DFT analysis of the [3 + 2] heterocyclization reaction of ((1,2,4-triazole(1,3,4-oxadiazole)-3(2)-yl)methyl)thiopyrimidines

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The article examines the mechanisms of the heterocyclization reaction using density functional theory (DFT) methods. A quantum-chemical analysis of the starting compounds, transition states, and products was conducted, with energy barriers and key reaction stages identified. Particular attention was given to the influence of electronic and steric effects on the stability of the resulting heterocycles. The application of solvent models (PCM) allowed for more realistic simulation of reaction conditions. The study's findings provide a deeper understanding of chemical transformations in heterocyclic systems and can be utilized to optimize synthetic methods in medicine, agrochemistry, and materials science.

The aim of this work is to perform a DFT analysis of the heterocyclization reaction of ((1,2,4-triazole(1,3,4-oxadiazol)-3(2)-yl)methyl) thiopyrimidines and to evaluate the stability of the transition states, as well as the influence of substituents on the activation energy.

Materials and methods. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-500 spectrometer (500 MHz and 125 MHz, respectively) in DMSO-d_6, using TMS as the internal standard (Agilent Technologies, Santa Clara, California, USA). LC-MS analysis was performed using an Agilent 1260 Infinity HPLC System equipped with a diode-array detector and proton ionization. Elemental analysis (C, H, N, S) was conducted on an ELEMENTAR vario EL cube, with sulfanilamide as the standard. Melting points were determined using the capillary method on a Stanford Research Systems Melting Point Apparatus 100 (SRS, USA). The reagents were sourced from Sigma-Aldrich (Merck). All calculations were performed using the molecular visualization program GaussView 5.0.8 and the Gaussian 09 Rev E.01 software package.

Results. This article presents the results of a study on the mechanisms of [3 + 2] and [4 + 1] heterocyclization for the synthesis of 1,2,4-triazole and 1,3,4-oxadiazole derivatives. The reaction stages are analyzed in detail, including the formation of intermediates and cyclization, culminating in aromatization and the formation of stable heterocyclic structures. Thermodynamic analysis was conducted using the Gaussian 09 software package, incorporating calculations of enthalpy, entropy, and Gibbs free energy in both the gas phase and ethanol medium. The resulting energy profiles illustrate the key stages of the reactions and define the temperature conditions required for their execution. Special attention is given to the role of the solvent and other factors influencing process efficiency.

Conclusions. The DFT analysis revealed that the [3 + 2] heterocyclization reaction for forming the 1,2,4-triazole ring proceeds through several sequential stages, with the cyclization stage being the most energy-intensive. The obtained thermodynamic parameters confirm the feasibility of the reaction at temperatures above 85 °C in the gas phase and 78 °C in ethanol solution. The heterocyclization mechanism involves a nucleophilic attack by the amino group of hydrazide, thiol-thiourea tautomerism, ring closure, and structure aromatization. The most significant energy transitions are associated with the activation of the thiourea group and the formation of a new heterocyclic bond.

Keywords: 1,2,4-triazole, 1,3,4-oxadiazole, DFT-analysis of the reaction, [3 + 2] heterocyclization, [4 + 1] heterocyclization.

Current issues in pharmacy and medicine: science and practice. 2025;18(1):5-11

DFT-аналіз реакції [3 + 2] гетероциклізації ((1,2,4-тріазол(1,3,4-оксадіазол)-3(2)-іл)метил)тіопіримідинів

Ю. В. Карпенко

Розглянуто механізми реакції гетероциклізації за допомогою методів теорії функціоналу густини (DFT). Здійснили квантово-хімічний аналіз вихідних сполук, перехідних станів і продуктів, визначили енергетичні бар'єри та ключові стадії реакції. Особливу увагу приділили впливу електронних і стеричних ефектів на стабільність утворених гетероциклів. Застосування моделей розчинника (PCM) забезпечило більш реалістичне моделювання умов реакції. Результати дослідження сприяють детальнішому розумінню хімічних перетворень у гетероциклічних системах і можуть бути використані для оптимізації синтетичних методик у медицині, агрохімії та матеріалознавстві.

Мета роботи – здійснити DFT-аналіз реакції гетероциклізації ((1,2,4-тріазол(1,3,4-оксадіазол)-3(2)-іл)метил)тіопіримідинів, оцінити стабільність перехідних станів і вплив замісників на енергію активації.

Матеріали і методи. Спектри ЯМР ^{1}H і ^{13}C записували на спектрометрі Bruker AC-500 (500 МГц і 125 МГц відповідно) в ДМСО-d_6, використовуючи ТМС як внутрішній стандарт (Agilent Technologies, Санта-Клара, Каліфорнія, США). Аналіз LC-MS здійснили на системі HPLC Agilent 1260 Infinity з діодним детектором, використали протонну іонізацію. Елементний аналіз (C, H, N, S) вико-

ARTICLE INFO

UDC 547.792'793.4'854.83.057:544.18
DOI: 10.14739/2409-2932.2025.1.321480

Current issues in pharmacy and medicine: science and practice. 2025;18(1):5-11

Keywords: 1,2,4-triazole, 1,3,4-oxadiazole, DFT-analysis of the reaction, [3 + 2] heterocyclization, [4 + 1] heterocyclization.

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Received: 20.12.2024 // Revised: 23.01.2025 // Accepted: 24.01.2025

нали на ELEMENTAR vario EL cube із сульфаніламідом як стандартом. Температуру плавлення визначали капілярним методом на апараті Stanford Research Systems Melting Point Apparatus 100 (SRS, США). Реагенти придбано у Sigma-Aldrich (Merck). Усі обрахунки здійснили за допомогою програми візуалізації молекулярної ланки Gauss-View 5.0.8 і програмного пакета Gaussian 09 Revesio-A.02-SMP.

Результати. Наведено результати дослідження механізмів [3 + 2] і [4 + 1] гетероциклізації для синтезу похідних 1,2,4-тріазолу та 1,3,4-оксадіазолу. Детально розглянуто стадії реакції, включаючи утворення проміжних продуктів і циклізацію, що завершується ароматизацією та утворенням стабільних гетероциклічних структур. Виконали термодинамічний аналіз за допомогою програмного пакета Gaussian 09, зокрема обчислення ентальпії, ентропії та енергії Гіббса в газовій фазі й етанольному середовищі. Отримані енергетичні профілі ілюструють ключові етапи реакцій і визначають температурні умови їхньої реалізації. Особливу увагу приділено ролі розчинника та інших факторів, що впливають на ефективність процесів.

Висновки. Результати DFT-аналізу показали: реакція [3 + 2] гетероциклізації для утворення 1,2,4-тріазольного кільця проходить через кілька послідовних стадій, найбільш енергомісткий – етап циклізації. Отримані термодинамічні параметри підтверджують можливість проведення реакції за температури вище ніж 85 °C у газовій фазі та 78 °C у розчині етанолу. Механізм гетероциклізації включає нуклеофільну атаку аміногрупи гідразиду, тіол-тіокарбамідну таутомерію, замикання кільця й ароматизацію структури. Найважливіші енергетичні переходи пов'язані з активацією тіокарбамідної групи й утворенням нового гетероциклічного зв'язку.

Ключові слова: 1,2,4-тріазол, 1,3,4-оксадіазол, DFT-аналіз реакції, [3+2] гетероциклізація, [4+1] гетероциклізація.

Актуальні питання фармацевтичної і медичної науки та практики. 2025. Т. 18, № 1(47). С. 5-11

Density Functional Theory (DFT) analysis of heterocyclization reactions enables the investigation of reaction mechanisms, energy barriers, transition states, and the stability of the resulting products. This approach relies on quantum mechanical calculations to provide insights into the electronic processes within chemical systems. In heterocyclization reactions, such as the formation of triazoles or pyrimidines, DFT allows for the evaluation of transition state stability and the influence of substituents on activation energy. This information is invaluable for designing efficient synthetic pathways and predicting reaction outcomes [1].

Heterocyclization reactions are fundamental processes in modern organic chemistry, enabling the synthesis of structurally complex heterocyclic compounds that find extensive application across various scientific and industrial fields. Heterocycles play a critical role in pharmaceuticals, agrochemistry, and materials science, serving as structural components of numerous biologically active substances, catalysts, and functional materials. Given the significance of these compounds, optimizing synthesis conditions and elucidating the reaction mechanisms underlying heterocyclization represent pressing challenges in contemporary chemistry.

DFT is a powerful tool for investigating reaction mechanisms, enabling the evaluation of energy parameters, transition states, and reaction pathways. This method not only allows for the prediction of chemical transformation outcomes but also provides deeper insights into the nature of electronic interactions that govern the course of a reaction. The application of DFT is particularly valuable in the study of heterocyclization, as these reactions are often accompanied by complex electronic and steric effects that are difficult to analyze using experimental methods alone.

This study presents a comprehensive DFT analysis of a heterocyclization reaction, focusing on identifying key energy barriers, characterizing transition states, and investigating the electronic properties of intermediates and final products. The calculations were performed with consideration of solvent effects, enabling the modeling of more realistic reaction conditions. The obtained results not only enhance the understanding of heterocyclization mechanisms but also provide a scientific foundation for the rational design of synthetic methods and the prediction of properties of the resulting compounds.

Thus, this work not only expands theoretical understanding of chemical transformations in heterocyclic systems but also holds practical significance for the development of applied fields such as the creation of new medicines, agrochemicals, and functional materials.

Aim

The aim of this work is to perform a DFT analysis of the heterocyclization reaction of ((1,2,4-triazole(1,3,4-oxadiazol)-3(2)-yl)methyl)thiopyrimidines and to evaluate the stability of the transition states, as well as the influence of substituents on the activation energy.

Materials and methods

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-500 spectrometer (500 and 125 MHz, respectively) in DMSO-d_6, using TMS as the internal standard (Agilent Technologies, Santa Clara, California, USA). LC-MS analysis was performed on an Agilent 1260 Infinity HPLC System with a diode-array detector using proton ionization. Elemental analysis (C, H, N, S) was carried out on an ELEMENTAR vario EL cube, with sulfanilamide as the standard. Melting points were determined using the capillary method in a Stanford Research Systems Melting Point Apparatus 100 (SRS, USA). The used reagents were purchased from Sigma-Aldrich (Merck).

The compounds were synthesized using a known method [2,3], and the constants obtained corresponded to the literature data.

Preparation of 4-methyl-5-((pyrimidin-2-ylthio)methyl)-4H-1,2,4-triazole-3-thiol **1.3** *(general methods).* A mixture of 10 mmol of 2-(pyrimidin-2-ylthio)acetohydrazide, 10 mmol of sodium hydroxide, and 50 mL of purified water is boiled

Table 1. Calculated thermochemical values using Gaussian for the [3 + 2] heterocyclization of 1,2,4-triazole

Parameter, units of measurement	Compound 1.1	Compound 1.2	Compound TS1	Compound 1.3
Gas				
E (Thermal), kJ/mol	454.67528	134.9591	616.88896	523.76986
S, kJ/mol-kelvin	$459.34462 \cdot 10^{-3}$	$260.5795 \cdot 10^{-3}$	$558.92801 \cdot 10^{-3}$	$720.83008 \cdot 10^{-3}$
$E_0 + H_{corr}$, kJ/mol	-3857.0019694	-2221.287382	-6072.04358126	-5753.9529980
$E_0 + G_{corr}$, kJ/mol	-3857.2202194	-2221.411191	-6072.30914811	-5754.1886325
Ethanol				
E (Thermal), kJ/mol	425.21992	139.8753	616.41198x`	490.02171
S, kJ/mol-kelvin	$478.87135 \cdot 10^{-3}$	$305.0764 \cdot 10^{-3}$	$563.53459 \cdot 10^{-3}$	$720.84815 \cdot 10^{-3}$
$E_0 + H_{corr}$, kJ/mol	-3873.1564562	-2221.306327	-6072.16739419	-5774.8174387
$E_0 + G_{corr}$, kJ/mol	-3873.3839863	-2221.451282	-6072.43514508	-5775.0644286

for 2 hours. After complete cooling, 2 mL of concentrated acetic acid is added to the filtrate. The formed precipitate is filtered and washed with purified water. For analysis, the product is purified by recrystallization from DMF. The final product appears as a light yellow powder, soluble in aqueous solutions of alkali, DMF, and 1,4-dioxane.

4-Methyl-5-((pyrimidin-2-ylthio)methyl)-4H-1,2,4-triazole-3-thiol (**1.3**). Yield 72 %, light yellow powder, mp 266 °C (DMF). 1H NMR, δ, ppm. (J, Hz): 3,55 (s, 3H, -N-CH_3), 4,43 (s, 2H, -CH_2-), 7,19 (t, J = 4,4 Hz, 1H, Ar), 8,53 (d, J = 4,4 Hz, 2H, Ar), 12,83 (s, 1H, -SH). Mass spectrum, m/z (Irel, %) 240 [M+H]+ (100). Anal. calcd. for $C_8H_9N_5S_2$: C: 40.15 %; H: 3.79 %; N: 29.26 %; S: 26.79 %; Found: C: 40.11 %; H: 3.82 %; N: 29.35 %; S: 26.71 %.

Preparation of 5-((pyrimidin-2-ylthio)methyl)-1,3,4-oxadiazole-2-thiol **1.5** *(general methods).* A mixture of 0.01 mol of 2-(pyrimidin-2-ylthio)acetohydrazide, 0.01 mol of carbon disulfide, and 0.02 mol of potassium hydroxide in 50 mL of ethanol is boiled for 8 hours. After complete cooling, the mixture is filtered, and 5 mL of concentrated acetic acid is added to the filtrate. The resulting precipitate is filtered and washed with purified water. For analysis, the product is purified by recrystallization from DMF. The final product is a light yellow powder, soluble in aqueous alkali solutions, DMF, and 1,4-dioxane.

5-((Pyrimidin-2-ylthio)methyl)-1,3,4-oxadiazole-2-thiol (**1.5**). Yield: 63 %, light yellow powder, melting point: 195 °C (DMF). ^{1}H NMR spectrum, δ, ppm (J, Hz): 4,51 (2H, s, SCH_2CO), 4,95 (1H, s, SH), 7,21 (1H, t, J=3,7 Hz, H_{arom}), 8,51 (2H, d, J=3,7 Hz, H_{arom}). Mass spectrum, m/z (I_{rel}, %): 227 $[M+H]^+$ (100). Found, %: C 37.18; H 2.62; N 24.82; S 28.25. $C_7H_6N_4OS_2$. Calculated, %: C 37.16; H 2.67; N 24.76; S 28.34.

Computational quantum chemical methods. All calculations were performed using the GaussView 5.0.8 molecular visualization program [4] and the Gaussian 09 Revesio-A.02-SMP software package [5]. Ground state geometries were fully optimized using the widely used B3LYP method [6,7], with the 6-311-G(d,p) [8] basis set, without symmetry constraints, and using the default convergence criteria. Geometry optimization was followed by frequency calculations. Stationary structures were confirmed by ensuring that all ground states had only real frequencies, and all transition states had exactly one imaginary frequency, using the same method and basis set as those used for geometry optimization. The polarizable continuum model (IEFPCM) [9] was employed to account for the effect of bulk solution at the same level of theory.

Results

The mechanism of [3 + 2] heterocyclization to form 1,2,4-triazole from carboxylic acid hydrazide and methyl isothiocyanate involves several consecutive steps *(Fig. 1)*.

First, the nucleophilic amino group of the hydrazide attacks the electrophilic carbon of methyl isothiocyanate, forming the intermediate thiosemicarbazide. This intermediate undergoes thiol-thiourea tautomerism, which activates it for subsequent cyclization. Next, the interaction between the activated thiourea group and the carbonyl group of the hydrazide leads to ring closure and the elimination of a water molecule. In the final stage, a stable aromatic structure of 1,2,4-triazole with an added S-alkyl fragment is formed. Reaction conditions, such as temperature, pH of the medium, and the choice of solvent, play a crucial role in ensuring the efficiency of the process.

Thermodynamic calculations, performed using the Gaussian 09 Revesio-A.02-SMP software package, are presented in *Table 1*.

To calculate the enthalpy of a reaction in the standard way, Hess's law is applied:

$$\Delta_r H°(298K) = \Sigma\, \Delta_f H°_{prod}\,(298K) - \Sigma\, \Delta_f H°_{react}\,(298K).$$

Using calculations in Gaussian *(Table 1)*, the enthalpy of reaction can be simply calculated using the following equation:

$$\Delta_r H°(298K) = (E_0 + H_{corr})_{products} - (E_0 + H_{corr})_{reactants}.$$

For the [3 + 2] heterocyclization reaction equation, which forms 4-methyl-5-((pyrimidin-2-ylthio)methyl)-4H-1,2,4-triazole-3-thiol, the enthalpy of the reaction in both the gas

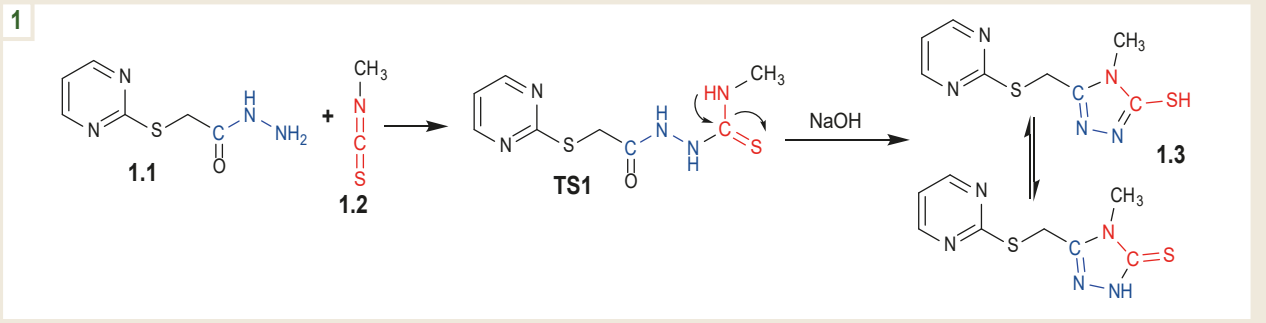

Fig. 1. Mechanism of [3 + 2] heterocyclization of 1,2,4-triazole.

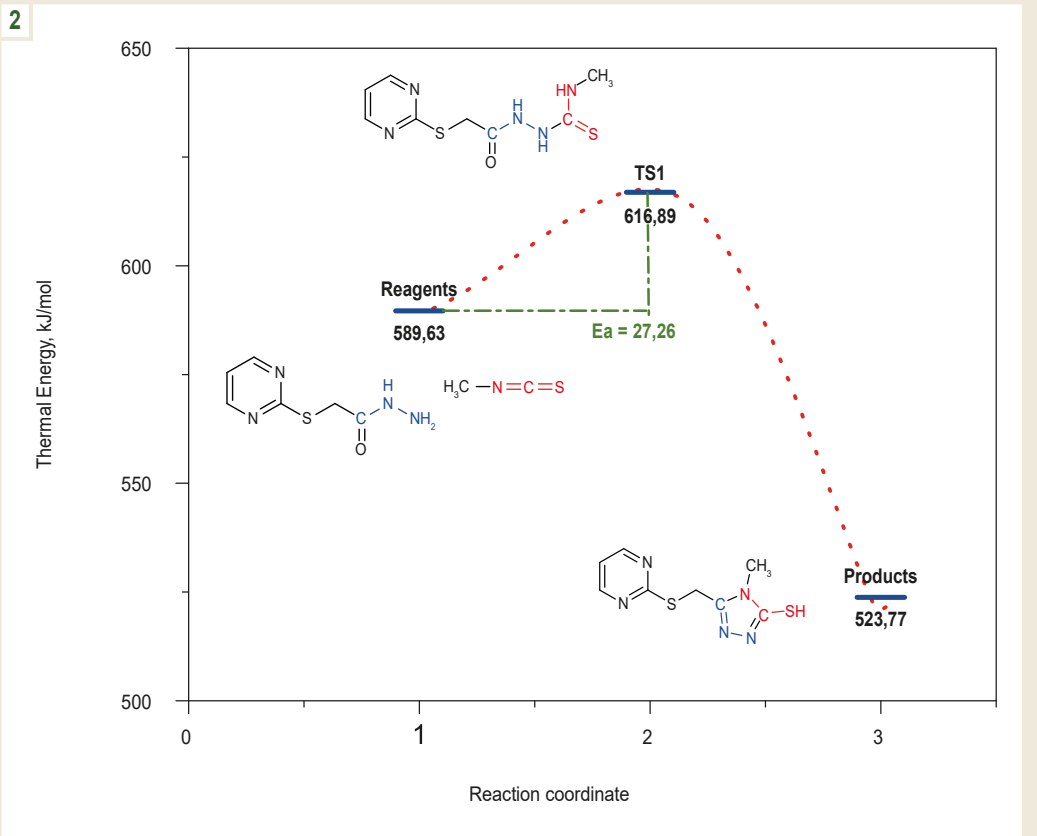

Fig. 2. Energy profile of the [3 + 2] heterocyclization of 1,2,4-triazole.

phase and ethanol solution (using the polarizable continuum approximation, IEFPCM) is:

$\Delta_r H°(298K, gas) = (E_0 + H_{corr})_{products} - (E_0 + H_{corr})_{reactants} =$
$= -5753.9529980 - (-3857.0019694 + (-2221.287382)) =$
$= 324.3363$ kJ/mol;

$\Delta_r H°(298K, ethanol) = (E_0 + H_{corr})_{products} - (E_0 + H_{corr})_{reactants} =$
$= -5774.8174387 - (-3873.1564562 + (-2221.306327)) =$
$= 319.645345$ kJ/mol;

$\Delta_r S°(298K, gas) = S_{products} - S_{reactants} = 720.83008 \cdot 10^{-3} -$
$- (260.5795 \cdot 10^{-3} + 459.34462 \cdot 10^{-3}) =$
$= 0.90596$ kJ/mol-kelvin;

$\Delta_r S°(298K, ethanol) = S_{products} - S_{reactants} =$
$= 739.45085 \cdot 10^{-3} - (260.5795 \cdot 10^{-3} + 478.87135 \cdot 10^{-3}) =$
$= 0.92403$ kJ/mol-kelvin.

The same short path can be used to calculate the Gibbs free energy of the reaction:

$\Delta_r G°(298K, gas) = (E_0 + G_{corr})_{products} - (E_0 + G_{corr})_{reactants} =$
$= -5754.1886325 - (-3857.2202194 + (-2221.411191)) =$
$= 324.442778$ kJ/mol;

$\Delta_r G°(298K, ethanol) = (E_0 + G_{corr})_{products} - (E_0 + G_{corr})_{reactants} =$
$= -5775.0644286 - (-3873.3839863 + (-2221.451282)) =$
$= 319.77084$ kJ/mol.

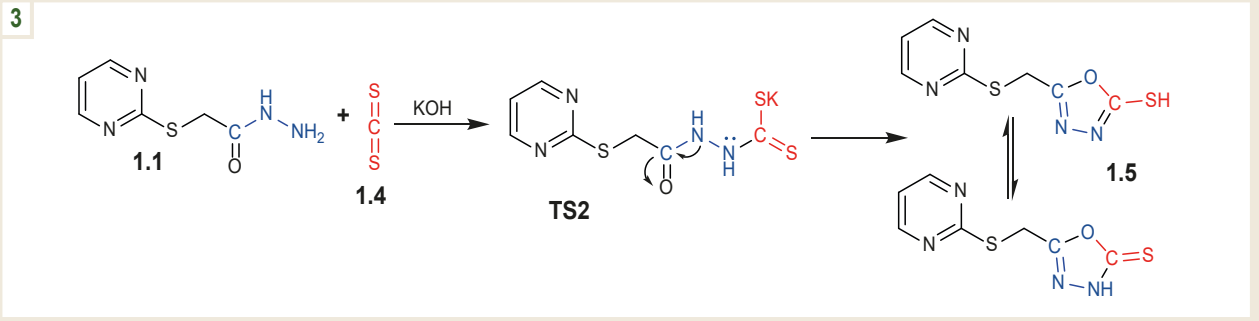

Fig. 3. Mechanism of [4 + 1] heterocyclization of 1,3,4-oxadiazole.

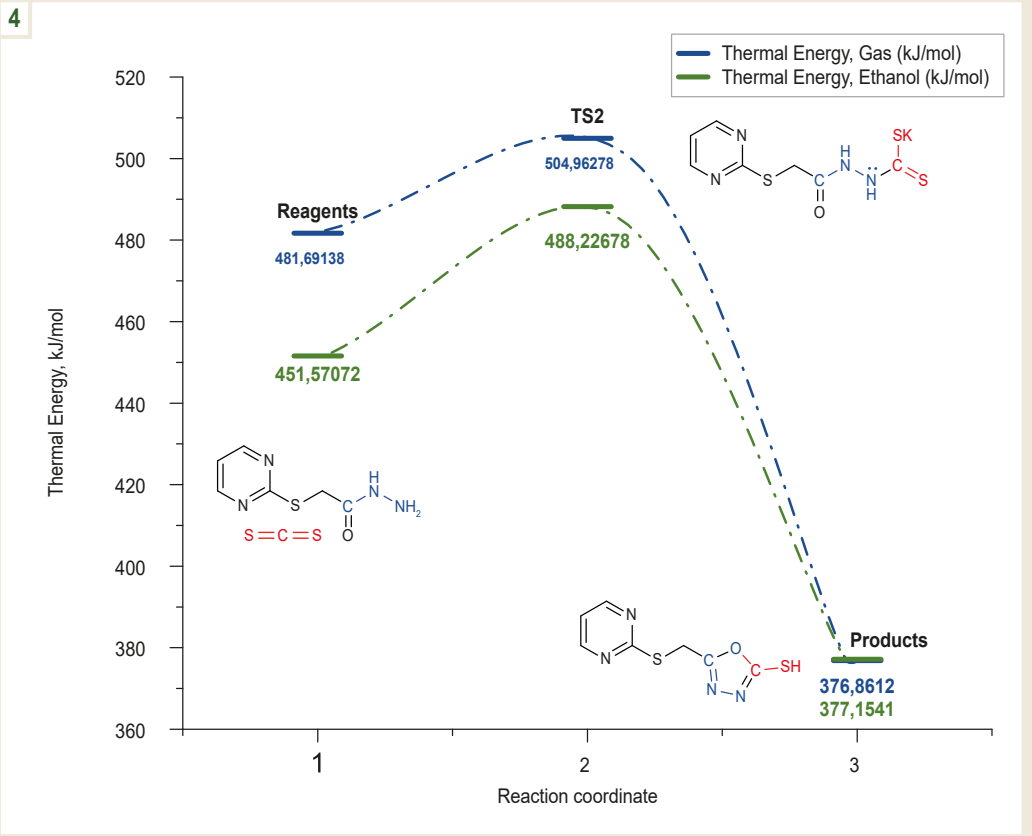

Fig. 4. Energy profile of the [4 + 1] heterocyclization of 1,3,4-oxadiazole.

The obtained data indicate the fundamental impossibility of carrying out the reaction at a temperature of T = 298 K. Using the Gibbs free energy equation, we can calculate the temperature at which heterocyclization becomes feasible:

$$T\,(gas) = \Delta H / \Delta S = 324.3363 / 0.90596 = 358\ K\ (85\ °C);$$

$$T\,(ethanol) = \Delta H / \Delta S = 324.3363 / 0.92403 = 351\ K\ (78\ °C).$$

Fig. 2 shows the energy profile of the [3 + 2] heterocyclization of 1,2,4-triazole, illustrating the changes in the system's free energy at each reaction step. The process begins with the interaction of hydrazide and methyl isothiocyanate, leading to the formation of an intermediate thiosemicarbazide complex. This step has a relatively low energy barrier due to the high nucleophilicity of the amino group.

Subsequent thiol-thiourea tautomerism activates the thiourea group, as indicated by a small increase in energy. The following cyclization, which involves the formation of a new heterocyclic bond, is the most critical and energy-intensive step, requiring the overcoming of a significant energy barrier. After this, the system stabilizes through aromatization and the formation of a 1,2,4-triazole ring, as reflected by a sharp decrease in energy in the profile.

The mechanism of [4 + 1] heterocyclization to form 1,3,4-oxadiazole from carboxylic acid hydrazide and carbon disulfide consists of several sequential stages *(Fig. 3)*.

The reaction begins with a nucleophilic attack by the amino group of hydrazide on the electrophilic carbon atom of

Table 2. Calculated thermochemistry values using Gaussian for the [4 + 1] heterocyclization of 1,3,4-oxadiazole

Parameter, units of measurement	Compound 1.1	Compound 1.4	Compound TS2	Compound 1.5
Gas				
E (Thermal), kJ/mol	454.67528	27.0161	504.96278	376.8612
S, kJ/mol-kelvin	$459.34462 \cdot 10^{-3}$	$235.9358 \cdot 10^{-3}$	$612.84722 \cdot 10^{-3}$	$699,85886 \cdot 10^{-3}$
$E_0 + H_{corr}$, kJ/mol	-3857.0019694	-3484.739996	-9872.39785174	-5693.5003987
$E_0 + G_{corr}$, kJ/mol	-3857.2202194	-3484.852097	-9872.68903304	-5693.7316233
Ethanol				
E (Thermal), kJ/mol	425.21992	26.3508	488.22678	377.1541
S, kJ/mol-kelvin	$478.87135 \cdot 10^{-3}$	$236.0153 \cdot 10^{-3}$	$619.77174 \cdot 10^{-3}$	$719.65248 \cdot 10^{-3}$
$E_0 + H_{corr}$, kJ/mol	-3873.1564562	-3484.743774	-9872.60398487	-5693.5612968
$E_0 + G_{corr}$, kJ/mol	-3873.3839863	-3484.855913	-9872.89845897	-5693.7932912

carbon disulfide, leading to the formation of an intermediate dithiocarbamate complex. This intermediate then undergoes intramolecular cyclization: the sulfur atom interacts with the carbonyl group of the hydrazide fragment, forming a heterocyclic structure. In the final stage, the ring undergoes aromatization, accompanied by the elimination of the H_2S molecule and the formation of a stable aromatic system of 1,3,4-oxadiazole.

Thermodynamic calculations, performed using the Gaussian 09 Revesio-A.02-SMP software package, are presented in *Table 2.*

For the [4 + 1] heterocyclization reaction equation, which forms 5-((pyrimidin-2-ylthio)methyl)-1,3,4-oxadiazole-2-thiol, the enthalpy of the reaction in both the gas phase and ethanol solution (using the polarizable continuum approximation, IEFPCM) is:

$$\Delta_r H°(298K, gas) = (E_0 + H_{corr})_{products} - (E_0 + H_{corr})_{reactants} =$$
$$= -5693.5003987 - (-3857.0019694 + (-3484.739996)) =$$
$$= 1648.2416 \text{ kJ/mol};$$

$$\Delta_r H°(298K, ethanol) = (E_0 + H_{corr})_{products} - (E_0 + H_{corr})_{reactants} =$$
$$= -5693.7932912 - (-3873.1564562 + (-3484.855913)) =$$
$$= 1664.2191 \text{ kJ/mol};$$

$$\Delta_r S°(298K, gas) = S_{products} - S_{reactants} = 699.85886 \cdot 10^{-3} -$$
$$- (235.9358 \cdot 10^{-3} + 459.34462 \cdot 10^{-3}) =$$
$$= 4.57844 \text{ kJ/mol-kelvin}$$

$$\Delta_r S°(298K, ethanol) = S_{products} - S_{reactants} = 719.65248 \cdot 10^{-3} -$$
$$- (236.0153 \cdot 10^{-3} + 478.87135 \cdot 10^{-3}) =$$
$$= 4.76853 \text{ kJ/mol-kelvin.}$$

The same method can be used to calculate the Gibbs free energy of the reaction:

$$\Delta_r G°(298K, gas) = (E_0 + G_{corr})_{products} - (E_0 + G_{corr})_{reactants} =$$
$$= -5693.7316233 - (-3857.2202194 + (-3484.739996)) =$$
$$= 1648.3984 \text{ kJ/mol};$$

$$\Delta_r G°(298K, ethanol) = (E_0 + G_{corr})_{products} - (E_0 + G_{corr})_{reactants} =$$
$$= -5693.7932912 - (-3873.3839863 + (-3484.743774)) =$$
$$= 1664.5664 \text{ kJ/mol.}$$

The obtained data indicate the fundamental impossibility of carrying out the reaction at a temperature of T = 298 K. Using the Gibbs free energy equation, we calculate the temperature at which heterocyclization becomes feasible:

$$T(gas) = \Delta H / \Delta S = 1648.2416 / 4.57844 = 360 \text{ K } (87 °C);$$

$$T(ethanol) = \Delta H / \Delta S = 1664.2191 / 4.76853 = 349 \text{ K } (76 °C).$$

Fig. 4 shows the energy profile of the [4 + 1] heterocyclization of 1,3,4-oxadiazole, demonstrating the sequential changes in the system's energy during the reaction between carboxylic acid hydrazide and carbon disulfide. In the first stage, the formation of an intermediate dithiocarbamate complex occurs, accompanied by a slight increase in energy due to overcoming the initial energy barrier for nucleophilic attack.

The subsequent intramolecular cyclization is the most energy-intensive step, as indicated by the peak in the profile. This stage requires overcoming a significant energy barrier to close the heterocyclic ring. The final step is aromatization, accompanied by the elimination of the H_2S molecule, which leads to a sharp decrease in energy and the formation of a stable aromatic product.

Discussion

The results of the thermodynamic analysis of the [3 + 2] heterocyclization reaction of 1,2,4-triazole indicate significant energetic and entropic differences between the compounds at different stages of the reaction, both in the gas phase and in ethanol. The transition state TS1 exhibits the highest values of thermal energy, which indicates its energetic tension and the great complexity of its structure. At the same time, the most thermodynamically stable compound is **1.1**, which has the lowest values of Gibbs energy ($E_0 + G_{corr}$) in both environments, indicating its preference as the final reaction product.

In the ethanol medium, compared to the gas phase, a decrease in Gibbs energy is observed for all compounds, highlighting the stabilizing effect of the solvent. This effect is particularly noticeable for **1.2**, whose entropy increases significantly in solution, indicating an increase in molecular mobility. Compound **1.3**, which has the highest entropy in both media, is characterized by significant branching or degrees of freedom in its structure.

The overall energy profile of the reaction confirms that heterocyclization proceeds through the high-barrier transition state TS1, after which the thermodynamically favorable compound **1.1** is formed.

When considering the [4 + 1] heterocyclization of 1,3,4-oxadiazole, the results of the thermodynamic analysis demonstrate significant differences in the energetic characteristics of the compounds at different stages, both in the gas phase and in ethanol solution. In the gas phase, the transition state TS2 exhibits the highest values of thermal energy and entropy, indicating the energetic complexity and tension of this stage. Compound **1.4**, on the other hand, is characterized by the lowest values of thermal energy and entropy, indicating its simple structure and high stability in the gas phase.

In the ethanol phase, a decrease in thermal energies is observed for all compounds, especially for TS2, indicating the stabilizing effect of the solvent. Similarly, the decrease in Gibbs energy in the ethanol phase for all compounds confirms that the solvent contributes to the thermodynamic stability of the molecules.

Overall, the transition state TS2 exhibits the highest energy barriers, while the stability of the final compounds, particularly **1.1**, emphasizes the thermodynamic directionality of the reaction. The obtained results confirm that the solvent (ethanol) lowers the energy barriers, contributing to the stabilization of both the transition and final states. This is important for optimizing the conditions for the synthesis of heterocyclic compounds.

The obtained data provide a better understanding of the mechanisms of this reaction and allow us to predict the stability of the products in different environments, which may be useful for developing new methods for the synthesis of heterocyclic compounds.

Conclusions

1. The DFT analysis showed that the [3 + 2] heterocyclization reaction forming the 1,2,4-triazole ring proceeds through several consecutive stages, the most energy-intensive of which is the cyclization stage. The obtained thermodynamic parameters confirm the possibility of carrying out the reaction at temperatures above 85 °C in the gas phase and 78 °C in an ethanol solution.

2. The mechanism of heterocyclization involves the nucleophilic attack of the amino group of the hydrazide, thiol-thiourea tautomerism, ring closure, and aromatization of the structure. The most significant energy transitions are associated with the activation of the thiourea group and the formation of a new heterocyclic bond.

3. The characterization of the synthesized compounds was confirmed by ^{1}H NMR, ^{13}C NMR, LC-MS, and elemental analysis. All results indicate high purity of the products, and the obtained spectra match the expected data for the target structures.

Conflicts of interest: author has no conflict of interest to declare.
Конфлікт інтересів: відсутній.

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