ_2), **3** (μ_3), and 2,6-diphenylpyridine **5** (μ_5) was calculated using the formulas:

$$\mu_2 = (m_2/M_2) \cdot 10^3,$$

$$\mu_3 = (m_3/M_3) \cdot 10^3,$$

$$\mu_5 = (m_5/M_5) \cdot 10^3,$$

where m_5 and M_5 were the weight and the molecular weight of pyridine **5**, respectively.

Share theoretical yields of triphenylbenzene **2** and *m*-terphenyl **3** were calculated using the formulas:

$$y_2^{theor} = M_2/(3 \cdot M_1),\ y_3^{theor} = M_3/(3 \cdot M_1),$$

and that of pyridine **5** was calculated by the following equation:

$$y_5^{theor} = M_5/(2 \cdot M_1),$$

where M_1 was the molecular weight of acetophenone **1**.

Theoretical yields (g) of compounds **2**, **3**, and **5** were defined by the equations:

$$Y_2^{theor} = m_1 \cdot y_2^{theor},$$

* https://sdbs.db.aist.go.jp/sdbs/cgi-bin/landingpage?sdbsno=4910.

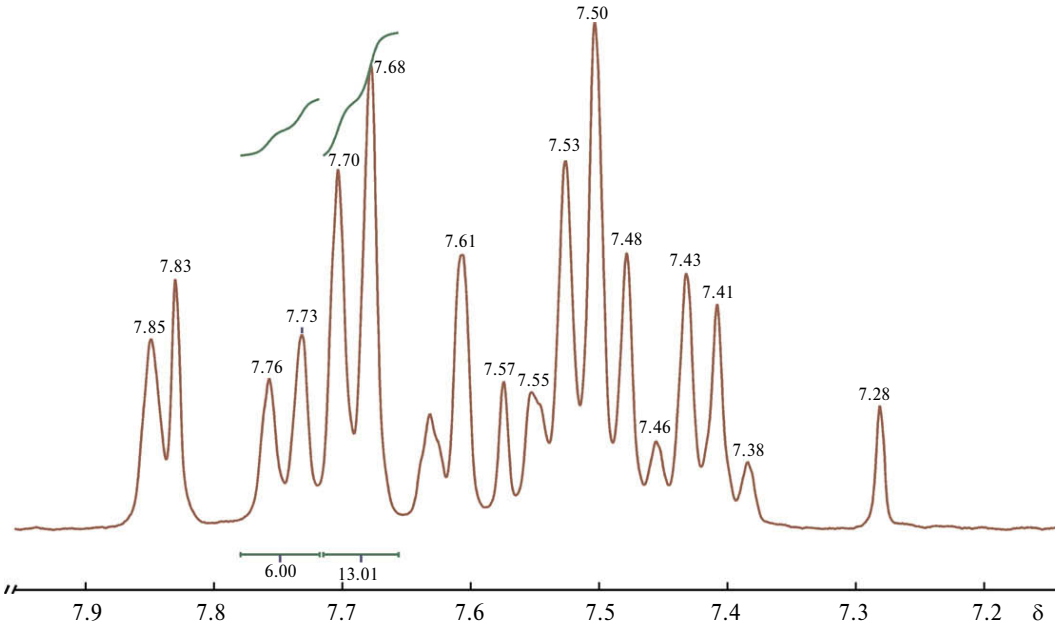


Fig. 1 ^{1}H NMR spectrum of a reaction fraction (see Table 1, run *7*).

$$Y_3^{theor} = m_1 \cdot y_3^{theor},$$

$$Y_5^{theor} = m_1 \cdot y_5^{theor},$$

where m_1 was the weight of acetophenone used in the synthesis (g).

Real yields of the products (%) were calculated using the following formulas:

$$Y_2 = (m_2/Y_2^{theor}) \cdot 100,$$

$$Y_3 = (m_3/Y_3^{theor}) \cdot 100,$$

$$Y_5 = (m_5/Y_5^{theor}) \cdot 100.$$

Molar fractions of products (%) were calculated according to the equations:

$$x_2 = (\mu_2/\Sigma_\mu) \cdot 100,\ x_3 = (\mu_3/\Sigma_\mu) \cdot 100,\ x_5 = (\mu_5/\Sigma_\mu) \cdot 100,$$

where $\Sigma_\mu = \mu_2 + \mu_3 + \mu_5$ was the sum of millimoles of the products.

This work was performed under financial support of the Russian Foundation for Basic Research (Project No. 20-03-00087). The NMR studies were carried out under financial support of Ministry of Science and Higher Education of the Russian Federation with the use of the equipment of the Center for molecule composition studies of INEOS RAS.

No human or animal subjects were used in this research.

The authors declare no competing interests.

References

1. N. Meng, H. Li, Y. Liu, Y. Liao, *Electrochim. Acta*, 2022, **402**, 139531, DOI: 10.1016/j.electacta.2021.139531.
2. M. G. Kotp, S. U. Sharma, J.-T. Lee, A. F. M. EL-Mahdy, S.-W. Kuo, *J. Taiwan Inst. Chem. Eng.*, 2022, **134**, 104310; DOI: 10.1016/j.jtice.2022.104310.
3. X. Liu, J. Du, Y. Ye, Y. Liu, S. Wang, X. Meng, X. Song, Z. Liang, W. Yan, *Chinese J. Chem. Eng.*, 2022, **42**, 64; DOI: 10.1016/j.cjche.2021.09.032.
4. Y. Chen, L. Tong, G. Lin, X. Liu, *Mater. Chem. Phys.*, 2022, **277**, 125433; DOI: 10.1016/j.matchemphys.2021.125433.
5. W. Guo, M. Chen, Y. Zhang, W. Yang, Q. Guo, M. Zh. F. Cheng, *J. Mater. Res.*, 2017, **33**, 1131; DOI: 10.1557/jmr.2017.387.
6. I. A. Khotina, O. A. Filippov, A. I. Kovalev, *Mendeleev Commun.*, 2020, **30**, 366; DOI: 10.1016/j.mencom.2020.05.035.
7. A. I. Kovalev, A. V. Pastukhov, E. S. Tkachenko, Z. S. Klemenkova, I. R. Kuvshinov, I. A. Khotina, *Polym. Sci., Ser. C*, 2020, **62**, 205; DOI: 10.1134/S1811238220020071.
8. A. I. Kovalev, E. S. Mart´yanova, I. A. Khotina, Z. S. Klemenkova, Z. K. Blinnikova, E. V. Volchkova, T. P. Loginova, I. I. Ponomarev, *Polym. Sci., Ser. B*, 2018, **60**, 675; DOI: 10.1134/S156009041805007X.
9. A. I. Kovalev, I. A. Khotina, *Mendeleev Commun.*, 2022, **32**, 244; DOI: 10.1016/j.mencom.2022.03.030.
10. A. I. Kovalev, S. A. Babich, M. A. Kovaleva, N. S. Kushakova, Z. S. Klemenkova, Z. K. Blinnikova,

A. Yu. Popov, I. A. Khotina, *Polym. Sci., Ser. B*, 2022, **64**, 155; DOI: 10.1134/S156009042201002X.
11. R. A. Dvorikova, P. V. Dorovatovski, A. V. Mitrophanova, V. N. Khrustalev, A. I. Kovalev, *Russ. Chem. Bull.*, 2022, **71**, 717; DOI: 10.1007/s11172-022-3471-9.
12. A. I. Kovalev, I. A. Khotina, *Russ. Chem. Bull.*, 2021, **70**, 1994; DOI: 10.1007/s11172-021-3307-z.
13. N. S. Kushakova, A. V. Naumkin, I. B. Suntsova, D. V. Kupriyanova, V. G. Kharitonova, S. A. Babich, A. I. Kovalev, I. A. Khotina, *Russ. Chem. Bull.*, 2020, **69**, 1138; DOI: 10.1007/s11172-020-2880-x.
14. V. V. Mezheritskiy, G. N. Dorofeenko, *Khimiya Getrocikl. Soedinenii* [*Chem. Heterocycl. Compd.*], 1970, 232 (in Russian).
15. G. N. Dorofeenko, S. V. Krivun, *Zh. Obshch. Khimii* [*J. Gen Chem. USSR*], 1964, **34**, 105 (in Russian).
16. V. V. Mezheritskiy, G. N. Dorofeenko, *Khimiya Getrocikl. Soedinenii* [*Chem. Heterocycl. Compd.*], 1970, 236.
17. I. A. Khotina, R. Consonni, N. S. Kushakova, W. Porzio, U. Giovanella, A. I. Kovalev, M. A. Babushkina, A. S. Peregudov, S. Destri, *Eur. Polym. J.*, 2013, **49**, 4224; DOI: 10.1016/j.eurpolymj.2013.10.002.
18. A. I. Kovalev, Yu. I. Lyakhovetskii, M. M. Teplyakov, A. L. Rusanov, P. V. Petrovskii, S. O. Yakushin, *Russ. Chem. Bull.*, 1993, **42**, 1529; DOI: 10.1007/BF00699189.
19. X. Xiao, J. Luo, Z. Gan, W. Jiang, Q. Tang, *R. Soc. Chem. Adv.*, 2020, **10**, 12113; DOI: 10.1039/d0ra00578a.

Received September 28, 2022;
in revised form November 24, 2022;
accepted December 1, 2022