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Synthesis and X-ray crystal structure of (*E*)-9-(N,N-Dimethylaminomethylidene)-8,9-dihydropyrido[2,3-d]pyrrolo[1,2-a]pyrimidin-5(7H)-one

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(E)-9-(N,N-Dimethylaminomethylidene)-8,9-dihydropyrido[2,3-d]pyrrolo[1,2-a]pyrimidin-5(7H)-one,
Vilsmeier reagent,
X-ray analysis

Abstract: 2,3-Trimethylenepyrido[2,3-d]pyrimidin-4-one reacts with the Vilsmeier reagent to give α-Dimethylaminomethylidene derivative. X-ray structure analysis has been carried out for the product of the reaction.

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INTRODUCTION

It well known that the Vilsmeier reagent reacts with an electron-rich arene to produce an aryl aldehyde or ketone. Several heterocycles were treated by this reagent especially to obtain formyl derivatives (Shvedov, Chizhov, and Grinev, 1971; Pechkin, Elchaninov, Lukyanov, and Alekseenko, 2004; Chornous, Bratenko, and Vovk, 2006; Attaryan, et.al., 2006, Terenin, et.al., 2008; Samsoniya, Trapaidze, and Nikoleishvili, 2013). Subsequent hydrolysis of an intermediate allowed to corresponding products. Dimethyleaminomethylidene derivatives are usually formed as intermediates (Shakhidoyatov, 2001).

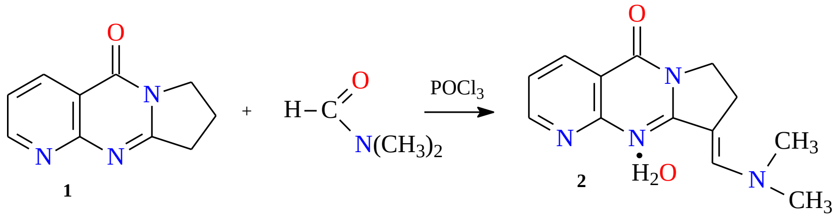
In the previous reports we have described synthesis, the reaction results of 2,3-trimethylenepyrido[2,3-d]pyrimidin-4-one with aromatic aldehydes (Khodjaniyazov, 2015; Khodjaniyazov and Ashurov, 2016), and selective reduction with sodium borohydride (Khodjaniyazov, et al., 2016). In this current paper we present the results of a reaction of 2,3-trimethylenepyrido[2,3-d]pyrimidin-4-one with the Vilsmeier reagent.

MATERIALS AND METHODS

The research objects are 2,3-trimethylenepyrido[2,3-d]pyrimidin-4-one (**1**), the Vilsmeier reagent (dimethylformamide as a substituted amide with phosphorus oxychloride), and product of their action (**2**). Research methods are methods of organic synthesis and structural investigation of the synthesized compound by X-ray crystal structure analysis. The reaction proceeds as following scheme 1.

Reaction of 2,3-trimethylenepyrido[2,3-d]pyrimidin-4-one with the Vilsmeier reagent

A round bottom flask with freshly distilled DMF (3ml, 39 mmol) was cooled by ice water bath and $POCl_3$ (1ml, 10.7 mmol) was added dropwise. The mixture was stirred (30 min), then a 2,3-trimethylenepyrido[2,3-d]pyrimidin-4-one (0.51 g, 2.7 mmol) was added into the reaction mixture. The yellow color reaction mixture turned to gray color after 15 min stirring; left for 3h. Then the reaction mixture was heated in a water bath for 1.5 h at 70^0C; left for another day. Water (3.8ml) was poured into the flask. TLC monitoring showed that the initial compound fully transformed. The reaction mixture was treated by ammonia solution up to pH 9. R_f value of a product is 0.4 and it is not appeared under UV-light on TLC. The obtained solution was extracted by chloroform two times. The chloroform part was dried over Na_2SO_4 and solvent was removed. Yield is 0.41 g (70% theoretical). LC-MS (+ESI): 243 (M^+).



Scheme 1

Crystal growing

Single crystals of (*E*)-9-(N,N-Dimethylaminomethylidene)-8,9-dihydropyrido[2,3-d]pyrrolo[1,2-a]pyrimidin-5(7H)-one (**2**) was grown as a monohydrate from acetone solution by slow evaporation of the solvent at room temperature.

X-ray diffraction experiment

The unit cell parameters of the crystals are determined and refined with CCD Xcalibur Ruby diffractometer (Oxford Diffraction) using CuKα-radiation, graphite monochromator (T = 293 K). The three-dimensional set of reflections received at the appropriate diffractometer. The amendment was introduced to the absorption by Multi-scan [1]. A three-dimensional data set of reflections was obtained on the same diffractometer. Absorption corrections were applied using a semi-empirical method in the SADABS program (Oxford Diffraction, 2007).

The structures were solved by direct methods using SHELXS-2014 and refined using SHELXL-2014 programs (Sheldrick, 2008). All non-hydrogen atoms were refined by anisotropic full-matrix least-squares methods (over F^2). Positions of H atoms were found geometrically and refined with fixed isotropic thermal parameters Uiso = nUeq, where n = 1.5 for methyls and 1.2 for others and Ueq is the equivalent isotropic thermal parameter of the corresponding C atoms.

Results from the X-ray diffraction experiments were deposited at the Cambridge Crystallographic Data Centre (CCDC). Materials X-ray diffraction as a CIF file deposited at the Cambridge center of crystal data (CCDC), from which can be obtained free on request at the following link: www.ccdc.cam.ac.uk/data_request/cif

RESULTS AND DISCUSSION

Reaction of 2,3-trimethylenepyrido[2,3-d]pyrimidin-4-one with the Vilsmeier reagent allowed to formation of its α-dimethylaminomethylidene-derivative, i.e. (*E*)-9-(N,N-dimethylamino-methylidene)-8,9-dihydropyrido[2,3-d]pyrrolo[1,2-a]pyrimidin-5(7H)-one. Chemical transformations of heterocyclic compounds with active α-methylene group have been investigating in our department. For example, the formylation of deoxyvasicinone, benzene analog of the initial compound, allowed to α-hydroxy- and -dimethylaminomethylidene-deoxyvasicinone depending on treatment condition of reaction mixture (Turdibaev, Elmuradov, Khakimov, and Shakhidoyatov, 2011). Furthermore, activation of α-methylene protons due to neighbor carbonyl group observed at fictionalization of 3,4,5,6,7,8-hexahydrospiro[chromene-2,1'-cyclohexane]one-2' during Vilsmeier-Haack reaction (Fedotova, Lipatova, Tsimbalenko, and Scherbakov, 1998). But in this report an intermediate was not separated. Dimethylaminomethylidene fragment connected to exocyclic nitrogen atom of 1,3-dimethyl-2,4,5-trioxo-7-amino-8H-pyrido[2,3-d]pyrimidine which was treated by DMF/$SOCl_2$ in $CHCl_3$. (Burova, Bystriakova, Smirnova, and Safonova, 1990). *X*-ray crystal structures of 1-(N,N-dimethylaminomethylidene)-3-phenylisoindolenine and 1-formyl-3-phenylisoindole were studied (Bonnett, Hursthouse, North, and Trotter. 1984).

The structure of the reaction product according to the X-ray analysis is shown in Fig. 1.In the study it was found that the structure is a monohydrate. Host molecule, consisting of the condensed heterocycles ***A***, ***B*** and ***C***, is rather tough. Rings ***A***, ***B*** and ***C*** are planar (within ± 0.0052, ± 0.0124 and ± 0.0043 Å respectively).

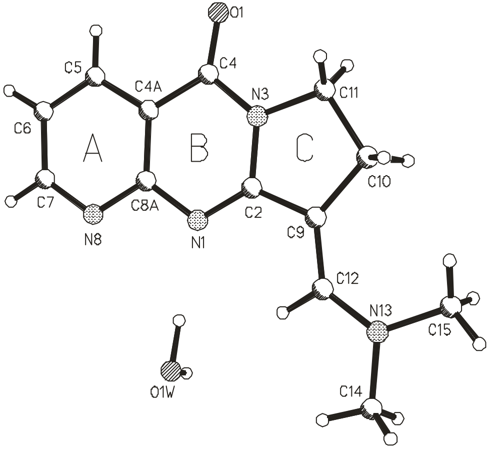


Fig.1. Spatial structure and numbering of the atoms in **2**

A nitrogen and carbon atoms of dimethylaminomethylidene fragment are also planar, which are caused by presence of a conjugated system with participating of a double bond C9-C12 and unshared electron pairs of N13. The torsion angle C9 C12 N13 C15 is -5.99^0. The location of dimethylaminomethylidene fragment relative to the plane of the pyrido[2,3-d]pyrrolo[1,2-a]pyrimidin-5(7H)-one moiety is almost similar. Nitrogen atoms in the molecule involved in the conjugated system, which is confirmed by the values of the distances C-N bonds (Table 1.).

Table 1: C-N bonds lengths in the structure of **2**, Å.

C7-N8	N8-C8A	C8A-N1	N1-C2	C2-N3	N3-C4	N3-C11	C12-N13
1.333(5)	1.354(4)	1.369(4)	1.312(4)	1.384(4)	1.365(4)	1.456(5)	1.329(5)

Table 2: Intermolecular and intramolecular hydrogen bonds geometries in the structure **2** (d: the distance, D: donor, A: acceptor)

D-H…A	d (D-H), Å	d (H…A), Å	d (D…A), Å	<(DHA), °	Symmetry
O1W-H1W...N1	1.02(6)	2.02(6)	3.041(5)	179(6)	
O1W-H2W...O1	0.78(5)	2.38(5)	3.151(6)	170(4)	*-x,1-y,1-z*
C6-H6A...O1	0.93	2.60	3.330(5)	136	*-x,-1/2+y,3/2-z*
C7-H7A...N8	0.93	2.59	3.388(5)	144	*-x,-y,1-z*
C12-H12A...N1	0.93	2.52	2.913(4)	105	

Packing of molecules in the crystal is shown in Fig. 2.

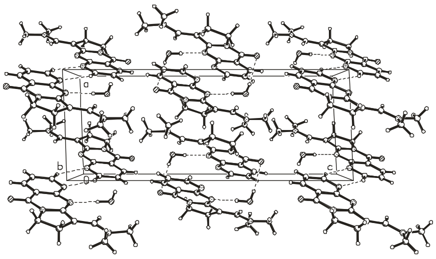


Fig.2. H-bonding in the structure of 2.

The crystal cell between the host molecules and crystalline water observe the formation of the weak hydrogen bonds (Rajnikant, Dinesh, and Kamni. 2005), (Table 2).

Furthermore, weak π ... π interactions were observed in the structure of **2** between the aromatic rings (Estarellas, et.al, 2009). (Table 3).

Table 3: The geometrical parameters of π…π interactions in the structure of **2**.

π…π	d (π…π), Å	Symmetry
ring ***C***…ring ***A***	3.817(2)	*-x,1-y,1-z*
ring ***B***…ring ***B***	3.784(2)	*-x,1-y,1-z*

Table 4 presents the principal crystallographic parameters and the characteristics of the X-ray diffraction experiments and crystal structure refinement calculations.

Table 4: Basic crystallographic parameters and characteristics of the X-ray diffraction for structure **2**.

Molecular formula	$C_{13}H_{14}N_4O \cdot H_2O$
Mr	260.30
Crystal symmetry	Monoclinic
Space group	P 21/c
Z	4
a, Å	7.5037(15)
b, Å	8.7592(18)
c, Å	19.297(4)
α, °	90
β, °	92.27(3)
γ, °	90
V, $Å^3$	1267.3(4)
ρ, g/cm^3	1.265
Crystal dimension (mm)	0.50x0.45x0.30
Range scanned, 2θ°	4.568≤θ≤67.684°
μ_{exp} (cm^{-1})	0.686
No. reflection collected	2589
No. reflection with I>2σ(I)	1306
R_1(I>2σ(I) and total)	0.0604(0.1207)
wR_2	0.1572 (0.2134)
GOOF	0.910
Largest diff. peak and hole (e $Å^{-3}$)	0.176 and -0.169 e.$Å^3$
CCDC	1476418

CONCLUSION

Formation of (*E*)-9-(N,N-Dimethylaminomethylidene)-8,9-dihydropyrido[2,3-d]pyrrolo[1,2-a]pyrimidin-5(7H)-one was observed at a reaction of 2,3-trimethylenepyrido[2,3-d]pyrimidin-4-one with the Vilsmeier reagent. The single crystal structure as a monohydrate form was studied by X-ray diffraction method.

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