

Theoretical and Experimental Study of the Transformation of 2-Pyridone-5-amide into Nitrile

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Abstract—Molecular and crystal structures of 2,4-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide (**1**), 2,4-dimethyl-6-oxo-1,6-dihydropyridine-3-carbonitrile (**2**), and 2-chloro-4,6-dimethylnicotinonitrile (**3**), which are the products of sequential transformations, are studied by means of single crystal diffraction. The procedure for synthesizing each compound is described. All of the compounds are characterized using IR and ¹H NMR spectra. Possible reaction pathways are simulated using the density functional theory (DFT).

Keywords: pyridone-2, X-ray diffraction, single crystals, ¹H NMR, density functional theory (DFT)

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INTRODUCTION

In this work, the transformation of 2-pyridone-5-amide into nitrile was investigated via X-ray mapping; this required study of the initial materials and the intermediate and final products of multistage reactions by means of diffraction to track changes in the interatomic distances and bond angles. If possible, the intermediates were also investigated. In addition to our structural study, all products were characterized using ¹H NMR spectra. Our first works in this area were published in the late 1990s [1]. This work describes only a small part of the multistage process of obtaining and converting 4,6-dimethyl-5-cyano-2-pyridone.

column chromatography, a white crystalline solid (as needles) was obtained with a yield of 62%.

A similar method was used to obtain chloropyridine (**1**) without transforming the side amide group into a nitrile group. The reaction was conducted in freshly distilled POCl₃ in the presence of triethylbenzylammonium chloride to increase the concentration of Cl⁻ ions. Chloropyridine (**3**), however, was obtained instead of expected reaction product (**4**). The yield was 70%, higher than in two-step synthesis.

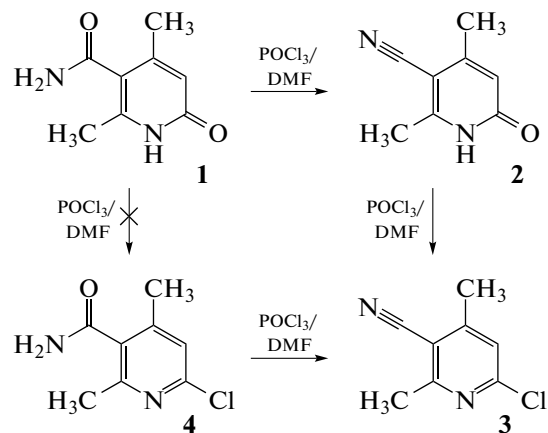
All of the synthesized compounds were characterized by ¹H NMR spectra, X-ray structure analy-

EXPERIMENTAL

Our study is briefly described by Scheme 1.

As is well known, Vilsmeier reagent (DMF/POCl₃) can be used to dehydrate an amide group, converting it into a nitrile group [2]. We transformed the amide group of pyridone (**1**) into a nitrile group (**2**) using this approach. The reaction mixture was refluxed for 5 h yielding a dark brown preparation. The product was isolated via extraction in a Soxhlet apparatus with chloroform. A light yellow product was obtained with a yield of 52%.

The next step was to obtain chloropyridine (**3**). Pyridone (**2**) was added to a mixture of DMF with POCl₃ and refluxed for 5 h. After purification via



Scheme 1.

Table 1. Physicochemical parameters of the test compounds

Compound	¹ H NMR	IR, cm ⁻¹	T _{melt} , °C
1	7.68–7.45 (2H, m, NH ₂); 5.97 (1H, Ph); 2.12 (3H, Me) 2.04 (3H, Me) (DMSO- <i>d</i> ₆)	3349 (amide NH) 1652 (amide CN) 1675 (secondary amide C=O) 1623 (amide C=O) 1374 (amide CN)	268
2	6.12 (1H, Ar); 2.34 (3H, Me); 2.16 (3H, Me) (DMSO- <i>d</i> ₆)	1660 (secondary amide C=O) 2215 (CN)	294
3	7.14 (1H, Ar); 2.72 (3H, Me); 2.50 (3H, Me) (CDCl ₃)	2223 (CN)	62

sis, and melting temperature. The data are presented in Table 1.

To explain the high reactivity of the side amide groups, a possible reaction path was simulated by means of density functional theory (DFT). DFT calculations were performed using GAMESS software [3] with B3LYP exchange-correlation functional [4, 5] and 6-311G basis sets [6], supplemented by diffuse functions for atoms that change their coordination numbers during a reaction or are

involved in hydrogen bonds. The effect of the solvent was considered using the continuum model, and dielectric constant of the medium was assumed to be 78.4.

A 5-amide derivative of pyridone-2 was selected as the reference. According to the calculation results, the reaction between amide groups and POCl₃ proceeds in two stages. In the first stage, in which POCl₃ is attacked, chloride ions cleave to form Cl⁻O₂P(OR)⁺ ion pairs (see Scheme 2 (1–2a) and (1–4)). Activation energies at this stage are virtually identical for the side and cyclic amide groups. In the second step, chloride ions are attacked by carbon atoms bound to oxygen to form PO₂Cl₂⁻. For the cyclic amide group, this stage proceeds as the direct substitution of PO₂Cl₂⁻ groups by chloride ions (4) and is characterized by an activation energy of ~60 kJ/mol. The side amide group is transformed in two stages to form a metastable intermediate compound in which the attacked carbon atom is in the sp³ hybridized state (1–2b). The activation energy of this step is only about 37 kJ/mol (Scheme 2).

The main crystallographic characteristics and individual refinement parameters of the studied structures are presented in Table 2.

The structures were resolved and refined using the SHELX programs [11]. A graphic representation of the studied structures was obtained with the PLATON software [12] (Figs. 1–3).

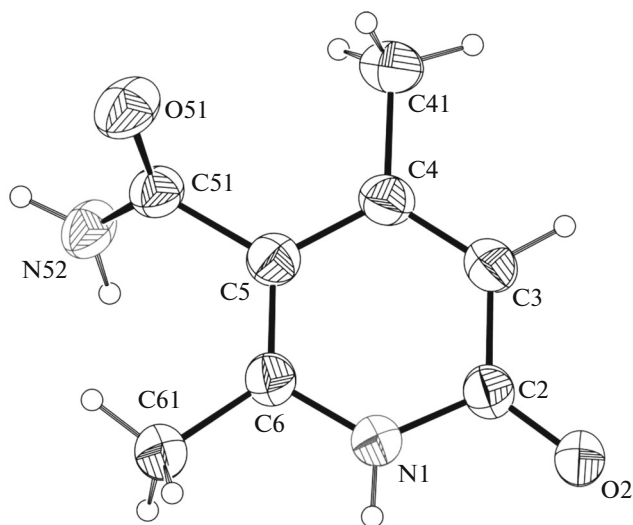


Fig. 1. Structure and numbering scheme for compound 1. Thermal ellipsoids are presented with a probability of 30%. The hydrogen atoms are represented by circles of arbitrary radii.

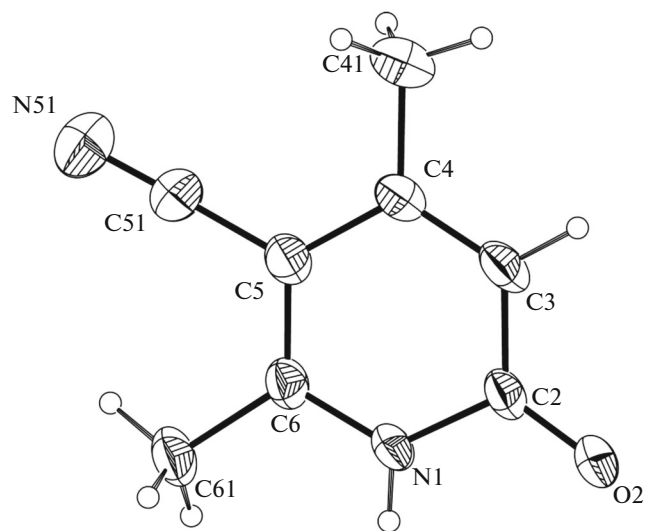
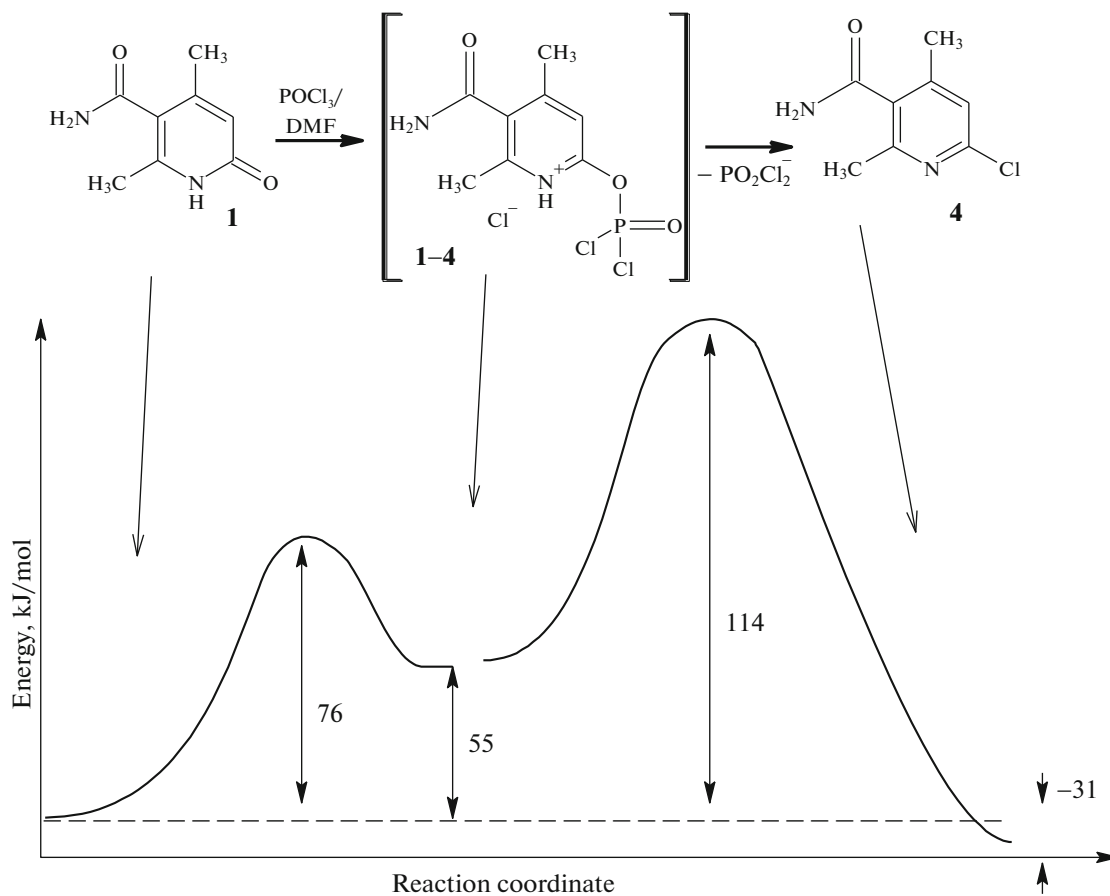
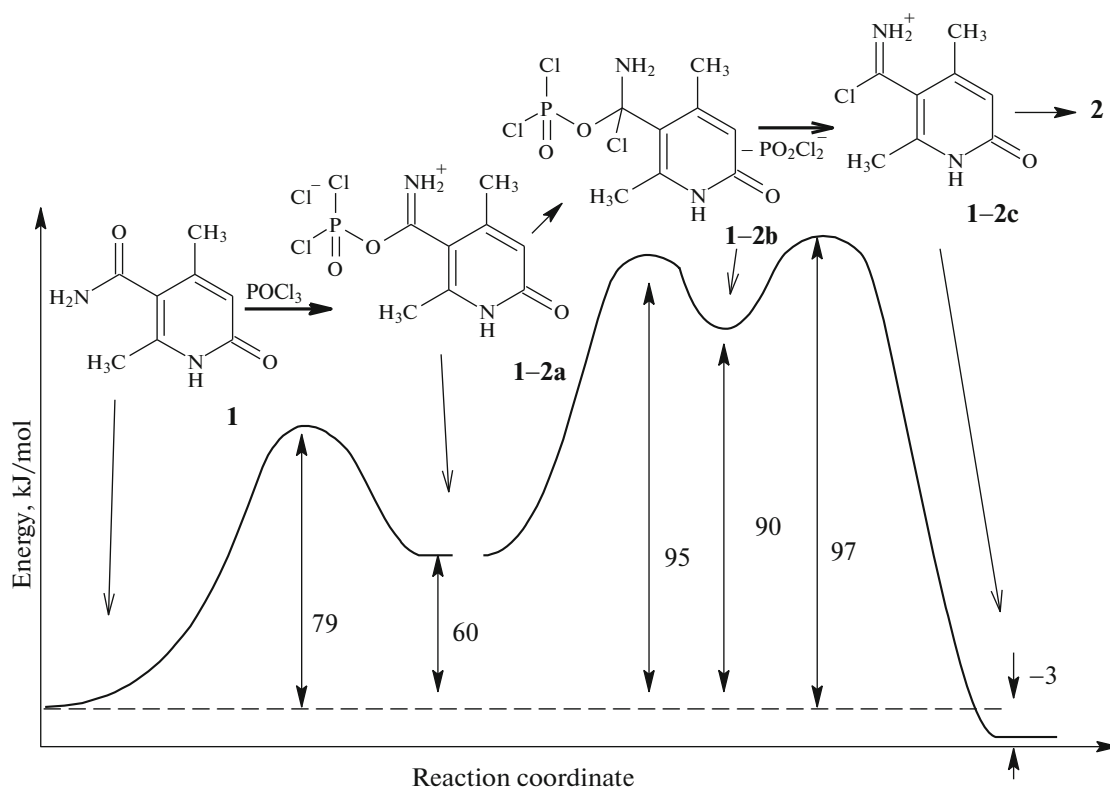


Fig. 2. Structure and numbering scheme for compound 2. Thermal ellipsoids are presented with a probability of 30%. Hydrogen atoms are represented by circles of arbitrary radii.



Scheme 2.

Table 2. Crystallographic parameters and data from refining the test structures

Empirical formula	C ₈ H ₁₀ N ₂ O ₂ , 1	C ₈ H ₈ N ₂ O, 2	C ₈ H ₇ ClN ₂ , 3
<i>M</i>	166.18	148.16	166.61
<i>T</i> , K	295(2)	295(2)	110(2)
Wavelength, Å	1.54186	1.54186	0.71073
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>C</i> 2/ <i>m</i>
<i>a</i> , Å	4.8627(2)	10.1524(17)	15.155(2)
<i>b</i> , Å	11.7567(5)	5.4301(6)	6.6754(9)
<i>c</i> , Å	15.2029(5)	15.103(3)	8.4383(12)
β, deg	103.562(3)	114.717(12)	109.361(2)
<i>V</i> , Å ³	844.90(6)	756.3(2)	805.39(19)
<i>Z</i>	4	4	4
ρ _{calc} , g/cm ³	1.306	1.301	1.374
μ, cm ⁻¹	0.795	0.727	0.404
<i>F</i> (000)	352	312	344
Crystal size, mm	0.10 × 0.10 × 0.10	0.10 × 0.10 × 0.10	0.44 × 0.12 × 0.06
Range for data collection θ, deg	4.807–70.720	4.795 to 71.409	2.558 to 32.058
<i>hkl</i> index range	−5 ≤ <i>h</i> ≤ 3, −14 ≤ <i>k</i> ≤ 13, −15 ≤ <i>l</i> ≤ 18	−12 ≤ <i>h</i> ≤ 12, −6 ≤ <i>k</i> ≤ 6, −18 ≤ <i>l</i> ≤ 18	−22 ≤ <i>h</i> ≤ 22, −9 ≤ <i>k</i> ≤ 9, −12 ≤ <i>l</i> ≤ 12
Reflections collected	3358	2857	8400
Independent reflections [<i>R</i> _{int}]	1592 [0.0281]	1423 [0.0613]	1437 [0.0238]
Absorbance	Empirical (DIFABS) [7]	Empirical (DIFABS)	Empirical (SADABS) [8]
Data/restraints/parameters	1592/0/120	1423/0/107	1437/12/67
GOOF (<i>F</i> ²)	0.961	0.705	1.086
<i>R</i> ₁ / <i>wR</i> ₂ , <i>I</i> > 2σ(<i>I</i>)	0.0426/0.0752	0.0548/0.0651	0.0333/0.0939
<i>R</i> ₁ / <i>wR</i> ₂ , all data	0.0459/0.0776	0.1115/0.0788	0.0369/0.0966
Δρ _{max} /Δρ _{min} , e/Å ³	0.163/−0.147	0.180/−0.158	0.535/−0.364
Diffraction model	STADI VARY Pilatus-100K [9]	STADI VARY Pilatus-100K	Bruker APEX-II CCD [10]

The geometrical parameters of the molecules (individual bond lengths and valence angles) are summarized in Tables 3–5.

Our structural data were deposited at the Cambridge structural database [13] and the following CCDC numbers were assigned: CCDC 1481961 (**1**), CCDC 1481962 (**2**), and CCDC 1481963 (**3**).

RESULTS AND DISCUSSION

Before studying this chain of multistage reaction transformations, it was believed that in the first stage, POCl₃ molecules bonded with the oxygen atoms of the amide groups to form adducts (**1–2d**) and (**1–4a**) (Scheme 3).

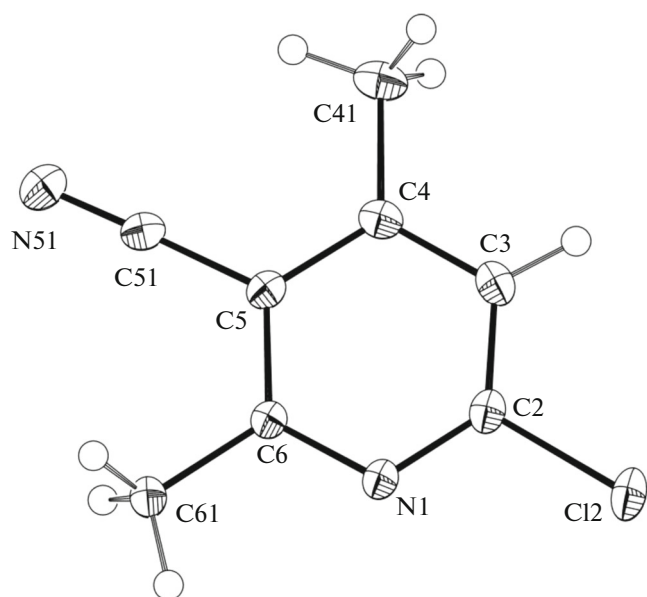
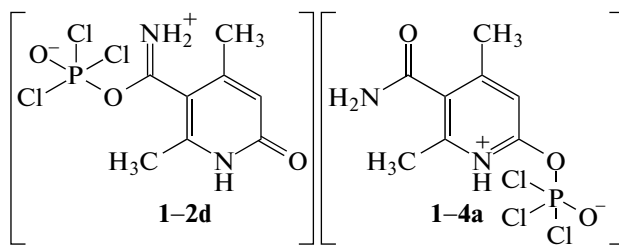


Fig. 3. Structure and numbering scheme for compound **3**. Thermal ellipsoids are presented with a probability of 30%. Hydrogen atoms are represented by circles of arbitrary radii.



Scheme 3.

DFT simulations, however, showed that this bonding is accompanied by P–C bond cleavage with formation of chloride ions. Being intermediates, ion pairs (**1–2a**) and (**1–4**) (Scheme 2) correspond to the minimum on the potential energy surface.

The next step of the reaction proceeds in one stage with high activation energy for the cyclic amide groups and two stages with much lower activation energy for the side groups (intermediate **1–2b**). This two-stage transformation is possible only because of the high conformational flexibility of the amide groups, but not

Table 3. Selected bond lengths d (Å) and valence angles ω (deg) in compound **1**

Bond	d	Bond	d
N1–C6	1.3603(11)	N1–C2	1.3655(10)
N1–C2	1.3655(10)	N1–H1	0.858(12)
C2–O2	1.2531(10)	C2–C3	1.4209(11)
C3–C4	1.3663(12)	C4–C5	1.4239(11)
C4–C41	1.5052(12)	C5–C6	1.3617(12)
C5–C51	1.5075(11)	C6–C61	1.4947(11)
C51–O51	1.2229(10)	C51–N52	1.3188(11)
N52–H52A	0.849(14)	N52–H52B	0.892(13)
Angle	ω	Angle	ω
C6–N1–C2	125.25(7)	C6–N1–H1	117.2(7)
C2–N1–H1	117.5(7)	O2–C2–N1	119.15(7)
O2–C2–C3	125.67(7)	N1–C2–C3	115.18(7)
C4–C3–C2	121.80(7)	C3–C4–C5	119.15(7)
C3–C4–C41	120.67(7)	C5–C4–C41	120.19(8)
C6–C5–C4	119.53(7)	C6–C5–C51	119.54(7)
C4–C5–C51	120.92(7)	N1–C6–C5	118.97(7)
N1–C6–C61	114.57(7)	C5–C6–C61	126.38(7)
O51–C51–N52	122.41(8)	O51–C51–C5	122.27(8)
N52–C51–C5	115.31(7)	C51–N52–H52A	119.8(8)
C51–N52–H52B	121.5(8)	H52A–N52–H52B	118.4(11)

Table 4. Selected bond lengths d (Å) and valence angles ω (deg) in compound **2**

Bond	d	Bond	d
N1–C6	1.351(3)	N1–C2	1.393(2)
N1–H1	0.83(2)	C2–O2	1.240(3)
C2–C3	1.409(4)	C3–C4	1.370(3)
C4–C5	1.424(3)	C4–C41	1.494(4)
C5–C6	1.377(3)	C5–C51	1.412(4)
C51–N51	1.148(3)	C6–C61	1.501(2)
Angle	ω	Angle	ω
C6–N1–C2	123.7(2)	C6–N1–H1	116.9(14)
C2–N1–H1	119.5(14)	O2–C2–N1	118.3(2)
O2–C2–C3	125.98(18)	N1–C2–C3	115.7(2)
C4–C3–C2	122.89(19)	C3–C4–C5	118.0(2)
C3–C4–C41	121.70(19)	C5–C4–C41	120.3(2)
C6–C5–C51	118.34(18)	C6–C5–C4	120.0(2)
C51–C5–C4	121.6(2)	N51–C51–C5	178.6(3)
N1–C6–C5	119.66(18)	N1–C6–C61	116.2(2)
C5–C6–C61	124.1(2)		

Table 5. Selected bond lengths d (Å) and valence angles ω (deg) in compound **3**

Bond	d	Bond	d
N1–C2	1.3242(19)	N1–C6	1.3399(17)
C2–C3	1.387(2)	C2–Cl2	1.7388(15)
C3–C4	1.391(2)	C4–C5	1.406(2)
C4–C41	1.5023(15)	C5–C6	1.4074(19)
C5–C51	1.4408(19)	C6–C61	1.4985(14)
C51–N51	1.152(2)		
Angle	ω	Angle	ω
C2–N1–C6	117.35(12)	N1–C2–C3	126.10(13)
N1–C2–Cl2	115.09(11)	C3–C2–Cl2	118.81(11)
C2–C3–C4	117.69(13)	C3–C4–C5	117.08(13)
C3–C4–C41	121.17(12)	C5–C4–C41	121.75(12)
C4–C5–C6	120.68(13)	C4–C5–C51	121.01(13)
C6–C5–C51	118.31(13)	N1–C6–C5	121.10(13)
N1–C6–C61	117.09(11)	C5–C6–C61	121.81(11)
N51–C51–C5	178.44(16)		

for the cyclic amides. This explains the high reactivity of the side amide groups, relative to the cyclic ones. As a result, product (**4**) does not form in the corresponding synthesis.

Structural studies of compounds (**1**) and (**2**) confirmed that pseudo-diene moiety [–C3=C4–C5=C6–] is present in the heterocycle (see Tables 3 and 4).

CONCLUSIONS

Three new pyridine derivatives were synthesized and characterized by IR and ^1H NMR spectra, and their melting points were determined. Their molecular structures were established via single crystal X-ray diffractometry. In addition, a possible reaction path was simulated by means of DFT, and the energies of formation of possible intermediates were calculated. This allowed us to describe rationally the chain of transformations of compounds **1** to **3**.

ACKNOWLEDGMENTS

Our structural studies of compounds **1** and **2** were performed on a STOE STADIVARI PILATUS-100K diffractometer purchased with the financial support within the Moscow State University Development Program. The experimental data for compound **3** were obtained using diffractometry equipment at the shared

resource center of the Institute of General and Inorganic Chemistry of the Russian Academy of Sciences.

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