

THE INTERACTION OF 4,5-DIFORMYL-2,3,6,7,8,10-HEXAHYDROACRIDINE-8a(1H)-CARBONITRILE WITH N-NUCLEOPHILES

E.V.Zalizna¹, T.P.Polishuk, S.A.Varenichenko¹, O.K.Farat², V.I.Markov¹

¹Ukrainian State University of Chemical Technology
49005 Dnipropetrovsk, Ukraine. E-mail: kzalizna@gmail.com

²Department of Chemistry, M.V.Lomonosov Moscow State University

Key words: hydroacridines; Schiff bases; macrocycles

Schiff bases are of practical interest as initial materials both for the combinatorial synthesis for libraries of compounds, and for preparation of complexes with metals; thus, currently the intensity of research in this direction is increasing. The possibilities of practical use of complex compounds with organic ligands are quite broad varying from effective catalysts of various chemical processes to molecular sensors. While studying formylation of 5,6,7,8-tetrahydro-1H-spiro[cyclohexane-1,2-quinazolin]-4'(3'H)-one a new domino reaction, which makes it possible to obtain tricyclic acridine systems, has been carried out. In spite of the reduced electrophilicity of the aldehyde groups in 4,5-diformyl-2,3,6,7,8,10-hexahydroacridine-8a(1H)-carbonitrile the latter is shown to react with various amines in benzene with azeotropic removal of water using p-TsOH as a catalyst, and with hydroxylamine hydrochloride in i-PrOH. New Schiff bases and oxime obtained are of potential interest as ligands for formation of chelate complexes. The reaction of dialdehyde with N₂H₄·H₂O instead of the expected hydrazone resulted in obtaining a macrocyclic compound – a derivative of hexaazacyclooctadecine. The structure of the compounds obtained corresponds to the data of ¹H NMR-spectroscopy, mass spectrometry and elemental analysis. The preliminary studies have shown that azomethines – 4,5-phenyl(cyclohexyl)iminomethyl-2,3,6,7,8,10-hexahydroacridine-8a(1H)-carbonitrile create complexes with copper and nickel ions.

ВЗАЄМОДІЯ 4,5-ДИФОРМИЛ-2,3,6,7,8,10-ГЕКСАГІДРОАКРИДИН-8a(1H)-КАРБОНІТРИЛУ З N-НУКЛЕОФЛАМИ
Е.В.Залізна, Т.П.Поліщук, С.А.Варениченко, О.К.Фарат, В.І.Марков

Ключові слова: гідроакридини; основи Шиффа; макроцикли

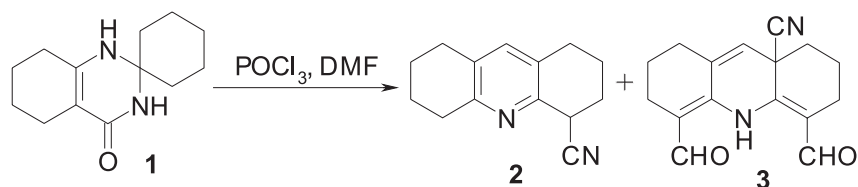
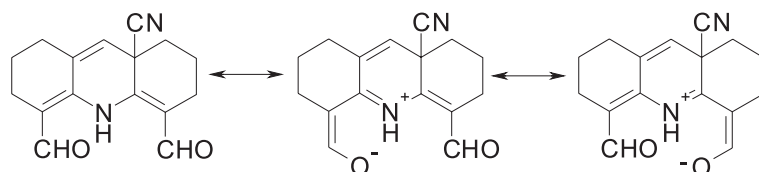
Основи Шиффа становлять практичний інтерес в якості вихідних як для комбінаторного синтезу бібліотек речовин, так і для створення комплексів з металами, і останнім часом інтенсивність досліджень у даному напрямку тільки збільшується. Можливості практичного використання комплексів з органічними лігандами досить широкі: від ефективних каталізаторів хімічних процесів до молекулярних сенсорів. У ході вивчення формілювання 5',6',7',8'-тетрагідро-1'H-спіро[циклогексан-1,2'-хіназолін]-4'(3'H)-ону нами була відкрита нова доміно-реакція, яка дозволяє вийти на трициклічні гідровані акридинові системи. Показано, що незважаючи на знижену електрофільність альдегідних груп у 4,5-диформіл-2,3,6,7,8,10-гексагідроакридину-8a(1H)-карбонітрилі, він реагує з різними амінами у бензолі з азеотропною відгонкою води з використанням в якості каталізатора p-TsOH, а також з солянокислим гідроксиламіном у i-PrOH. Отримані основи Шиффа та оксим становлять потенційний інтерес у якості лігандів для утворення хелатних комплексів. У результаті реакції діальдегіду з N₂H₄·H₂O замість очікуваного гідрозону отримано макроциклічну сполуку – похідну гексаазаціклооктадецину. Будова всіх отриманих сполук підтверджена даними ЯМР ¹H-спектроскопії, мас-спектрометрії і елементного аналізу. Попередні дослідження продемонстрували, що азометини – 4,5-феніл(циклогексил)імінотетил-2,3,6,7,8,10-гексагідроакридин-8a(1H)-карбонітрилу утворюють комплексні сполуки з іонами нікелю та міді.

ВЗАИМОДЕЙСТВИЕ 4,5-ДИФОРМИЛ-2,3,6,7,8,10-ГЕКСАГИДРОАКРИДИН-8a(1H)-КАРБОНИТРИЛА С N-НУКЛЕОФИЛАМИ

Е.В.Зализная, Т.П.Полещук, С.А.Варениченко, О.К.Фарат, В.И.Марков

Ключевые слова: гидроакридины; основания Шиффа; макроциклы

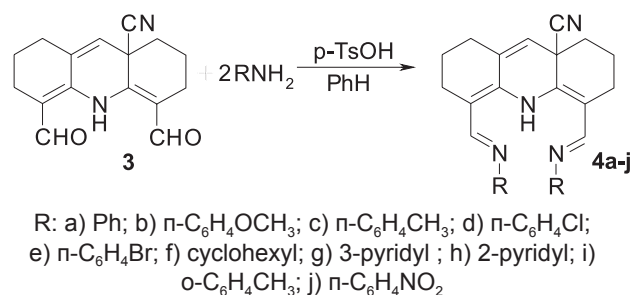
Основания Шиффа представляют практический интерес в качестве исходных как для комбинаторного синтеза библиотек веществ, так и для создания комплексов с металлами, и в последнее время интенсивность исследований в данном направлении только увеличивается. Возможности практического использования комплексных соединений с органическими лигандами весьма широки: от эффективных катализаторов различных химических процессов до молекулярных сенсоров. В ходе изучения формилирования 5',6',7',8'-тетрагидро-1'H-спиро[циклогексан-1,2'-хиназолин]-4'(3'H)-она нами была найдена новая домино-реакция, которая позволяет выйти на трициклические гидрированные акридиновые системы. Показано, что несмотря на сниженную электрофильность альдегидных групп в 4,5-диформил-2,3,6,7,8,10-гексагидроакридин-8a(1H)-карбонитриле, он реагирует с различными аминами в бензоле с азеотропной отгонкой воды с применением в качестве катализатора p-TsOH, а также с солянокислым гидроксилламином в i-PrOH. Полученные основания Шиффа и оксим представляют потенциальный интерес в качестве лигандов для образования хелатных комплексов. В результате реакции диальдегида с N₂H₄·H₂O вместо ожидаемого гидразона получено макроциклическое соединение – производное гексаазациклооктадецина. Строение всех полученных соединений согласуется с данными ЯМР ¹H-спектроскопии, масс-спектрометрии и элементного анализа. Предварительные исследования показали, что азометини – 4,5-фенил(циклогексил)иминометил-2,3,6,7,8,10-гексагидроакридин-8a(1H)-карбонитрила образуют комплексные соединения с ионами никеля и меди.

Scheme 1. Formylation of azine **1** under Vilsmeier-Haack conditions.Scheme 2. Localization of the charge in diformyl **3**.

Recently azomethines, e.g., carbazole series, are widely used as organic ligands [1-9]. It allows obtaining spatial molecules with binding transition metal centres. On the basis of the complexes the highly effective nanoscale sensors can be created. Therefore, it is very important to synthesize precursors, in particular Schiff bases, with a suitable geometry to create chelate complexes with metals. Earlier when studying formylation of various azine and oxazine systems the domino-reaction – rearrangement of spiroquinazoline **1** into tricyclic acridine systems **2** and **3** was found [13] (Scheme 1). In our previous papers the results of studying the reactivity of carbonitrile **2** were presented [14-15]. However, the synthetic potential of 4,5-diformyl-2,3,6,7,8,10-hexahydroacridine-8a(1H)-carbonitrile **3** has remained completely unstudied.

Due to the peculiar structure of dialdehyde **3** and based on it obtaining of the Schiff bases required for complexation geometry has become possible. According to the data of ^1H NMR-spectroscopy the formyl group forms a hydrogen bond with proton of the nitrogen endocyclic atom, and it is proven by the strong chemical shift of its signal in the lowest field values (δ 13.03 ppm). In the IR-spectrum the decrease in the absorption frequency to $\nu = 1667\text{ cm}^{-1}$ confirms that formyl groups are in conjugation with the N-H group, it is supposed to lead to a decrease in the reactivity of CHO-groups. According to the data of X-ray diffraction analysis C=O bonds are longer in 1.219 Å than the standard C=O double bond distance in aldehydes – 1.192 Å. From the analysis of the structures (Scheme 2) it is obvious that the electrophilicity of carbon atoms in carbonyl groups is significantly lower compared to the aldehyde group unconjugated with an electron-donating substituent. Consequently, aldehyde groups in dialdehyde **3** are vinylogs of amides and, taking into account their low reactivity, it is interesting to study the possibility of forming Schiff bases.

Among several variants of the reaction [16-18] the method of boiling with various amines in benzene

Scheme 3. The synthesis of Schiff bases **4a-j**.

with azeotropic water distillation with *p*-TsOH as a catalyst has been chosen (Scheme 3).

The reaction of dialdehyde **3** with the excess of amine and the catalytic amount of a catalyst lasts for 15 min and results in a good yield of Schiff bases **4a-j**. The structure of compounds **4a-j** obtained corresponds to the data of ^1H NMR-spectroscopy, mass spectrometry and elemental analysis (Tab. 1, 2). The signal for the NH proton in the spectra of compound **4a-j** is observed as a broadened singlet in the downfield region at about ~ 12.5 ppm, the characteristic signal of the olefin CH-proton [19] is observed as a singlet in the region at about ~ 6 ppm, in the range of 8.1 and 8.6 ppm there are signals of two azomethine protons CH=NR.

The reaction of dialdehyde **3** with hydroxylamine hydrochloride resulted in obtaining a colourless 4,5-bis[(*E*)-(hydroxyimino)methyl]-2,3,6,7,8,10-hexahydroacridine-8a(1H)-carbonitrile **5**, being of interest as an organic ligand due to its structure (Scheme 4).

The reaction of dialdehyde **3** with hydrazine hydrate resulted in formation of condensation product **6** – 2,3,5,7,8,9,15,16,18,19,20,21,22-dodecahydro-4,6:19,17-dimethenotetrabenzo[*d,g,m,p*][1,2,6,10,11,15]-hexaazacyclooctadecine-4,19(1*H*,14*H*)-dicarbonitrile characterized with a saturated dark red colour in the solution (Scheme 4). This structure was proposed on the basis of ^1H NMR- and mass-spectra. The signals for NH-groups protons in the NMR-spectra are observed as broadened singlets in the downfield region

Table 1

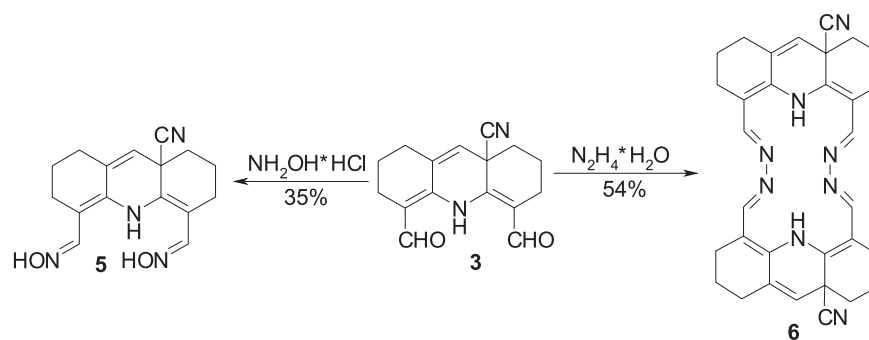
Yields, MP and elemental analysis of compounds **4a-j**; **5-6**

Compound	Yields %	MP, °C	Found, %			Empirical formula, Da	Calculated, %		
			C	H	N		C	H	N
4a	43	168-170	80.37	6.26	13.43	C ₂₈ H ₂₆ N ₄ 418,55	80.35	6.26	13.39
4b	51	193-194	75.31	6.29	11.70	C ₃₀ H ₃₀ N ₄ O ₂ 478,60	75.29	6.32	11.71
4c	51	170-172	80.68	6.79	12.56	C ₃₀ H ₃₀ N ₄ 446,60	80.68	6.77	12.55
4d	77	186-188	68.99	4.95	11.49	C ₂₈ H ₂₄ Cl ₂ N ₄ 487,44	69.00	4.96	11.49
4e	47	220-221	58.33	4.18	9.75	C ₂₈ H ₂₄ Br ₂ N ₄ 576,34	58.35	4.20	9.72
4f	68	189-190	78.08	8.88	13.04	C ₂₈ H ₃₈ N ₄ 430,64	78.10	8.89	13.01
4g	44	200-202	74.23	5.76	19.99	C ₂₆ H ₂₄ N ₆ 420,52	74.26	5.75	19.98
4h	83	205-206	74.28	5.78	19.96	C ₂₆ H ₂₄ N ₆ 420,52	74.26	5.75	19.98
4i	53	210-211	80.72	6.74	12.51	C ₃₀ H ₃₀ N ₄ 446,6	80.68	6.77	12.55
4j	50,7	189-190	66.19	4.79	16.53	C ₂₈ H ₂₄ N ₆ O ₄ 508,54	66.13	4.76	16.53
5	35	154-156	64.11	6.09	18.74	C ₁₆ H ₁₈ N ₄ O ₂ 298,35	64.41	6.08	18.78
6	54	265	72.73	6.10	21.26	C ₃₂ H ₃₂ N ₈ 528,67	72.70	6.10	21.20

Table 2

Data of NMR ¹H and mass-spectra of compounds **4a-j**; **5-6**

Compound	MS: m/z (I,%)	NH	9-CH (pyridine cycle)	CH=NR	Aromatic protons	Aliphatic protons
4a	419 [M+H] ⁺ (55)	12.5	5.9 (1H,s,CH)	8.5 (1H,s,CH=NR) 8.1 (1H,s,CH=NR)	7.0-7.4 (10H, m, H Ar)	2.2-2.6 (4H, m, 2CH ₂); 1.7-2.0 (8H, m, 4CH ₂)
4b	479 [M+H] ⁺ (53)	12.9	5.9 (1H,s,CH)	8.5 (1H,s,CH=NR) 8.1 (1H,s,CH=NR)	6.5-6.9 (4H, m, 4 H Ar) 7.0-7.2 (4H, m, 4 H Ar)	3.8 (6H, s, 2CH ₃); 2.2-2.6 (4H, m, 2CH ₂); 1.7-2.0 (8H, m, 4CH ₂)
4c	447 [M+H] ⁺ (100)	12.6	6.0 (1H,s,CH)	8.6 (1H,s,CH=NR) 8.1 (1H,s,CH=NR)	6.7-7.0 (4H, m, 4 H Ar) 7.1-7.3 (4H, m, 4 H Ar)	2.1 (6H, s, 2CH ₃); .6-2.4 (4H, m, 2CH ₂); 1.6-1.9 (8H, m, 4CH ₂)
4d	487 [M] ⁺ (35)	12.6	5.9 (1H,s,CH)	8.5 (1H,s,CH=NR) 8.0 (1H,s,CH=NR)	6.8-7.0 (4H, m, 4 H Ar) 7.1-7.4 (4H, m, 4 H Ar)	2.1-2.4 (4H, m, 2CH ₂); 1.6-1.9 (8H, m, 4CH ₂)
4e	577 [M+H] ⁺ (27)	13.0	5.9 (1H,s,CH)	8.7 (1H,s,CH=NR) 8.9 (1H,s,CH=NR)	7.0-7.2 (4H, m, 4 H Ar) 7.3-7.5 (4H, m, 4 H Ar)	2.1-2.4 (4H, m, 2CH ₂); 1.6-1.9 (8H, m, 4CH ₂)
4f	431 [M+H] ⁺ (100)	12.8	5.8 (1H,s,CH)	7.9 (1H,s,CH=NR) 8.4 (1H,s,CH=NR)		2.1-2.4 (4H, m, 2CH ₂); 1.0-1.7 (28H, m, 14CH ₂)
4g	421 [M+H] ⁺ (100)	12.7	5.8 (1H,s,CH)	8.0 (1H,s,CH=NR) 8.4 (1H,s,CH=NR)	7.4-7.6 (4H, m, 4 H Ar) 8.1-8.3 (4H, m, 4 H Ar)	1.9-2.2 (4H, m, 2CH ₂); 1.4-1.7 (8H, m, 4CH ₂)
4h	421 [M+H] ⁺ (40)	11.9	6.0 (1H,s,CH)	7.8 (1H,s,CH=NR) 7.5 (1H,s,CH=NR)	7.0 (2H, m, 2 H Ar) 7.2 (2H, m, 2 H Ar) 8.1 (2H, m, 2 H Ar) 8.3 (2H, m, 4 H Ar)	1.8-2.4 (6H, m, 3CH ₂); 1.3-1.7 (6H, m, 3CH ₂)
4j	447 [M+H] ⁺ (10)	13.1	5.9 (1H,s,CH)	8.1 (1H,s,CH=NR) 8.6 (1H,s,CH=NR)	7.2-7.6 (4H, m, 4 H Ar) 7.9-8.3 (4H, m, 4 H Ar)	2.2-2.4 (6H, m, 3CH ₂); 1.2-1.8 (6H, m, 3CH ₂)
4l	509 [M+H] ⁺ (9)	13.1	5.9 (1H,s,CH)	8.1 (1H,s,CH=NR) 8.6 (1H, s, CH=NR)	7.1-7.3 (4H, m, 4 H Ar) 7.5-7.8 (4H, m, 4 H Ar)	2.1-2.2 (6H, m, 3CH ₂); 1.4-1.9 (6H, m, 3CH ₂)
6	528 [M] ⁺ (34)	11.3	5.9 (2H,s, 2CH)	7.7 (4H, s, 4CH=NR)		2.1-2.4 (8H, m, 3CH ₂); 1.5-1.9 (16H, m, 3CH ₂)

Scheme 4. The synthesis of dioxime **5** and macrocycle **6**.

(11.3 ppm), there are also the signals of azomethine protons (δ 7.64 and 7.70 ppm). In mass spectrum the peaks of appropriately protonated molecular ions $[MH]^+ = 528$ Da are observed.

Experimental Part

The ^1H NMR-spectra of compounds were recorded in DMSO-d_6 on a Varian VXR 200 instrument (200 MHz). The internal standard for all NMR-spectra was TMS. The FAB spectra were recorded with the use of a VG7070 spectrometer. Desorption of ions from the solution of the samples in *meta*-nitrobenzyl alcohol was performed with a beam of argon atoms with energy of 8 keV. Elemental analysis was performed on a LECO CHNS-900 instrument. The reactions and the purity of the compounds obtained were monitored by TLC on Merck Silicagel 60 F-254 plates with CHCl_3 -2-PrOH (10:1) as an eluent.

The synthesis of Schiff bases 4a-j (general method): Dissolve the mixture of the diformyl derivative **3** (2.68 g, 0.01 Mol), 0.02 Mol of amine and 0.3 g of *p*-TsOH in benzene (200 mL), reflux for 15 min with continuous removal of water using the Dean-Stark trap. Cool the reaction mixture, evaporate the solvent (~160 mL). Filter the precipitate, and recrystallize from benzene.

4,5-Bis[(*E*)-(hydroxyimino)methyl]-2,3,6,7,8,10-hexahydroacridine-8a(1H)-carbonitrile (5**):** Dissolve diformyl derivative **3** (2.68 g, 0.01 Mol) in

30 mL of *i*-PrOH, add 1.7 g (0.025 Mol) of hydroxylamine hydrochloride, and reflux for 2 h. Cool the reaction mixture to 10°C. Filter the precipitate of product **5**, and recrystallize from acetonitrile.

The NMR-spectra, δ , ppm: 10.64 (1H, s, NH); 8.74 (1H, s, OH); 8.43 (1H, s, OH); 6.27 (2H, s, 2CH=NR); 5.56 (1H, s, CH); 2.31-2.38 (4H, m, 2CH₂); 1.63-1.81 (8H, m, 4CH₂).

2,3,5,7,8,9,15,16,18,19,20,21,22-dodecahydro-4,6:19,17-dimethenotetrabenzo[*d,g,m,p*][1,2,6,10,11,15]-hexaazacyclooctadecine-4,19(1H,14H)-dicarbonitrile (6**):** Dissolve diformyl derivative **3** (2.68 g, 0.01 Mol) in 1,4-dioxane, add 0.02 Mol of hydrazine hydrate, and reflux for 30 min. Cool the solution to the room temperature, and add water. Filter the precipitate of product **6**, and recrystallize from DMF.

Conclusions

Thus, this paper shows the possibility of the synthesis of Schiff bases using the reaction of 4,5-diformyl-2,3,6,7,8,10-hexahydroacridine-8a(1H)-carbonitrile with various amines under acid catalysis with azeotropic removal of water. The reaction of dialdehyde with $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ resulted in obtaining a macrocyclic compound – a derivative of hexaazacyclooctadecine instead of the expected hydrazone. The preliminary studies have shown that products **4a** and **4f** form complexes with copper and nickel ions. The results of the study will be presented in ongoing papers.

References

- Hollas A. M., Weixing G., Bhuvanesh N., Ozerov O. *Inorganic Chemistry*, 2011, Vol. 50, pp.3673-3679. Cited 9 times. doi: dx.doi.org/10.1021/ic200026p
- Maeda C., Yoshioka N. *Org. Letters*, 2012, Vol. 14(8), pp.2122-2125. Cited 3 times. doi: 10.1021/ol300585v
- Gaixia D., Yanling W., Zhang W., Dong Y. et al. *Dalton Trans.*, 2013, Vol. 42, pp.2178-1286. Cited 6 times. doi: 10.1039/c2dt31932b
- Barbe J.-M., Habermeyer B., Khoury T., Gros C. P., Richard P., Chen P., Kadish K. M. *Inorganic Chem.*, 2010, Vol. 49, pp.8929-8940. Cited 11 times. doi: 10.1021/ic101170k
- Britovsek G. J., Gibson V. C., Hoarau O. D., Spitzmesser S. K., White A. J. P., Williams D. J. *Inorganic Chem.*, 2003, Vol. 42, pp.3454-3465. Cited 7 times. doi: 10.1021/ic034040q CCC
- Chen P., Lau H., Habermeyer B., Gros C. P., Barbe J.-M., Kadish K. M. *J. Porphyrins Phthalocyanines*, 2011, Vol. 15, pp.467-479. Cited 16 times. doi: 10.1142/S1088424611003410
- Gaunt J. A., Gibson V. C., Haynes A., Spitzmesser S. K., White A. J. P., Williams D. J. *Organometallic*, 2004, Vol. 23, pp.1015-1023. Cited 18 times. doi: 10.1021/om034309d CCC
- Gibson V. C., Spitzmesser S. K., White A. J. P., Williams D. J. *Dalton Trans.*, 2003, pp.2718-2727. Cited 8 times. doi: 10.1039/B301902K
- Silva J. de A., Domingos V. F., Marto D., Costa L. D., Silva M. R., Gil J. M., Sobral A. J. F. N. *Tetrahedron Let.*, 2013, Vol. 54, pp.2449-2451. Cited 13 times. doi: 10.1016/j.tetlet.2013.02.071
- Markov V. I., Farat O. K., Varenichenko S. A., Zalznaya K. V., Zubatyuk R. I., Shishkin O. V. *Chem. Heterocycl. Compd.*, 2013, No.8, pp.1158-1165.
- Varenichenko S. A., Farat O. K., Markov V. I. *Chem. Heterocycl. Compd.*, 2015, Vol. 11, pp.1602-1607. Cited 3 times. doi: 10.1007/s10593-014-1626-9
- Farat O. K., Markov V. I., Varenichenko S. A., Dotsenko V. V., Mazepa A. V. *Tetrahedron*, 2015, Vol. 71, pp.5554-5561. Cited 2 times. doi: 10.1016/j.tet.2015.06.069

13. Markov V. I., Farat O. K., Varenichenko S. A., Velikaya E. V. *Mendeleev Communications*, 2012, Vol. 22, pp.101-102. Cited 5 times. doi: 03.017 10.1016/j.mencom.2012
14. Markov V. I., Farat O. K., Velikaya E. V., Varenichenko S. A. *Ukr. Khim. Zhurn., Ukr. Chem. J.*, 2011, Vol. 11, pp.54-59.
15. Zaloznaya E. V., Farat O. K., Gorobets N. Yu., Markov V. I., Zubatyuk R. I., Mazepa A. V., Vashchenko E. V. *Chem. Heterocycl. Compd.*, 2015, Vol. 51, pp.327-333. Cited 89 times. doi: 10.1007/s10593-015-1703-8
16. Wheeler O. H., Patai S., *The chemistry of the carbonyl group*. New York, Interscience, 1966, Vol. 1, chapter 11, p.529.
17. Patel I. J., Parmar S. J., *E-J. of Chem.*, 2010, Vol. 7, pp.617-628.
18. Kobayashi T., Sakakura T., Tanaka M. *Tetrahedron Let.*, 1985, Vol. 26(29), pp.3464.
19. Prech E., Bjul'mann F., Affol'ter K. *Opredelenie stroeniya organicheskikh soedineniy. Tablitsy spektral'nykh dannykh [Determining the structure of organic compounds. Tables of Spectral Data]. Directory. Mir, M., 2006, p.438.*

Надійшла до редакції 16.04.2016 р.

Acknowledgements

The authors express acknowledgements for the grant given by the Ministry of Science and Education of Ukraine No. 0115U003159 "New synthetic methods of synthesis of nitrogen and sulphur-containing biological activity compounds".