The presentation of regioselectivity of 1-ethyl-3-[4-(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepin-3-yl)phenyl]thiourea cyclization with α-bromoketone

An important step in creation of potential drugs is to confirm the structure of the compounds synthesized. This requires the use of modern physical and physico-chemical methods of research. Nowadays a promising scientific direction for searching biologically active substances is the study of 2-R-imino-1,3-thiazoline derivatives.

Aim. To study regioselectivity of the cyclization reaction of 1-ethyl-3-[4-(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepin-3-yl)phenyl]thiourea with 2-bromo-1-phenylethanone.

Results. The true structure of the interaction product was determined by the methods of ^1H NMR spectroscopy and X-ray analysis. Quantum chemical calculations of the electronic structure, geometry and thermodynamic parameters of the initial thiourea three tautomers were given. Activating energy of tautomer 1A below than 1B one, the state of 1B has modest lower relative energy, consequently tautomer 1A is more credible state. Thus, the conclusion can be made that the reaction will proceed by 1-1A-3A.

Experimental part. Quantum chemical calculations of the electronic structure, geometry and thermodynamic parameters of the initial thiourea three tautomers were determined by the density functional theory (DFT) methods using the GAUSSIAN W09 computer program. The effect of the solvent was considered within the framework of polarized continuum model (PCM).

Conclusions. Based on the physico-chemical studies and quantum chemical calculations of the reaction cyclization direction the conclusion has been made that the cyclization reaction of 1-ethyl-3-[4-(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepin-3-yl)phenyl]thiourea 1 with 2-bromo-1-phenylethanone 2 is regioselective, and it leads to formation of more thermodynamically advantageous (stable) isomer 3A.

Key words: 5H-[1,2,4]triazolo[4,3-a]azines; cyclization; quantum chemical calculations; continuum; activation energy; relative energy; B3LYP/6-31+G(d) and M06-2X/6-31+G(d) GAUSSIAN W09 program methods; thermodynamics parameters; saddle point

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The main task of pharmaceutical and organic chemistry is modeling of new biologically active substances and their synthesis. An important step in creation of potential drugs is to confirm the structure of the compounds synthesized. This requires the use of modern physical and physico-chemical methods of research.

Nowadays a promising scientific direction for searching biologically active substances is the study of 2-R-imino-1,3-thiazoline derivatives.

According to the literature data substances containing the iminothiazoline nucleus proved themselves as antimicrobial [1], anti-inflammatory and analgesic agents [2, 3]; substances with triazole and azepine cycles showed themselves as antifungal [4] and anticorrosive [5] agents.

Continuing the search for new biologically active substances among 2-R-phenyliminothiazole derivatives [6-9] the new series of derivatives containing the triazolazepine fragment were synthesized by the condensation reaction of 1-ethyl-3-[4-(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepin-3-yl)phenyl]thiourea with 2-bromo-1-phenylethanone [10].

Theoretically, cyclization is possible in two ways. Therefore, the aim of our work is to determine regioselectivity of the interaction of 1-ethyl-3-[4-(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepin-3-yl)phenyl]thiourea with 2-bromo-1-phenylethanone by 'H NMR-spectroscopy, and based on quantum chemical calculations of parameters of the initial thiourea isomers, as well as the final confirmation of the cyclization direction using X-ray analysis.

Materials and Methods

The synthesis was carried out by the condensation reaction of 1-ethyl-3-[4-(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepin-3-yl)phenyl]thiourea with 2-bromo-1-phenylethanone according to the procedure described in the works [10, 11]. Due to tautomerism of asymmetric thiourea I the reaction of cyclization is theoretically possible by directions A and B (Scheme):

In the 'H NMR-spectrum of compound 3 synthesized (Fig. 1) the signals of aromatic protons as multiplets at 7.50-7.60 ppm (the aromatic system in position C-4 of the thiazole cycle) and as a doublets at 7.41 and 7.69 ppm (the aromatic system bound with an exocyclic Nitrogen atom), as well as the signal of the methine proton of the thiazole cycle as a singlet at 6.50 ppm were identified. A set of signals of the azepine cycle protons was presented in the spectrum as multiplets at 7.50-7.60 ppm (the aromatic system in position C-4 of the azepine cycle) and as a singlet at 6.50 ppm (the aromatic system in position C-4 of the azepine cycle). The signals of the ethyl residue protons were at 3.90 ppm as a quartet (the methylene group bound with an endo-azepine cycle) and at 1.15 ppm as a triplet (the methyl group bound with the methylene cycle).

Quantum chemical calculations were conducted by the licensed version of the GAUSSIAN W09 program [12]. It allowed calculating the spatial structure and physico-chemical properties of molecular systems with high accuracy and reliability both in the gas-phase and in the condensed state. Tautomers are different spatial configurations of the molecular system. The certain local minimum on the surface of the potential...
energy corresponds to every permanent configuration. For every spatial configuration of the molecular system, in particular for permanent and transitional configurations, it is possible to calculate energies and thermodynamic parameters, such as enthalpy, free energy, entropy, etc. Transition between two permanent configurations requires overcoming of a certain power barrier, i.e. passing through a saddle point on the surface of the potential energy. The system configuration in the saddle point corresponds to the transitional structure (between two local minima). The presence of one imaginary frequency in the vibration spectrum of the equilibrium structure found confirms that it is actually the transitional one.

Activation energy was calculated as a difference in energies of the transitional and permanent struc-
ture (taking into account the “zero” vibrations energy). Within the framework of the model of the continuum polarized [13] a solvent is considered to be the continuous, homogeneous dielectric continuum characterized by the values of static and high-frequency dielectric constants. The molecule of the dissolved substance is located in the cavity with the solvent around it. The cavity is constrained by a set of spheres centered on the nuclei of atoms.

Calculations were conducted for tautomers \(1, 1A\) and \(1B\) in a free state and in the medium to be polarized (water). The most popular B3LYP functional and a relatively new M06-2X functional were used. Using M06-2X it is possible to achieve greater accuracy when calculating thermodynamic and kinetic characteristics [14], even if simple basic sets, such as 6-31 + G(d), are applied.

Using the methods of B3LYP/6-31 + G(d) and M06-2X/6-31 + G(d) methods has shown that both in the gas phase and in water tautomer \(1A\) is more energy advantageous. Activating energy of tautomer \(1A\) belower than \(1B\) one (Fig. 2, 3), the state of \(1B\) has modest lower relative energy (Fig. 4), consequently tautomer \(1A\) is more credible state. This fact allows to make the conclusion, which coincides with the results of the X-ray structure analysis, that the reaction of the synthesis will go in direction of \(3A\) isomer formation – hydrobromide 3-ethyl-4-phenyl-N-[4-(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepin-3-yl)phenyl]-1,3-thiazol-2(3H)-imine.

Fig. 2. Comparison of the activation energy of \(1\leftrightarrow1A, 1\leftrightarrow1B\) transitional states in each medium by each method

Fig. 3. Activation energies of tautomeric transformation for the \(1A\leftrightarrow1B\) transitional state in the gas phase calculated by B3LYP (M06-2X in brackets) method
Activation energies of tautomeric transformation for the 1A-1B transitional state in the gas phase calculated by B3LYP (M06-2X in brackets) method are presented in Fig. 3. When comparing quantum chemical calculations of the relative energy of 1A and 1B tautomers (Fig. 4) the conclusion can be made that the reaction will proceed by 1→1A→3A.

The X-ray analysis of compound 3 conducted indicates formation of isomer 3A – hydrobromide 3-(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepin-3-yl)phenyl-1,3-thiazol-2(3H)-imine. The results of studying the reaction regioselectivity by the density functional theory (DFT) methods using the GAUSSIAN W09 computer program coincide with the results of the physico-chemical studies. It indicates the promising application of quantum chemical calculations of the electronic structure, geometry and thermodynamic parameters of the initial thiourea tautomers in cyclization reactions of other asymmetric thioureas with α-bromoketones.

**Conflicts of Interest:** authors have no conflict of interest to declare.

**References**

1. Synthesis and antimicrobial activity of some novel 2-(substitutedfluorobenzoylmino)-3-(substitutedfluorophenyl)-4-methyl-1,3-thiazolines / A. Saeed, U. Shaheen, A. Haniff et al. // J. of Fluorine Chem. – 2010. – Vol. 131, Issue 3. – P. 333–339. doi: 10.1016/j.jfluchem.2009.11.005.

2. Synthesis of acridinium-thiolo derivatives and their evaluation for anti-inflammatory, analgesic and kinase inhibition activities / M. S. Mordhi, N. Singh, A. M. Lahoti et al. // Bioorg. & Med. Chem. – 2005. – Vol. 13, Issue 13. – P. 4291–4299. doi: 10.1016/j.bmc.2005.04.017.

3. Antinflamatory, Analgesic and Kinase inhibition activities of some Acridine derivatives / S. M. Sondhi, G. Bhattacharjee, R. K. Jameel et al. // Central Eur. J. of Chem. – 2004. – Vol. 2, Issue 1. – P. 1–15. doi: 10.2478/bf02476181.

4. Synthesis of 2-Acetylcyclohexylsulfonamides and Evaluation on Their Fungicidal Activity / X. Li, Z. Cui, X. Chen et al. // Int. J. Mol. Sci. – 2013. – Vol. 14, Issue 11. – P. 22544–22557. doi: 10.3390/ijms141122544.

5. Синтез, противокоррозионная и биоцидная активность производных триазоазепина / А. М. Демченко, К. Г. Назаренко, А. П. Макей и др. // Журн. прикладной химии. – 2004. – № 77 (5). – C. 794–797.

6. Synthesis of 2-(4-aryl(adamantyl)-2-phenylthiazol-3-yl)-ethanol derivatives and prediction of their biological activity / H. O. Veromina, I. V. Drapak, L. O. Perekhoda et al. // Der Pharma Chemica. – 2016. – Vol. 8, Issue 3. – P. 64–70.

7. Синтез походящих N-[4-метил-4-(6,7,8,9-тетрагидро-5H-[1,2,4]триазоло-3-а]-азепинов / С. А. Демченко, Г. О. Єрьоміна, Л. О. Перехода, А. М. Демченко // Матер. XXIV Укр. конф. з орг. хімії (Полтава, 19–23 вересня 2016 р.). – Полтава, 2016. – С. 217.

8. The anti-inflammatory and antioxidant properties of 4-(4-chlorophenyl)-2-phenyliminothiazol-3-yl-ethanol / O. Yu. Kosho, H. O. Veromina, L. O. Perekhoda, Z. G. Veromina // News of Pharmacy. – 2016. – Vol. 4, Issue 88. – P. 66–69.

9. The antioxidant properties of 1-[2-(phenylimino)-4-methyl-3-[3-(morpholine-4-yl)propyl]-3-hydroxy-1,3-thiazol-5-yl]ethane-1-one derivatives under conditions of artificial oxidative stress in vitro / L. Perekhoda, H. Veromina, I. Drapak et al. // SJMPS – 2017. – Vol. 3, Issue 1. – P. 55–59.

10. Синтез та властивості походів 3-[4’-амінотриазоло]-6,7,8,9-тетрагідро-5H-[1,2,4]триазоло[3,4-a]азепинів / С. А. Демченко, Г. О. Єрьоміна, Л. О. Перехода, А. М. Демченко // Метер.Укр. конф. з.орг.хімії (Полтава, 19–23 вересня 2016 р.). – Полтава, 2016. – С. 217.

11. Пат. на корисну модель № 111015 Україна, МПК C 07 B 43/00 A 61 K 31/427 A 61 P 29/00. Гідробромід (3-етил-4-феніл-3А-[1,2,4]триазоло-[4,3-a]азепин-3-йл)феніл-1,3-тіазол-2(3H)-иміне. Заявл. 26.04.2016; опубл. 25.10.2016, Бюл. № 20.
13. Tomasi, J. Quantum mechanical continuum solvation models / J. Tomasi, B. Mennucci, R. Cammi // Chem. Rev. – 2005. – Vol. 105, Issue 8. – P. 2999–3094. doi: 10.1021/cr9904009.

14. Zhao, Y. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals / Y. Zhao, D. G. Truhlar // Theor. Chem. Account. – 2007. – Vol. 120, Issue 1–3. – P. 215–241. doi: 10.1007/s00214–007–0310-x.

References
1. Saeed, A., Shaheen, U., Hameed, A., Kazmi, F. (2010). Synthesis and antimicrobial activity of some novel 2–(substituted fluorobenzoylimino)–3–(substituted fluorophenyl)–4–methyl–1,3–thiazolines. Journal of Fluorine Chemistry, 131 (3), 333–339. doi: 10.1016/j.jfluchem.2009.11.005.

2. Sondhi, S. M., Singh, N., Lahoti, A. M., Bajaj, K., Kumar, A., Lozach, O., Meijer, L. (2005). Synthesis of acridinyl–thiazolino derivatives and their evaluation for anti-inflammatory, analgesic and kinase inhibition activities. Bioorganic & Medicinal Chemistry, 13 (13), 4291–4299. doi: 10.1016/j.bmc.2005.04.017.

3. Sondhi, S., Bhattacharjee, G., Jameel, R., Shukla, R., Raghubir, R., Lozach, O., & Meijer, L. (2004). Antiinflammatory, analgesic and kinase inhibition activities of some acridine derivatives. Open Chemistry, 2 (1), 1–15. doi: 10.2478/bf02476181.

4. Li, X., Cui, Z., Chen, X., Wu, D., Qi, Z., Ji, M. (2013). Synthesis of 2–Acloyxycyclohexylidiamides and Evaluation on Their Fungicidal Activity. International Journal of Molecular Sciences, 14 (11), 22544–22557. doi: 10.3390/ijms141122544.

5. Demchenko, A. M., Nazarenko, K. N., Makei, A. P., Prikhodko, S. V., Kurnakova, I. N., Tretiak, A. P. (2004). Zhurnal prykladnoi khimii, 77 (5), 794–797.

6. Yeromina, H. O., Drapak, I. V., Perekhoda, L. O., Yaremchenko, V. D., Demchenko, A. M. (2016). Synthesis of 2–(4–aryl(adamantyl)–2–phenyliminothiazol–3–yl)–ethanol derivatives and prediction of their biological activity. Der Pharma Chemica, 8 (3), 64–70.

7. Perekhoda, L. O., Yeromina, H. O., Drapak, I. V., Sych, I. A., Demchenko, A. M., Komykhov, S. O. (2016). Zhurnal orhanichnoi ta farmatsevtychnoi khimii, 14, 3 (55), 52–57.

8. Koshova, O. Yu., Yeromina, H. O., Perekhoda, L. O., Yeromina, Z. G. (2016). The anti–allergic and antihistaminic properties of hydrobromide 2–[4–{(4–chlorophenyl)–2–phenyliminothiazol–3–yl}–ethanol. News of Pharmacy, 4 (80), 66–69.

9. Perekhoda, L., Yeromina, H., Drapak, I., Kolzar, N., Smokhik, O., Demchenko, N. (2017). The antioxidants properties of 1–{2–(R–phenylimino)–4–methyl–3–(3–{morpholine–4–yl}–propyl)–2,3–dihydro–1,3–thiazol–5–yl}–ethane–1–one derivatives under conditions of artificial oxidative stress in vitro. SMP, 3 (1), 55–59.

10. Demchenko, S. A., Yeromina, H. O., Perekhoda, L. O., Demchenko, A. M. (2016). Materiały XXIV Ukrainskoi konferentsii z organichnoi khimii, Poltava, 217. 11. Demchenko, S. A., Yeromina, H. O., Perekhoda, L. O., Yadlovs’ky, O. Ye., Bobkova, L. S., Demchenko, A. M. Patent №111015 Ukraina MPK C07B 43/00 A61K 31/427 A61P 29/00, № u2016 04704; declared 26.04.2016; published 25.10.2016, №20.

12. Gaussian 09, Revision A02. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. Marenich, J. Bloino, G. G. Janesko, R. Gomperts, B. Mennucci, M. Cossi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox. Gaussian, Inc., Wallingford CT, 2016.

13. Tomasi, J., Mennucci, B., Cammi, R. (2005). Quantum Mechanical Continuum Solvation Models. Chemical Reviews, 105 (8), 2999–3094. doi: 10.1021/cr9904009.

14. Zhao, Y., Truhlar, D. G. (2007). The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. Theoretical Chemistry Accounts, 120 (1–3), 215–241. doi: 10.1007/s00214–007–0310-x.