DOI: 10.6060/ivkkt.20266902.7259

УДК: 547.574

СИНТЕЗ И АНТИОКИСЛИТЕЛЬНАЯ АКТИВНОСТЬ АЗОМЕТИНОВ НА ОСНОВЕ 2-АМИНОТИАЗОЛА С ФРАГМЕНТОМ ЭКРАНИРОВАННОГО ФЕНОЛА

В.Н. Кошелев, О.В. Снастина, Р.Ш. Муминов, А.П. Сивакова

Владимир Николаевич Кошелев (ORCID 0000-0001-5755-5291), Ольга Вячеславовна Снастина (ORCID 0000-0002-0162-2528)*, Руслан Шухратович Муминов, Анна Павловна Сивакова

Кафедра органической химии и химии нефти, РГУ нефти и газа (НИУ) им. И.М. Губкина, Ленинский пр-т, 65, Москва, Российская Федерация, 119991
E-mail: koshelev.v@gubkin.ru, primerova92@yandex.ru*, rmuminov23@gmail.com, sivakova.anya@gmail.com

В настоящей работе был синтезирован ряд азометинов на основе 2-аминотиазола с фрагментом экранированного фенола. Синтез включал бромирование 4-гидрокси-2,6-ди-терт-бутилацетофенона бромидом меди (II). Кипячение полученного бромоацетофенона с тиокарбамидом в ацетоне в течение 24 ч привело к образованию 2-амино-4-арилтиазола с выходом 98%. Затем в ходе конденсации 2-аминотиазола с рядом ароматических альдегидов (4-нитробензальдегид, 2-гидрокси-3-нитробензальдегид, 3-нитробензальдегид, 3,5-дибром-2-гидроксибензальдегид, 4-диметиламинобензальдегид) в присутствии серной кислоты в качестве катализатора, были получены азометины с выходами от 35 до 71%. Структура полученных соединений была подтверждена с помощью ИК-спектрометрии, ^{1}H и ^{13}C ЯМР-спектроскопии. ИК спектры полученных веществ содержат полосы поглощения в области 1665-1630 $см^{-1}$, характерные для валентного колебания C=N азометиновой группы, полосы поглощения при 1621 $см^{-1}$, соответствующие C=N колебаниям в тиазольном кольце. Протонные спектры содержат пики протонов CH=N в области 9-10 ppm. Антиоксидантная активность полученных соединений была исследована двумя методами: ABTS (2,2'-азино-бис(3-этилбензотиазолин-6-сульфокислота – проявляется антирадикальная активность) и PFRAP (восстановительная сила феррицианида калия – выявление способности восстанавливать ионы железа Fe^{3+}). В качестве контрольного образца использовали распространенный промышленный антиоксидант – 4-метил-3,5-ди-терт-бутилфенол. Все синтезированные азометины показали высокую активность, за исключением соединения 4e (4-(2-((4-(диметиламино)2,6-ди-трет-бутилбензилиден)амино)тиазол-4-ил)фенол) в методе ABTS, которое оказалось менее активным по сравнению со стандартом. В обоих методах соединения на основе 3-нитробензальдегида и 3,5-ди-бром-2-гидроксибензальдегида проявили более высокую антиоксидантную активность.

Ключевые слова: тиазол, 2,6-ди-*трет*-бутилфенол, антиоксидант, антирадикальная активность

SYNTHESIS AND ANTIOXIDANT ACTIVITY OF AZOMETHINES BASED ON 2-AMINOTHIAZOLE WITH STERICALLY HINDERED PHENOL FRAGMENT

V.N. Koshelev, O.V. Snastina, R.Sh. Muminov, A.P. Sivakova

Vladimir N. Koshelev (ORCID 0000-0001-5755-5291), Olga V. Snastina (ORCID 0000-0002-0162-2528)*, Ruslan Sh. Muminov, Anna P. Sivakova

Department of Organic Chemistry and Petroleum Chemistry, Gubkin Russian State University of Oil and Gas (National Research University), Leninsky ave., 65, Moscow, 119991, Russia
E-mail: koshelev.v@gubkin.ru, primerova92@yandex.ru*, rmuminov23@gmail.com, sivakova.anya@gmail.com

In the present work, a series of azomethines based on 2-aminothiazole with a shielded phenol fragment were synthesized. The synthesis involved bromination of 4-hydroxy-2,6-di-tert-butylacetophenone with copper (II) bromide. Reflux the resulting bromoacetophenone with thiocarbamide in acetone for 24 h resulted in the formation of 2-amino-4-arylthiazole in 98% yield. Then,

during the condensation of 2-aminothiazole with a series of aromatic aldehydes (4-nitrobenzaldehyde, 2-hydroxy-3-nitrobenzaldehyde, 3-nitrobenzaldehyde, 3,5-dibromo-2-hydroxybenzaldehyde, 4-dimethylaminobenzaldehyde) in the presence of sulfuric acid as a catalyst, azomethines were obtained in yields from 35 to 71%. The structure of the obtained compounds was confirmed using IR spectrometry, ^{1}H and ^{13}C NMR spectroscopy. The IR spectra of the obtained substances contain absorption bands in the region of 1665-1630 cm^{-1}, characteristic of the C=N stretching vibration of the azomethine group, absorption bands at 1621 cm^{-1}, corresponding to C=N vibrations in the thiazole ring. The proton spectra contain peaks of CH=N protons in the region of 9-10 ppm. The antioxidant activity of the obtained compounds was studied by two methods: ABTS (2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid - showing antiradical activity) and PFRAP (potassium ferricyanide reducing power - revealing the ability to reduce iron ions Fe^{3+}), a common industrial antioxidant, 4-methyl-3,5-di-tert-butylphenol, was used as a reference sample. All synthesized azomethines showed high activity, with the exception of compound 4e (2,6-di-tert-butyl-4-(2-((4-(dimethylamino)benzylidene)amino)thiazol-4-yl)phenol) in the ABTS method, which turned out to be less active compared to the standard. In both methods, compounds based on 3-nitrobenzaldehyde and 3,5-di-bromo-2-hydroxybenzaldehyde showed higher antioxidant activity.

Keywords: thiazole, 2,6-di-*tert*-butylphenol, antioxidant, antiradical activity

Для цитирования:
Кошелев В.Н., Снастина О.В., Муминов Р.Ш., Сивакова А.П. Синтез и антиокислительная активность азометинов на основе 2-аминотиазола с фрагментом экранированного фенола. *Изв. вузов. Химия и хим. технология*. 2026. Т. 69. Вып. 2. С. 15–20. DOI: 10.6060/ivkkt.20266902.7259.

For citation:
Koshelev V.N., Snastina O.V., Muminov R.Sh., Sivakova A.P. Synthesis and antioxidant activity of azomethines based on 2-aminothiazole with sterically hindered phenol fragment. *ChemChemTech* [*Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol*.]. 2026. V. 69. N 2. P. 15–20. DOI: 10.6060/ivkkt.20266902.7259.

INTRODUCTION

Oxidative stress is an intensification of oxidative processes occurring in the body. In this case, antioxidants produced by the body itself are unable to cope with the action of prooxidase components (active forms of oxygen, such as singlet oxygen and peroxide compounds, hydroxyl radicals, etc.). As a result, free radical oxidation reactions are stimulated, antioxidant activity decreases, free radicals accumulate, and the process progresses to an even greater extent. As a result, the structure of proteins, lipids, and other macromolecules of the body changes, which leads to the emergence and development of various pathologies, including cancer [1-3].

Antioxidant activity can be exhibited by various compounds synthesized in vivo. An example of such an antioxidant of non-enzymatic nature is α-tocopherol, which contains a phenolic ring in its molecule.

Due to their high antioxidant activity, sterically hindered phenols are often used as a structural unit of biologically active substances [4], additives in the food industry [5-7], and also as an antioxidant additive to oils [8, 9].

Thiazole compounds are of great importance for pharmaceuticals, biochemistry, and clinical and experimental medicine. Thus, various thiazole derivatives can exhibit antiprotozoal [10], antiulcer [11], antiviral [12], antitumor [13], anti-inflammatory [14], antifungal [15], antituberculosis [16], neuroprotective [17, 18] and other types of biological activity. Thiazole-based drugs have an analgesic [19] and antiallergic [20] effect.

Thiazoles are the starting compounds for the synthesis of fungicides, biocides, and dyes [21]. Also, worth noting are studies in the field of antioxidant activity of thiazole derivatives, which have shown the ability to absorb radicals. [22-24].

The azomethine fragment in the molecule can also provide a number of useful properties. Thus, Schiff bases can exhibit antimicrobial, antiviral and antitumor activity [24-26]. Azomethines (for example, oxphalin (1-(3,4-dihydroxybenzylidene)-2,4,6-trimethylaniline)) are capable of inhibiting the action of lipoxygenase and exhibiting anti-inflammatory activity [27]. Lipoxygenases, in turn, in mammals participate in the pathogenesis of several inflammations, such as arthritis, psoriasis and bronchial asthma [28-30]. Azomethines are also characterized by antimicrobial, antimalarial, and fungicidal activity [31-34].

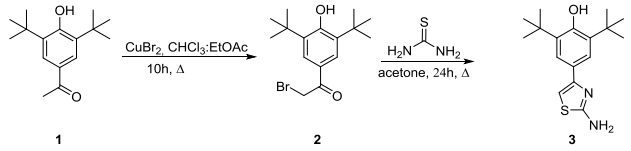
An interesting application of Schiff bases is their use as corrosion inhibitors [35]. Antioxidant ac-

tivity of some azomethine derivatives has been reported [36,37]. They are used as pigments and dyes, catalysts, semi-finished products in organic synthesis, and polymer stabilizers [38].

The aim of the work is to synthesize new azomethines that combine a thiazole fragment and 2,6-di-*tert*-butylphenol in their structure and to study the antioxidant activity of the obtained compounds.

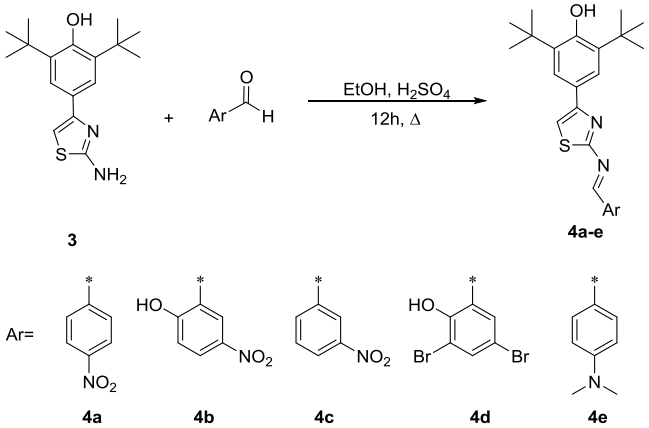
RESULTS AND DISCUSSION

The target azomethines were synthesized according to Schemes 1 and 2. In the first stage, 4-hydroxy-3,5-di-*tert*-butylacetophenone 1 was brominated with copper (II) bromide as a halogenating agent, with the yield of target bromide 2 of 91%.



Scheme 1. Scheme for bromacetophenone 2 synthesis
Схема 1. Схема синтеза бромацетофенона 2

2-Aminothiazole 3 was synthesized by the interaction of bromoacetophenone 2 with thiourea. The reaction was carried out by reflux the starting reagents in ethanol for 12 h. The target product was obtained in 98% yield. The IR spectrum contains an absorption band at 1621 cm^{-1}, corresponding to the stretching vibrations of the C=N bond in thiazole, absorption bands in the region of 3100 cm^{-1}, characteristic of the amino group, and bands, characteristic for phenolic ring: 3580 cm^{-1} corresponding to O-H bond stretching vibration, 1153 cm^{-1} corresponding to C-O bond stretching vibrations. The H^1 NMR spectrum contains a singlet at 7.75 ppm, corresponding to the CH proton in the thiazole ring, as well as peaks characteristic of *tert*-butylphenol: a singlet of two aromatic protons at 7.35 and a singlet of the OH proton of phenol at 6.99 ppm.



Scheme 2. Scheme for the preparation of azomethines **4a-e**
Схема 2. Схема получения азометинов **4a-e**

Azomethines **4a-e** were obtained by reaction between thiazole 3 with a number of aldehydes. The best yields were obtained by refluxing the starting materials in ethanol in the presence of catalytic amounts of sulfuric acid. All spectra show the absence of a band characteristic of aromatic amines (3500-3300 cm^{-1}), while bands are present in the region of 1665-1630 cm^{-1}, indicating the presence of the azomethine group. The proton spectra contain peaks of CH=N protons in the region of 9-10 ppm, peaks corresponding to aromatic protons of phenol at 7.03-7.10 ppm, and strong field signals indicating the presence of *tert*-butyl groups.

The ABTS method was used to study the ability of the compounds to interact with cation radicals (Fig. 1). All synthesized azomethines showed high activity, with the exception of compound **4e**, which was less active than the standard – 4-methyl-3,5-di-*tert*-butylphenol (BHT). The highest activity was shown by azomethines **4c** and **4d** based on meta-nitrobenzaldehyde and 3,5-di-bromo-2-hydroxybenzaldehyde.

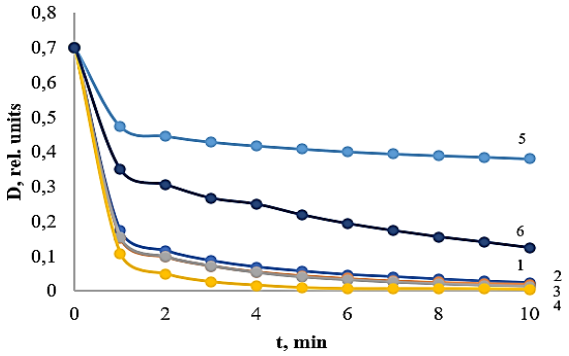


Fig. 1. Results of the antioxidant activity by ABTS method
1 – **4a**, 2 – **4b**, 3 – **4c**, 4 – **4d**, 5 – **4e**, 6 – BHT
Рис. 1. Результаты исследования антиокислительной активности по методу ABTS 1 – **4a**, 2 – **4b**, 3 – **4c**, 4 – **4d**, 5 – **4e**, 6 – BHT

To study the ability of compounds to exhibit electron-donor properties, the PFRAP method was used, based on the analysis of iron-reducing activity. The results of the measurements are presented in Fig. 2.

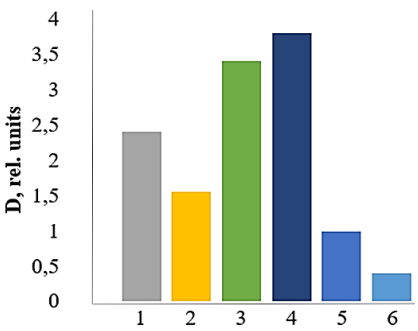


Fig. 2. Results of the antioxidant activity by PFRAP Assay 1 – **4a**, 2 – **4b**, 3 – **4c**, 4 – **4d**, 5 – **4e**, 6 – BHT
Рис. 2. Результаты исследований по методу PFRAP 1 – **4a**, 2 – **4b**, 3 – **4c**, 4 – **4d**, 5 – **4e**, 6 – BHT

All synthesized compounds showed higher activity compared to BHT, the most active compounds were **4c** and **4d**.

EXPERIMENTAL PART

Melting points were determined using a Stuart SMP30 apparatus. IR spectra were recorded using an Agilent Carry 600 spectrometer equipped with an attenuated total reflectance (ATR) device. ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker Avance II 300 spectrometer (1H, 300 MHz; 13C, 75 MHz); Me4Si was used as an internal standard. Antioxidant activity was determined using a PE-2201 UV-VIS spectrophotometer.

*Preparation of 2-bromo-1-(3,5-di-tert-butyl-4-hydroxyphenyl)ethan-1-one **2***

Copper (II) bromide (17 mmol) was added to a solution of 4-acetyl-2,6-di-*tert*-butylphenol 1 (8 mmol) in 40 ml of a mixture of $CHCl_3$:EtOAc (1:1). The mixture was refluxed with stirring for 10 h, after which the reaction mixture was filtered, the filtrate was evaporated and filled with hexane, and stored under a layer of hexane. The product was obtained with a yield of 91%, m.p. 107-109 °C. (lit. 107.5-108.5 °C [39]).

*Preparation of 4-(2-aminothiazol-5-yl)-2,6-di-tert-butylphenol **3***

Bromoacetophenone 2 (0.5 g, 0.001 mol) was dissolved in 15 ml of ethanol, thiourea (0.125 g, 0.001 mol) was added. The mixture was refluxed with stirring for 10 h, resulting in the 2-aminothiazole derivative in 97% yield, white crystals, m.p. 190-192 °C. ^{1}H NMR (DMSO-d^{6}, δ, ppm, $^{3}J_{HH}$, Hz): 7.71 (s, 1H, CH thiazole), 7.35 (s, 2H, Har), 6.99 (s, 1H, OH), 1.40 (s. 18H, t-Bu). ^{13}C NMR (DMSO-d6, δ, ppm): 170.68, 155.75, 140.13, 125.77, 123.23, 120.90, 100.53, 35.17, 30.67. IR, ν, cm^{-1}: 1346, -C=N – 1621. ν_{N-H} – 3100, $\nu_{C=N}$ – 1621.

*Preparation of azomethines **4 a-e***

2-Aminothiazole **3** (1 equiv.) was dissolved in 10 ml of ethanol, aldehyde (1 equiv.) and a catalytic amount of sulfuric acid were added. The reaction mixture was refluxed with stirring for 24 h. The reaction progress was analyzed by TLC. After completion of the reaction, the mixture was poured into water. The mixture was extracted with butyl acetate, dried over sodium sulfate, the solvent was evaporated, the residue was taken up in water and purified by column chromatography on silica gel using a mixture of dichloroethane:ethanol 20:1 as an eluent.

4a: Orange crystals. Yield 35%, m.p. 126-128 °C. ^{1}H NMR (DMSO-d^{6}, δ, ppm, $^{3}J_{HH}$, Hz): δ 9.18 (s, CH=N), 8.17 (d, *J* = 9, 2H, Har), 7.56 (d, *J* = 9, 2H, Har), 7.23 (s, 1H, CH thiazole), 7.03 (s, 2H, Har), 6.85 (s, 1H, OH), 1.18 (s. 18H, t-Bu). ^{13}C NMR: 167.75, 154.20, 149.98, 147.22, 139.30, 128.17, 127.04, 125.26, 124.06, 118.60, 76.04, 64.20, 39.14, 30.79. IR, ν, cm^{-1}: ν_{NO_2} – 1519, 1346, $\nu_{C=N}$ – 1628.

4b: Orange crystals. Yield 68%, m.p. 143-145 °C. ^{1}H NMR (DMSO-d^{6}, δ, ppm, $^{3}J_{HH}$, Hz): 9.29 (s, CH=N), 8.55 (s, 1H, Har), 8.35 (d, *J*=9, 1H, Har), 7.99 (d, *J* = 9, 1H, Har), 7.10 (s, 2H, Har), 7.05 (s, 1H, CH thiazole), 6.90 (s, 1H, OH), 1.31 (s. 18H, t-Bu). IR, ν, cm^{-1}: ν_{NO_2} – 1524, 1340, $\nu_{C=N}$ – 1611.

4c: Orange crystals. Yield 41%, m.p. 197-198 °C. ^{1}H NMR (DMSO-d^{6}, δ, ppm, $^{3}J_{HH}$, Hz): 9.45 (s, CH=N), 8.42 (s, 1H, Har), 8.17 (d, *J* = 9, 1H, Har), 7.48 (d, *J* = 9, 1H, Har), 7.10 (m, 1H, Har), 7.03 (s, 2H, Har), 6.90 (s, 1H, OH), 1.33 (s. 18H, t-Bu). IR, ν, cm^{-1}: ν_{NO_2} – 1524, 1346, $\nu_{C=N}$ – 1611.

4d: Orange crystals. Yield 71%, m.p. 198-200°C. ^{1}H NMR (DMSO-d^{6}, δ, ppm, $^{3}J_{HH}$, Hz): 9.81 (s, 1H CH=N), 7.62 (s, 1H, CH thiazole), 7.25 (s, 1H, Har), 7.21 (s, 1H, OH), 7.03 (s, 2H, Har), 1.18 (s. 18H, t-Bu). IR, ν, cm^{-1}: $\nu_{C=N}$ – 1634.

4e: Orange crystals. Выход 38%. Т.пл. 312-314 °C. ^{1}H NMR (DMSO-d^{6}, δ, ppm, $^{3}J_{HH}$, Hz): 8.89 s (CH=N), 8.30 (s, 1H, CH thiazole), 7.68 (d, *J* = 9, 1H, Har), 7.15 (d, J = 9, 1H, Har), 7.03 (s, 2H, Har), 6.82 (s, 1H, OH), 2.89 (s, 6H, CH_3), 1.19 (s, 18H, t-Bu). ^{13}C NMR: 190.30, 167.72, 155.44, 139.39, 137.32, 129.02, 125.52, 125.10, 123.82, 123.74, 120.51, 111.55, 34.86, 30.38. IR, ν, cm$^{-1}\nu_{C=N}$ – 1628.

Antioxidant activity

ABTS. 2,2'-Azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (Sigma) radical cation (ABTS·+) was prepared by mixing 7 mM aqueous potassium persulfate solution and 2.45 mM ABTS ammonium salt solution. The resulting solution was kept in the dark at room temperature for 12-16 h before use. The working solution was prepared by diluting the previous volume of solution in ethanol until its absorbance at 734 nm was 0.70 ± 0.02. To 2.7 ml of the working solution, 300 μl of 250 mmol solution of the prepared compounds in DMSO were added. After 10 min, the absorbance at 734 nm was measured using a spectrophotometer. Percent inhibition calculated as ABTS (%) = (AbsControl - Abssasment)/AbsControl, where AbsControl is the absorbance of the ABTS radical in ethanol; Abssasment is the absorbance of the ABTS solution mixed with the sample/standard extract. All determinations were performed in triplicate.

Ferrum reducing capacity. To 100 μl of antioxidant solution (500 μM) were added 400 μl of EtOH (96%), 2.5 ml of H_2O, 750 μl of 1 M HCl, 750 μl of ferricyanide solution (1%), 250 μl of SDS (1%) and

250 μl of $FeCl_3$ $6H_2O$ (0.2%). The mixture was kept at 50 °C in a water bath for 20 min, allowed to cool to room temperature and the optical density was measured at 750 nm relative to the reagent without the test substance [40].

CONCLUSIONS

New azomethines were synthesized on the basis of 2-aminothiazole with a 2,6-di-*tert*-butylphenol fragment and a number of aromatic aldehydes. The yields were 35-71%. The structures of the obtained compounds were proven by ^1H, ^{13}C NMR and IR spectroscopy. The synthesized compounds, with the exception of substance **4e**, based on 4-dimethylaminobenzaldehyde showed a higher ability to interact with cation radicals compared to BHT. All the studied substances showed a higher iron-reducing activity compared to BHT; in both methods, azomethines based on 3-nitrobenzaldehyde and 3,5-dibromo-2-hydroxybenzaldehyde **4c** and **4d** showed a higher antioxidant activity.

The authors declare the absence a conflict of interest warranting disclosure in this article.

Авторы заявляют об отсутствии конфликта интересов, требующего раскрытия в данной статье.

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Поступила в редакцию 14.04.2025
Принята к опубликованию 02.10.2025

Received 14.04.2025
Accepted 02.10.2025