UDC 547.854.5+54.057 https://doi.org/10.24959/ophcj.19.962

N. I. Kobyzhcha[1], V. M. Holovatiuk[1], V. V. Rozhkov[2], V. I. Kashkovsky[1]

[1] V. P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry of the National Academy of Science of Ukraine. E-mail: vladimirxpu@ukr.net

[2] Institute of Organic Chemistry of the National Academy of Science of Ukraine

The synthesis of novel spirocyclic *N*-aryl-substituted 2-thiopyrimidine-4,6-diones

A convenient and efficient method for the synthesis of new unsaturated spiro-annulated *N*-aryl-4,6-dioxopyrimidine-2-thione derivatives has been developed. The resulting compounds can be potential biological active molecules or precursors for further chemical modification.

Aim. To develop the methods for the synthesis of new unsaturated spiro-annulated 2-thiopyrimidine-4,6-dione derivatives, which can be used as potentially biological active molecules or precursors for their formation.

Results and discussion. By condensation of *N*-aryl-substituted thioureas and allylmalonic acid using acetic anhydride or acetyl chloride the series of 5-allyl-substituted 2-thiopyrimidinediones has been synthesized. Their further alkylation with allyl bromide or metallyl chloride led to formation of 5,5-dialkenyl derivatives, which were converted to the corresponding unsaturated spirocyclic dioxopyrimidine-2-thiones by ring-closing metathesis.

Experimental part. The synthesis of the starting compounds and title products was performed by preparative chemical methods, TLC and column chromatography, elemental analysis, NMR-spectroscopy.

Conclusions. The efficient three-step synthetic route of new unsaturated spiro-annulated *N*-aryl-4,6-dioxopyrimidine-2-thione derivatives from the starting *N*-arylsubstituted thioureas and allylmalonic acid has been developed. The spiro-annulated products obtained can find application in biological and pharmaceutical science or as starting substrates for further chemical modification.

***Key words*:** nitrogen heterocycles; spiro-annulation; thiopyrimidine-4,6-dione, metathesis; Grubbs catalyst

Н. І. Кобижча, В. М. Головатюк, В. В. Рожков, В. І. Кашковський

Синтез нових спіроциклічних *N*-арилзаміщених 2-тіопіримідин-4,6-діонів

Розроблено зручний та ефективний метод синтезу нових ненасичених спіро-анельованих *N*-арилзаміщених 2-тіопіримідин-4,6-діонів. Одержані сполуки можуть бути потенційними біоактивними молекулами або прекурсорами для подальшої хімічної модифікації.

Мета роботи – розробка методів одержання нових ненасичених спіро-анельованих похідних 2-тіопіримідин-4,6-діону як потенційних біологічно активних сполук або напівпродуктів для їх отримання.

Результати та їх обговорення. Конденсацією *N*-арилзаміщених тіосечовин та алілмалонової кислоти із застосуванням оцтового ангідриду або ацетилхлориду синтезовано серію 5-алілзаміщених 2-тіопіримідиндіонів. При подальшому їх алкілуванні алілбромідом або металілхлоридом одержано 5,5-діалкенільні похідні, які реакціями метатезису із закриттям циклу було перетворено на відповідні ненасичені спіроциклічні діоксопіримідин-2-тіони.

Експериментальна частина. Синтез вихідних сполук та цільових продуктів класичними методами препаративної хімії; очистку та ідентифікацію отриманих сполук здійснено методами тонкошарової та колонкової хроматографії, елементним аналізом, ЯМР-спектроскопією.

Висновки. Розроблено ефективний тристадійний шлях отримання з вихідних тіосечовин та алілмалонової кислоти нових ненасичених спіро-анельованих похідних *N*-арил-4,6-діоксопіримідин-2-тіону. Одержані спіроциклічні продукти можуть знайти застосування в біології та фармацевтичній науці, або використовуватись як вихідні сполуки для подальшої хімічної модифікації.

***Ключові слова*:** азотовмісні гетеро цикли; спіро-анелювання; тіопіримідин-4,6-діон; метатезис; каталізатор Граббса

Н. И. Кобыжча, В. Н. Головатюк, В. В. Рожков, В. И. Кашковский

Синтез новых спироциклических *N*-арилзамещенных 2-тиопиримидин-4,6-дионов

Разработан удобный и эффективный метод синтеза новых ненасыщенных спиро-аннелированных *N*-арилзамещенных 2-тиопиримидин-4,6-дионов. Полученные соединения могут быть потенциальными биоактивными молекулами или исходными веществами для дальнейшей химической модификации.

Цель работы – разработка методов получения новых ненасыщенных спиро-аннелированных производных 2-тиопиримидин-4,6-диона как потенциальных биологически активных соединений или полупродуктов для их получения.

Результаты и их обсуждение. Конденсацией *N*-арилзамещенных тиомочевин и аллилмалоновой кислоты с использованием уксусного ангидрида или ацетилхлорида синтезирован ряд 5-аллилзамещенных 2-тиопиримидиндионов. При их последующем алкилировании аллилбромидом или металлилхлоридом получены 5,5-диалкенильные производные, которые реакциями метатезиса с закрытием цикла были конвертированы в соответствующие непредельные спироциклические диоксопиримидин-2-тионы.

Экспериментальная часть. Синтез исходных соединений и целевых продуктов классическими методами препаративной химии; очистка и идентификация полученных соединений проводились методами тонкослойной и колоночной хроматографии, методом элементного анализа, спектроскопией ЯМР.

Выводы. Разработан эффективный трехстадийный путь получения из исходных тиомочевин и аллилмалоновой кислоты новых ненасыщенных спиро-аннелированных производных *N*-арил-4,6-диоксопиримидин-2-тиона. Полученные спироциклические продукты могут найти применение в биологии и фармацевтической науке, а также использоваться как исходные соединения для дальнейшей химической модификации.

Ключевые слова: Азотсодержащие гетероциклы; спиро-аннелирование; тиопиримидин-4,6-дион; метатезис; катализатор Граббса

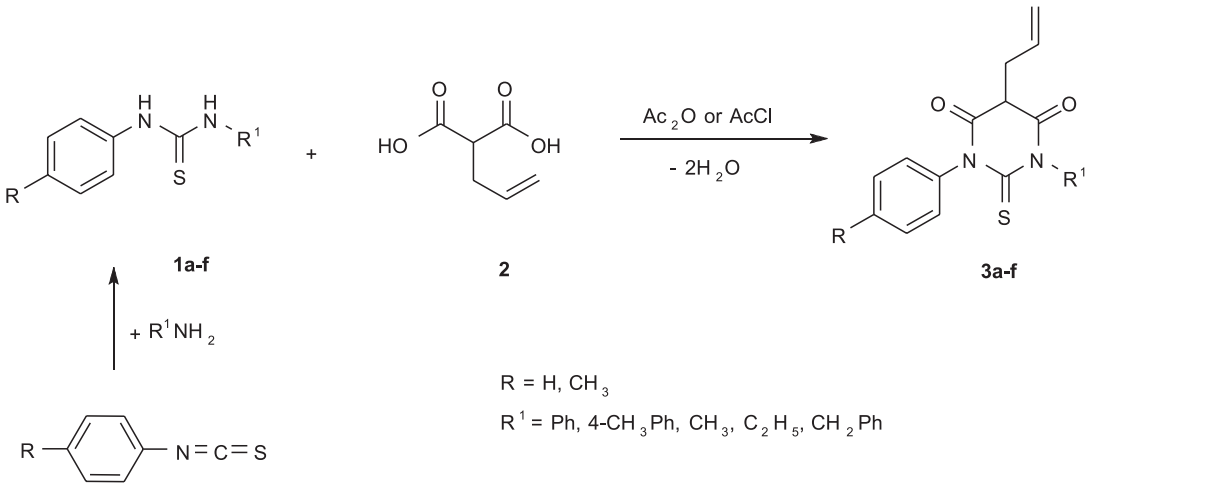
Barbituric acid derivatives have been shown to be a class of biologically significant heterocycles with a broad spectrum of pharmacological and physiological activities. Therefore, they are widely used in medicinal chemistry and drug discovery. The spiro analogs of (thio)barbituric acids have attracted significant attention in recent time since they show a wide range of activities, such as hypnotic and sedative [1-3], anticonvulsant [4], antibacterial [3, 5], anticancer [6], antifungal [5, 7], urease inhibitor [8] and others. Moreover, in many cases, spirobarbiturates have the higher therapeutic index than linear derivatives [2, 9, 10]. The possibility to obtain unsaturated spirobarbituric acids by ring-closing metathesis (RCM) were shown by Kotha and co-workers [11]. Their protocol was applied for the synthesis of 1,3-dialkyl-5,5-spirobarbiturates and some thiobarbiturates by RCM using the first generation Grubbs catalyst [12]. Recently, we have reported the synthesis of new spyrocyclic pyrimidinetriones with various aliphatic, heteroaliphatic, aromatic and functionalized substituents in positions 1 and 3 on the pyrimidine moiety from the corresponding 5,5-diallyl- or allylmetallyl-substituted derivatives via RCM [13]. It should be noted that the most effective catalyst for metathesis is the phosphine-free Grubbs-Hoveyda type complex. Herein, we present the convenient and effective method for the synthesis of new unsaturated spirocyclic *N*-aryl-substituted 4,6-dioxopyrimidine-2-thione derivatives.

The target spirocyclic molecules of *N*-aryldioxopyrimidine-2-thiones were prepared in 3 steps. In the beginning by condensation of disubstituted thioureas **1a-f** with commercially available allylmalonic acid **2** the series of monoallyl-substituted thiobarbituric acids **3a-f** were synthesized (Scheme 1). The corresponding thioureas were prepared from phenyl- or 4-tolylisothiocyanates and appropriate aliphatic and aromatic amines [14]. The condensation of malonic acid **2** with disubstituted arylthioureas **1a-f** were carried out utilizing acetic anhydride or acetyl chloride as dehydrating agents. The reactions with acetic anhydride were carried out at 110 °C for 3 h. At the same time, the use of acetyl chloride allowed decreasing the reaction temperature (60 °C) and making shorter the reaction time (45 min) (Tab. 1). The application of acetyl chloride has additional advantages. Firstly, it increases the yield of title compounds, and secondly, this method enables to form a minimal quantity of by-products.

In some cases the resulting thiobarbiturate derivatives were purified from impurities by column chromatography with silica gel using the mixture of benzene-hexane (3 : 1) as an eluent.

The next step was the synthesis of 5,5-dialkenyl-substituted dioxothiopyrimidines **6a-h** by C-alkylation of the resulting compounds **3a-f** with allyl bromide **4** or 2-methyl-3-chloro-1-propene (metallyl chloride) **5** (Scheme 2). In the case of allyl bromide **4** the reaction I was performed in dry acetonitrile in the presence of anhydrous K_2CO_3 as a base. 2-Methyl-3-chloro-1-propene **5** was less active than allyl bromide **4** and more sterically hindered, and therefore, for alkylation of barbiturates **3a, b** potassium tert-butoxide was used as a strong base. The attempts to use potassium carbonate or sodium ethoxide did not lead to formation of desirable products. Alkylation of compound **3a,b** with metallyl chloride **5** were performed in a highly polar aprotic solvent DMSO at 65 °C for 12-18 h (TLC control). The target 5,5-dialkenylsubstituted thiobarbiturates **6a-h** were purified by column chromatography with silica gel using the mixture of benzene-hexane (3 : 1) as an eluent. Yields of **6a-h** are listed in Tab. 2.

In order to convert 5,5-dialkenylthiobarbiturates **6a-h** into the corresponding spiro-annulated derivatives **7a-h** the ring-closing metathesis (RCM) was applied (Scheme 3). The phosphine-free Grubbs-Hoveyda type catalyst **8** was used for RCM. Upon the treatment with the ruthenium complex **8** (3-5 Mol. %) synthesized according to the known Hoveyda protocol [15] compounds **6a-h** were transformed into the corres-



Scheme 1. The synthesis of 5-allyl-substituted 2-thiopyrimidinediones

Table 1

Yields of new 5-allyl-substituted 2-thiopyrimidinediones

Entry	R	R^1	Product **3**	Isolated yields, %	
1	H	Ph	**3a**	34*	67**
2	CH_3	4-Tol	**3b**	29*	58**
3	CH_3	Ph	**3c**	24*	63**
4	H	CH_2Ph	**3d**	32*	71**
5	H	CH_3	**3e**	21*	65**
6	H	C_2H_5	**3f**	27*	59**

Notes: * – Reactions were carried out using thiourea **1a-e** (10 mmol), allylmalonic acid **2** (10 mmol), acetic anhydride (40 mmol), 110 °C, 3 h; ** – Reactions were performed using thiourea **1a-e** (10 mmol), malonic acid **2** (13 mmol), acetyl chloride (30 mmol), 60 °C, 45 min.

ponding spiro-annulated derivatives **7a-h** with over 70 %. Yields of the spirocyclic derivatives **7a-h** obtained are presented in Tab. 3.

The spirane ring was formed in the mixture of dichloromethane and toluene in the argon atmosphere at 40 °C for 2-3 h (Scheme 3). The concentration of the catalyst depends on allyl or methylallyl moieties on the thiobarbituric ring. More sterically hindered substrates demand the increase of the catalyst concentration. Products of metathesis were separated from the catalyst by column chromatography on silica gel using dichloromethane as an eluent, and the resulting crude thiopyrimidines **7a-h** were recrystallized from ethanol or the ethyl acetate-hexane mixture.

The synthetic route of RCM cyclization developed has some advantages compared to the protocols previously described. First of all, the reaction proceeds at moderate temperature (40 ˚C) and for relatively short time (2-3 h). The concentration of ruthenium catalyst **8** does not exceed 3-5 Mol. %.

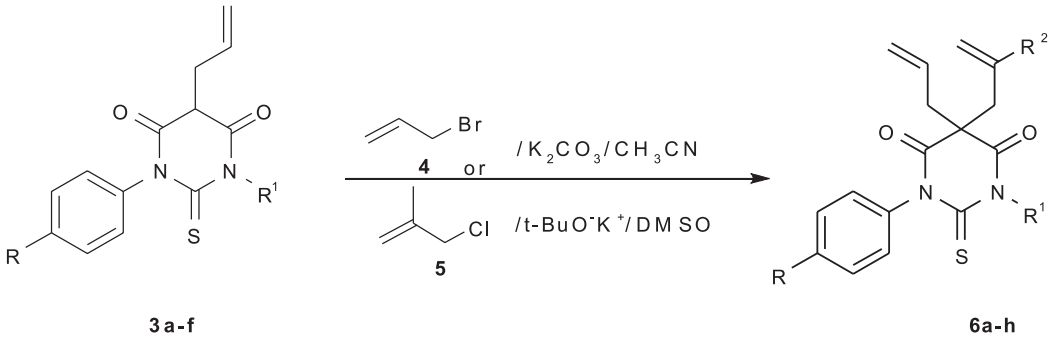
Formation of the cyclopentene ring was monitored by ^1H and ^{13}C NMR-spectroscopy. According to ^1H NMR data the disappearance of peaks at 5.94-5.63 ppm (–CH=) and 5.34-5.13 ppm (=CH_2), and the emergence of new signals at 5.72-5.65 ppm (–CH=CH–) indicate formation of the target thiobarbituric spiranes. In the case of ^{13}C NMR we observed the disappearance of carbon signals at 130.8-129.9 ppm (–CH=) and carbons at 121.5-121.0 ppm (=CH_2), and the appearance of the spirocycle double bond carbon peaks at 127.0–119.8 ppm (–CH=CH–).

The 5,5-spirocyclopentene *N*-aryl-4,6-dioxo-pyrimidine-2-thione derivatives **7a-h** synthesized can be useful for biological and pharmaceutical application. These spiranes can be used as building blocks for accessing a new type of thiobarbiturate derivatives. The double bond of cyclopentene ring can be also modified with various functional groups.

Experimental part

All reagents were commercial products used without further purification. Solvents were purified according to standard procedures. The ^1H and ^{13}C NMR-spectra were recorded on Varian Mercury 400 (400 and 100 MHz for ^1H and ^{13}C nuclei, respectively) and Bruker Avance DRX-500 (500 and 125 MHz for ^1H and ^{13}C nuclei, respectively) instruments. The ^{13}C NMR signals were assigned by using APT method. Chemical shifts were reported in ppm downfield from TMS (^1H, ^{13}C) as an internal standard. Elemental analysis was performed in the Analytical laboratory at the Institute of Bioorganic Chemistry and Petrochemistry of the NAS of Ukraine. Melting points were determined on a Boetius hot stage apparatus. The reaction progress was controlled by TLC on Silufol UV-254 plates using the mixture of benzene–acetonitrile (4 : 1) as an eluent. Purification of the compounds obtained was performed by column chromatography using silica gel 60 (particle size of 0.04-0.063 mm, 230-400 mesh).

5-Allyl-1-phenyl-4,6-dioxopyrimidine-2-thione derivatives **3a-f** were prepared by condensation of allylmalonic acid with disubstituted arylthioureas in the presence of dehydrating agents – acetic anhydride (method A) or acetyl chloride (method B).



Scheme 2. Alkylation of 5-allyl-*N*-aryldioxopyrimidine-2-thiones

Table 2

Yields of 5,5-dialkenyl-4,6-dioxopyrimidine-2-thione derivatives

Entry	R	R^1	R^2	Product **6**	Yield, %
1	H	Ph	H	**6a**	64***
2	CH_3	4-Tol	H	**6b**	58***
3	CH_3	Ph	H	**6c**	50***
4	H	CH_2Ph	H	**6d**	61***
5	H	CH_3	H	**6e**	47***
6	H	C_2H_5	H	**6f**	59***
7	H	Ph	CH_3	**6g**	49****
8	CH_3	4-Tol	CH_3	**6h**	51****

Notes: *** –Reaction was carried out using thiobarbitric acid **3a-e** (2 mmol), allyl bromide **4** (2.05 mmol), K_2CO_3 (2.5 mmol), acetonitrile, 50 °C, 3-5 h; **** Reaction was carried out using thiobarbituric acid **3a, b** (2 mmol), 2-methyl-3-chloro-1-propene **5** (2.2 mmol), potassium tert-butoxide (2 mmol), DMSO, 65 °C, 12-18h.

Method A (Exemplified by the synthesis of **3a**).

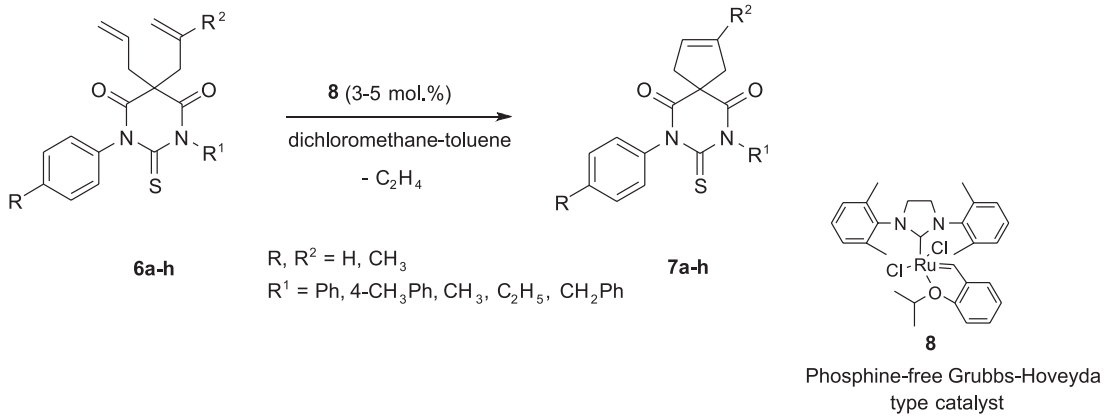
5-Allyl-1,3-diphenyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (3a). To the mixture of 1,3-diphenylthiourea **1a** (2.28 g, 10 mmol) and 3-allylmalonic acid **2** (1.44 g, 10 mmol) add acetic anhydride (3.80 g, 40 mmol), heat the resulting suspension and vigorously stir for 3 h at 110 °C. After completion of the reaction (TLC control) evaporate the excess of anhydride and acetic acid under reduced pressure, and pour the residue into cold water to precipitate a crude yellow product. Basificate the suspension to pH = 12 and stir with activated charcoal for 1 h, filter the mixture, and acidify the resulting solution with 15% aqueous hydrogen chloride to pH = 2. Collect the product by filtration and recrystallize from ethyl acetate–hexane or ethanol to provide the title thiopyrimidine **3a** as pale yellow crystals (1.14 g, 34%). M. p. – 134-136 °C. ^{1}H NMR, δ, ppm: 3.09 m (2H, CH_2), 3.98 t (1H, *J* = 4.8 Hz, CH), 5.36 m (2H, CH_2), 5.98 m (1H, CH), 7.15-7.22 m (4H, H_{Ar}), 7.48 m (6H, H_{Ar}). ^{13}C NMR, δ, ppm: 36.2 (CH_2), 50.3 (C-4), 121.0 (CH_2), 128.6 (C_{Ar}), 129.0 (C_{Ar}), 129.5 (C_{Ar}), 131.0 (CH), 138.8 (C_{Ar}), 166.6 (CO), 181.1 (CS). Anal. Calcd. for $C_{19}H_{16}N_2O_2S$: C 67.84, H 4.79, N 8.33. Found: C 67.75, H 4.71, N 8.27.

Method B (Exemplified by the synthesis of **3b**).

5-Allyl-2-thioxo-1,3-di(4-tolyl)dihydropyrimidine-4,6(1H,5H)-dione (3b). Heat di-*p*-tolylthiourea **1b** (2.56 g, 10 mmol), 3-allylmalonic acid **2** (1.87 g, 13 mmol) and acetyl chloride (2.35 g, 30 mmol) and vigorously stir for 45 min at 60 °C. Then evaporate all volatile components under reduced pressure, basificate the resulting residue to pH = 12 and stir with activated charcoal for 1 h. After that filter the mixture, and acidify the water solution with 15 % aqueous hydrogen chloride to pH = 2. Purify the crude product by column chromatography with silica gel using the mixture of benzene-hexane (3 : 1) and recrystallize from the ethyl acetate-hexane mixture (2 : 1). Compound **3b** was isolated as a yellow solid (1.75 g, 58 %). M. p. – 143-145 °C. ^{1}H NMR, δ, ppm: 2.43 s (6H, CH_3), 3.08 m (2H, CH_2), 3.97 t (1H, *J* = 5.2 Hz, CH), 5.36 m (2H, CH_2), 5.97 m (1H, CH), 7.04-7.11 m (4H, H_{Ar}), 7.32 m (4H, H_{Ar}). ^{13}C NMR, δ, ppm: 21.3 (CH_3), 36.2 (CH_2), 50.5 (C-4), 121.0 (CH_2), 128.2 (C_{Ar}), 130.2 (C_{Ar}), 131.1 (CH), 136.3 (C_{Ar}), 139.0(C_{Ar}), 166.7 (CO), 181.3 (CS). Anal. Calcd. for $C_{21}H_{20}N_2O_2S$: C 69.20, H 5.53, N 7.69. Found: C 69.31, H 5.42, N 7.61.

5-**Allyl-1-phenyl-2-thioxo-3-(4-tolyl)dihydropyrimidine-4,6(1H,5H)-dione (3c)**: M. p. – 106-108 °C. ^{1}H NMR, δ, ppm: 2.41 s (3H, CH_3), 3.08 m (2H, CH_2), 3.97 br t (1H, CH), 5.33-5.37 m (2H, CH_2), 5.95 m (1H, CH), 7.04-7.21 m (4H, H_{Ar}), 7.29 m (2H, H_{Ar}), 7.47 m (3H, H_{Ar}). ^{13}C NMR, δ, ppm: 21.3 (CH_3), 36.2 (CH_2), 50.3 (C-4), 121.0 (CH_2), 128.2 (C_{Ar}), 128.5 (C_{Ar}), 129.0 (C_{Ar}), 129.5 (C_{Ar}), 130.3 (C_{Ar}), 131.0 (CH), 136.2 (C_{Ar}), 138.9 (C_{Ar}), 139.1 (C_{Ar}), 166.7 (CO), 166.8 (CO), 181.2 (CS). Anal. Calcd. for $C_{20}H_{18}N_2O_2S$: C 68.55, H 5.18, N 7.99. Found: C 68.39, H 5.24, N 7.87.

5-Allyl-1-benzyl-3-phenyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (3d): M. p. – 82-84 °C. ^{1}H NMR, δ, ppm: 2.98 m (2H, CH_2), 3.84 t (1H, *J* = 4.4 Hz, CH), 5.17-5.20 m (2H, CH_2), 5.66 s (2H, CH_2Ph), 5.75 m (1H, CH), 7.06-7.13 m (2H, H_{Ar}), 7.28-7.34 m (3H, H_{Ar}),



Scheme 3. The synthesis of spirocyclic *N*-aryldioxopyrimidinethione derivatives via RCM

Table 3

Spirocyclyc thiobarbiturate derivatives obtained by RCM

Entry	R	R^1	R^2	Catalyst **8**, Mol.%	Product **7**	Yield, %
1	H	Ph	H	3	**7a**	89
2	CH_3	4-Tol	H	3	**7b**	92
3	CH_3	Ph	H	3	**7c**	83
4	H	CH_2Ph	H	3	**7d**	80
5	H	CH_3	H	4	**7e**	85
6	H	C_2H_5	H	3	**7f**	87
7	H	Ph	CH_3	5	**7g**	81
8	CH_3	4-Tol	CH_3	5	**7h**	77

7.42-7.47 m (5H, H_{Ar}). ^{13}C NMR, δ, ppm: 35.2 (CH_2), 49.7 (CH_2Ph), 50.2 (C-4), 120.1 (CH_2), 127.3 (C_{Ar}), 127.9 (C_{Ar}), 128.0 (C_{Ar}), 128.1 (C_{Ar}), 128.4 (C_{Ar}), 129.0 (C_{Ar}), 130.6 (CH), 135.3 (C_{Ar}), 138.8 (C_{Ar}), 165.9 (CO), 166.3 (CO), 180.4 (CS). Anal. Calcd. for $C_{20}H_{18}N_2O_2S$: C 68.55, H 5.18, N 7.99. Found: C 68.43, H 5.10, N 7.91.

5-Allyl-1-methyl-3-phenyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (3e): M. p. – 96-98 °C. ^{1}H NMR, δ, ppm: 2.99 m (2H, CH_2), 3.71 s (3H, CH_3), 3.82 t (1H, *J* = 5.2 Hz, CH), 5.21-5.27 m (2H, CH_2), 5.79 m (1H, CH), 7.14-7.06 br m (2H, H_{Ar}), 7.46 m (3H, H_{Ar}). ^{13}C NMR, δ, ppm: 35.3 (CH_2), 35.6 (CH_3), 50.1 (C-4), 120.5 (CH_2), 128.5 (C_{Ar}), 128.9 (C_{Ar}), 129.5 (CH), 131.2 (C_{Ar}), 139.2 (C_{Ar}), 166.5 (CO), 166.8 (CO), 181.1 (CS). Anal. Calcd. for $C_{14}H_{14}N_2O_2S$: C 61.29, H 5.14, N 10.21. Found: C 61.36, H 5.07, N 10.09.

5-Allyl-1-ethyl-3-phenyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (3f): M. p. – 85-87 °C. ^{1}H NMR, δ, ppm: 1.29 t (3H, *J* = 5.6 Hz, CH_3); 2.99 m (2H, CH_2), 3.79 t (1H, *J* = 4.4 Hz, CH), 4.47 q (2H, *J* = 5.6 Hz, CH_2), 5.24 m (2H, CH_2), 5.81 m (1H, CH), 7.07-7.14 m (2H, H_{Ar}), 7.43-7.50 m (3H, H_{Ar}). ^{13}C NMR, δ, ppm: 12.3 (CH_3), 35.9 (CH_2), 43.5 (CH_2), 50.0 (C-4), 120.5 (CH_2), 128.6 (C_{Ar}), 128.9 (C_{Ar}), 129.5 (CH), 131.0 (C_{Ar}), 139.2 (C_{Ar}), 166.3 (CO), 166.5 (CO), 180.5 (CS). Anal. Calcd. for $C_{15}H_{16}N_2O_2S$: C 62.48, H 5.59, N 9.71. Found: C 62.32, H 5.50, N 9.63.

The monoallyl substituted thiobarbiturates **3a-f** obtained were converted to the corresponding dialkenyl derivatives **6a-h** by alkylation of the active position 5 with allyl bromide **4** (method C) or 2-methyl-3-chloro-1-propene (metallyl chloride) **5** (method D).

Method C (Exemplified by the synthesis of **6a**).

5,5-Diallyl-1,3-diphenyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (6a). To the suspension of 5-allyl-1,3-diphenyl-2-thiopyrimidine-4,6-dione **3a** (0.67 g, 2.0 mmol) and anhydrous potassium carbonate (0.35 g, 2.5 mmol) in dry acetonitrile (5 ml) add dropwise allyl bromide **4** (0.25 g, 2.05 mmol). Heat the mixture with stirring for 3-5 h at 50 °C. After completion of the reaction (TLC control) filter all insoluble compounds, and evaporate the organic solvent. Purify the resulting residue by column chromatography using benzene-hexane (3 : 1) as an eluent to collect the yellow band. Analytically pure compound **6a** was obtained by recrystallization from ethanol as a pale yellow solid (0.48 g, 64 %). M. p. – 140-142 °C. ^{1}H NMR, δ, ppm: 2.90 d (4H, *J* = 7.2 Hz, CH_2), 5.30-5.34 m (4H, CH_2), 5.88 m (2H, CH), 7.14 d (4H, *J* = 7.6 Hz, H_{Ar}), 7.44-7.50 m (6H, H_{Ar}). ^{13}C NMR, δ, ppm: 43.6 (CH_2), 57.9 (C-4), 121.3 (CH_2), 128.5 (C_{Ar}), 128.9 (C_{Ar}), 129.5 (C_{Ar}), 130.7 (CH), 139.1 (C_{Ar}), 169.4 (CO), 180.4 (CS). Anal. Calcd. for $C_{22}H_{20}N_2O_2S$: C 70.19, H 5.35, N 7.44. Found: C 70.10, H 5.28, N 7.36.

Method D (Exemplified by the synthesis of **6g**).

5-Allyl-5-(2-methylallyl)-1,3-diphenyl-2-thioxodihydropyrimidine-4,6-(1H,5H)-dione (6g). Heat the mixture of 5-allyl-1,3-diphenyl-2-thiopyrimidine-4,6-dione **3a** (0.67 g, 2.0 mmol), 2-methyl-3-chloro-1-propene 5 (0.17 g, 2.2 mmol), and potassium *tert*-butoxide (0.22 g, 2.0 mmol) in dry DMSO (3 ml) for 12-18 h with vigorous stirring at 65 °C. After that pour the mixture into water and extract with dichlorometane (2 × 10 ml). Combine the organic layers and dry over anhydrous $MgSO_4$. Evaporate the solvent, and purify the residue by column chromatography using benzene-hexane (3 : 1). Analytically pure compound **6g** was obtained by re-crystallization from ethanol to give a yellow solid (0.38 g, 49 %). M. p. – 155-157 °C. ^{1}H NMR, δ, ppm: 1.84 br s (3H, CH_3), 2.90 m (4H, CH_2), 4.88 br d (1H, CH_2), 5.04 br d (1H, CH_2), 5.35 m (2H, CH_2), 5.88 m (1H, CH), 7.12-7.18 br m (4H, H_{Ar}), 7.45-7.49 m (6H, H_{Ar}). ^{13}C NMR, δ, ppm: 23.6 (CH_3), 45.2 (CH_2), 45.6 (CH_2), 56.8 (C-4), 114.6 (CH_2), 121.2 (CH_2), 128.0 (C_{Ar}), 128.4 (C_{Ar}), 129.0 (CH), 129.9 (CH), 138.7 (C_{Ar}), 139.9 (C_{Ar}), 169.0 (CO), 179.9 (CS). Anal. Calcd. for $C_{23}H_{22}N_2O_2S$: C 70.74, H 5.68, N 7.17. Found: C 70.85, H 5.61, N 6.99.

5,5-Diallyl-2-thioxo-1,3-di(4-tolyl)dihydropyrimidine-4,6(1H,5H)-dione (6b). M. p. – 145-147 °C. ^{1}H NMR, δ, ppm: 2.41 s (6H, CH_3), 2.89 d (4H, *J* = 7.2 Hz, CH_2), 5.28-5.32 m (4H, CH_2), 5.87 m (2H, CH), 7.03 d (4H, *J* = 7.6 Hz, H_{Ar}), 7.29 d (4H, *J* =7.6 Hz, H_{Ar}). ^{13}C NMR, δ, ppm: 21.3 (CH_3), 43.6 (CH_2), 57.9 (C-4), 121.2 (CH_2), 128.1 (C_{Ar}), 130.2 (CH), 130.8 (C_{Ar}), 136.4 (C_{Ar}), 138.9 (C_{Ar}), 169.5 (CO), 180.7 (CS). Anal. Calcd. for $C_{24}H_{24}N_2O_2S$: C 71.26, H 5.98, N 6.93. Found: C 71.18, H 5.89, N 6.87.

5,5-Diallyl-1-phenyl-2-thioxo-3-(4-tolyl)dihydropyrimidine-4,6(1H,5H)-dione (6c). M. p. – 154-156 °C. ^{1}H NMR, δ, ppm: 2.41 s (3H, CH_3), 2.89 d (4H, *J* = 6.0 Hz, CH_2), 5.28-5.33 br m (4H, CH_2), 5.87 m (2H, CH), 7.01 d (2H, *J* = 7.6 Hz, H_{Ar}), 7.13 d (1H, *J* = 7.2 Hz, H_{Ar}), 7.28 m (3H, H_{Ar}), 7.47 m (3H, H_{Ar}). ^{13}C NMR, δ, ppm: 21.3 (CH_3), 43.6 (CH_2), 57.9 (C-4), 121.2 (CH_2), 128.1 (C_{Ar}), 128.5 (C_{Ar}), 128.8 (C_{Ar}), 129.4 (C_{Ar}), 130.2 (CH), 130.8 (C_{Ar}), 136.6 (C_{Ar}), 138.8 (C_{Ar}), 139.2 (C_{Ar}), 169.4 (CO), 169.5

(CO), 180.5 (CS). Anal. Calcd. for $C_{23}H_{22}N_2O_2S$: C 70.74, H 5.68, N 7.17. Found: C 70.85, H 5.59, N 7.10.

5,5-Diallyl-1-benzyl-3-phenyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (6d). M. p. – 76-78 °C. ^{1}H NMR, δ, ppm: 2.81 m (4H, CH_2), 5.16 m (4H, CH_2), 5.60 m (2H, CH), 5.67 s (2H, CH_2Ph), 7.06 d (2H, *J* =6.8 Hz, H_{Ar}), 7.32 m (3H, H_{Ar}), 7.40 m (5H, H_{Ar}). ^{13}C NMR, δ, ppm: 43.6 (CH_2), 50.8 (CH_2Ph), 57.7 (C-4), 121.1 (C_{Ar}), 127.6 (C_{Ar}), 128.2 (C_{Ar}), 128.4 (C_{Ar}), 128.5 (128.5), 128.8 (C_{Ar}), 129.4 (C_{Ar}), 130.5 (CH), 135.8 (C_{Ar}), 139.7 (C_{Ar}), 169.1 (CO), 169.6 (CO), 180.3 (CS). Anal. Calcd. for $C_{23}H_{22}N_2O_2S$: C 70.74, H 5.68, N 7.17. Found: C 70.65, H 5.64, N 7.10.

5,5-Diallyl-1-methyl-3-phenyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (6e). M. p. – 80-82 °C. ^{1}H NMR, δ, ppm: 2.82 m (4H, CH_2), 3.71 s (3H, CH_3), 5.19-5.23 m (4H, CH_2), 5.69 m (2H, CH), 7.06 d (2H, *J* = 6.8 Hz, H_{Ar}), 7.47 m (3H, H_{Ar}). ^{13}C NMR, δ, ppm: 35.2 (CH_3), 43.4 (CH_2), 57.8 (C-4), 121.0 (CH_2), 128.5 (C_{Ar}), 128.8 (C_{Ar}), 129.4 (C_{Ar}), 130.6 (CH), 139.4 (C_{Ar}), 169.1 (CO), 169.6 (CO), 180.5 (CS). Anal. Calcd. for $C_{17}H_{18}N_2O_2S$: C 64.94, H 5.77, N 8.91. Found: C 64.87, H 5.71, N 8.87.

5,5-Diallyl-1-ethyl-3-phenyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (6f). M. p. – 90-91 °C. ^{1}H NMR, δ, ppm: 1.26 t (3H, *J* = 7.2 Hz, CH_3), 2.81 m (4H, CH_2), 4.47 q (2H, *J* = 7.2 Hz, CH_2), 5.20 m (4H, CH_2), 5.70 m (2H, CH), 7.05 d (2H, *J* =7.2 Hz, H_{Ar}), 7.43 m (3H, H_{Ar}). ^{13}C NMR, δ, ppm: 12.4 (CH_3), 43.6 (CH_2), 43.7 (CH_2), 57.4 (C-4), 121.0 (CH_2), 128.5 (C_{Ar}), 128.7 (C_{Ar}), 129.4 (C_{Ar}), 130.6 (CH), 139.5 (C_{Ar}), 169.1 (CO), 169.2 (CO), 179.8 (CS). Anal. Calcd. for $C_{18}H_{20}N_2O_2S$: C 65.83, H 6.14, N 8.53. Found: C 65.79, H 5.99, N 8.43.

5-Allyl-5-(2-methylallyl)-2-thioxo-1,3-di(4-tolyl)dihydropyrimidine-4,6(1H,5H)-dione (6h). M. p. – 162-164 °C. ^{1}H NMR, δ, ppm: 1.85 s (3H, CH_3), 2.41 s (6H, CH_3), 2.91 m (4H, CH_2), 4.88 br d (1H, CH_2), 5.03 br d (1H, CH_2), 5.34 m (2H, CH_2), 5.89 m (1H, CH), 6.99-7.06 br m (4H, H_{Ar}), 7.28 m (4H, H_{Ar}). ^{13}C NMR, δ, ppm: 21.2 (CH_3), 24.0 (CH_3), 45.6 (CH_2), 46.2 (CH_2), 57.3 (C-4), 115.2 (CH_2), 121.5 (CH_2), 127.9 (C_{Ar}), 130.2 (CH), 130.4 (C_{Ar}), 136.6 (C_{Ar}), 138.8 (C_{Ar}), 140.3 (C_{Ar}), 169.6 (CO), 180.6 (CS). Anal. Calcd. for $C_{25}H_{26}N_2O_2S$: C 71.74, H 6.26, N 6.69. Found: C 71.85, H 6.19, N 6.64.

The general procedure for the synthesis of spirocyclic 4,6-dioxopyrimidine-2-thiones 7a-h. To the solution of compound **6a-h** (5.8 mmol) in dry and deoxygenated dichloromethane and toluene (20 mL) add dropwise catalyst **8** (146 mg, 0.24 mmol) in dichloromethane at 40 °C under Ar. Stir the mixture for 2-4 h at the same temperature. After that evaporate the solvent, and separate the crude product from the ruthenium catalyst by column chromatography on silica gel using $CHCl_3$ as an eluent. Analytically pure compounds **7a-h** were obtained by re-crystallization from ethanol.

7,9-Diphenyl-8-thioxo-7,9-diazaspiro[4.5]dec-2-ene-6,10-dione (7a). M. p. – 170-172 °C. ^{1}H NMR, δ, ppm: 3.30 m (4H, CH_2), 5.70 br m (2H, CH), 7.21-7.26 br m (4H, H_{Ar}), 7.44-7.50 br m (6H, H_{Ar}). ^{13}C NMR, δ, ppm: 44.7 (CH_2), 57.1 (C-4), 127.0 (C_{Ar}), 128.2 (C_{Ar}), 128.9 (C_{Ar}), 129.5 (CH), 139.2 (C_{Ar}), 169.9 (CO), 180.9 (CS). Anal. Calcd. for $C_{20}H_{16}N_2O_2S$: C 68.94, H 4.63, N 8.04. Found: C 68.97, H 4.58, N 7.98.

8-Thioxo-7,9-di(4-tolyl)-7,9-diazaspiro[4.5]dec-2-ene-6,10-dione (7b). M. p. – 175-177 °C. ^{1}H NMR, δ, ppm: 2.42 s (6H, CH_3); 3.30 m (4H, CH_2), 5.70 m (2H, CH), 7.11 d (4H, *J* = 7.6 Hz, H_{Ar}), 7.32 d (4H, *J* = 7.6 Hz, H_{Ar}). ^{13}C NMR, δ, ppm: 21.3 (CH_3), 44.0 (CH_2), 57.1 (C-4), 127.0 (C_{Ar}), 128.0 (C_{Ar}), 130.2 (CH), 136.6 (C_{Ar}), 138.9 (C_{Ar}), 170.0 (CO), 181.2 (CS). Anal. Calcd. for $C_{22}H_{20}N_2O_2S$: C 70.19, H 5.35, N 7.44. Found: C 70.24, H 5.31, N 7.37.

7-Phenyl-8-thioxo-9-p-tolyl-7,9-diazaspiro[4.5]dec-2-ene-6,10-dione (7c). M. p. – 174-176 °C. ^{1}H NMR, δ, ppm: 2.41 s (3H, CH_3), 3.30 m (4H, CH_2), 5.69 m (2H, CH), 7.10 d (2H, *J* = 7.6 Hz, H_{Ar}), 7.18-7.30 m (4H, H_{Ar}), 7.43-7.51 m (3H, H_{Ar}). ^{13}C NMR, δ, ppm. 21.3 (CH_3), 44.0 (CH_2), 57.0 (C-4), 127.0 (C_{Ar}), 128.0 (C_{Ar}), 128.4 (C_{Ar}), 128.9 (C_{Ar}), 129.4 (C_{Ar}), 130.2 (CH), 136.5 (C_{Ar}), 138.9 (C_{Ar}), 139.2 (C_{Ar}), 170.0 (CO), 170.1 (CO), 181.1 (CS). Anal. Calcd. for $C_{21}H_{18}N_2O_2S$: C 69.59, H 5.01, N 7.73. Found: C 69.64, H 4.97, N 7.64.

7-Benzyl-9-phenyl-8-thioxo-7,9-diazaspiro[4.5]dec-2-ene-6,10-dione (7d). M. p. – 119-121 °C. ^{1}H NMR, δ, ppm: 3.15 m (4H, CH_2), 5.65 m (2H, CH_2), 5.67 s (2H, CH_2Ph), 7.13 d (2H, *J* = 7.2 Hz, H_{Ar}), 7.31-7.43 m (3H, H_{Ar}), 7.46-7.50 m (5H, H_{Ar}). ^{13}C NMR, δ, ppm: 43.8 (CH_2), 51.0 (CH_2Ph), 56.6 (C-4), 127.0 (C_{Ar}), 127.7 (C_{Ar}), 128.4 (C_{Ar}), 128.4 (C_{Ar}), 128.8 (C_{Ar}), 128.8 (C_{Ar}), 129.4 (CH), 135.8 (C_{Ar}), 139.6 (C_{Ar}), 169.8 (CO), 169.9 (CO), 180.8 (CS). Anal. Calcd. for $C_{21}H_{18}N_2O_2S$: C 69.59, H 5.01, N 7.73. Found: C 69.48, H 4.87, N 7.65.

7-Methyl-9-phenyl-8-thioxo-7,9-diazaspiro[4.5]dec-2-ene-6,10-dione (7e). M. p. – 177-179 °C ^{1}H NMR, δ, ppm: 3.18 m (4H, CH_2), 3.74 s (3H, CH_3), 5.68 m (2H, CH), 7.14 d (2H, *J* = 7.2 Hz, H_{Ar}), 7.42-7.49 m (3H, H_{Ar}). ^{13}C NMR, δ, ppm: 35.9 (CH_3), 44.5 (CH_2), 56.4 (C-4), 127.0 (C_{Ar}), 128.4 (C_{Ar}), 128.8 (C_{Ar}), 129.4 (CH), 139.4 (C_{Ar}), 170.1 (CO), 170.5 (CO), 181.0 (CS). Anal. Calcd. for $C_{15}H_{14}N_2O_2S$: C 62.92, H 4.93, N 9.78. Found: C 62.86, H 4.87, N 9.5.

7-Ethyl-9-phenyl-8-thioxo-7,9-diazaspiro[4.5]dec-2-ene-6,10-dione (10f). M. p. – 117-119 °C. ^{1}H NMR, δ, ppm: 1.29 t (3H, *J* = 6.8 Hz, CH_3), 3.16 m (4H, CH_2), 4.48 q (2H, *J* = 6.8 Hz, CH_2), 5.67 m (2H, CH), 7.13 d (2H, *J* =6.8 Hz, H_{Ar}), 7.42-7.49 m (3H, H_{Ar}). ^{13}C NMR, δ, ppm: 12.2 (CH_3), 43.9 (CH_2), 44.1 (CH_2), 56.5 (C-4), 127.0 (C_{Ar}), 128.4 (C_{Ar}), 128.8 (C_{Ar}), 129.4 (CH), 139.5 (C_{Ar}), 169.7 (CO), 170.0 (CO), 180.3 (CS). Anal. Calcd. for $C_{16}H_{16}N_2O_2S$: C 63.98, H 5.37, N 9.33. Found: C 63.89, H 5.32, N 9.27.

2-Methyl-7,9-diphenyl-8-thioxo-7,9-diazaspiro [4.5]dec-2-ene-6,10-dione (10g). M. p. – 145-147 °C. ^{1}H NMR, δ, ppm: 1.79 s (3H, CH_3), 3.17 m (2H, CH_2), 3.26 m (2H, CH_2), 5.25 m (1H, CH), 7.18-7.24 br d (4H, H_{Ar}), 7.42-7.52 m (6H, H_{Ar}). ^{13}C NMR, δ, ppm: 15.8 (CH_3), 45.0 (CH_2), 46.1 (CH_2), 57.8 (C-4), 119.8 (C_{Ar}), 128.5 (C_{Ar}), 128.9 (C^{10}), 129.5 (CH), 137.7 (C_{Ar}), 139.2 (C_{Ar}), 170.0 (CO), 181.0 (CS). Anal. Calcd. for $C_{21}H_{18}N_2O_2S$: C 69.59, H 5.01, N 7.73. Found: C 69.64, H 4.84, N 7.55.

2-Methyl-8-thioxo-7,9-di(4-tolyl)-7,9-diazaspiro [4.5]dec-2-ene-6,10-dione (10h). M. p. – 153-155 °C. ^{1}H NMR, δ, ppm: 1.78 s (3H, CH_3), 2.40 s (6H, CH_3), 3.15 m (2H, CH_2), 3.23 m (2H, CH_2), 5.24 m (1H, CH), 7.08 br d (4H, H_{Ar}), 7.27 br d (4H, H_{Ar}). ^{13}C NMR, δ, ppm: 15.7 (CH_3), 21.3 (CH_3), 44.8 (CH_2), 46.0 (CH_2), 57.8 (C-4), 119.7 (C_{Ar}), 128.1 (C^{10}), 130.2 (CH), 136.7 (C_{Ar}), 137.6 (C_{Ar}), 138.9 (C_{Ar}), 170.1 (CO), 181.3 (CS). Anal. Calcd. for $C_{23}H_{22}N_2O_2S$: C 70.74, H 5.68, N 7.17. Found: C 70.59, H 5.55, N 6.59.

Conclusions

The general and effective method for the facile synthesis of the novel unsaturated spirocyclic *N*-aryl-4,6-dioxopyrimidine-2-thiones derivatives has been developed. The synthetical pathway includes the condensation of disubstituted thioureas with allylmalonic acid and the preparation of 5,5-dialkenylsubstituted dioxothiopyrimidines by C-alkylation with allyl bromide or metallyl chloride. The latter ones are transformed into the corresponding spirocyclic thiobarbituric acids by utilizing the ring-closing metathesis of the phosphine-free third generation Grubbs-Hoveyda catalyst. The spiro-annulated products obtained can find application in biological and pharmaceutical science or as starting substrates for further chemical modification.

Conflict of interests: authors have no conflict of interests to declare.

References

1. Synthesis, hypnotic properties and molecular modeling studies of 1,2,7,9–tetraaza–spiro[4.5]dec–2–ene–6,8,10-triones / A. S. Girgis, H. Farag, N. S. Ismail, R. F. George // Eur. J. Med. Chem. – 2011. – Vol. 46 (10). – P. 4964–4969. https://doi.org/10.1016/j.ejmech.2011.07.058
2. US Pat. Appl., 2725380 A. Spiro barbituric acids / Arthur C. Cope. – declared 13.08.1949 ; published 29.11.1955.
3. Lee W. C. Comparative depression of several short acting barbiturates and spiro-barbiturates / W. C. Lee // Jap. J. Pharmacol. – 1953. – Vol. 2. – P. 123–126. https://doi.org/10.1254/jjp.2.123
4. Synthesis and anticonvulsant activity of certain spiro compounds derived from barbituric and thiobarbituric acids / A. N. Osman, M. M. Kandeel, M. M. Saidand, E. M. Ahmed // Ind. J. Chem. – 1996. – Vol. 35B. – P. 1073–1078. https://doi.org/10.1002/chin.199652179
5. Studies on spiroheterocycles Part–II : Heterocyclization of the spiro compounds containing cyclohexanone and thiobarbituric acid with different bidentate nucleophilic reagents / R. K. Behera, A. K. Behera, R. Pradhan et al. // Synth. Commun. – 2006. – Vol. 36. – P. 3729–3742. https://doi.org/10.1080/00397910600946231
6. Design, synthesis and anticancer activity of functionalized spiro–quinolines with barbituric and thiobarbituric acids / R. K. Bhaskarachar, V. G. Revanasiddappa, S. Hegde et al. // Med. Chem. Res. – 2015. – Vol. 24. – P. 3516–3528. https://doi.org/10.1007/s00044-015-1408-7
7. Studies on spiroheterocycles part-I: Installation of biologically active heterocyclic nuclei into spiro compounds derived from cyclohexanone and diphenyl thiobarbituric acid / R. K. Behera, A. K. Behera, R. Pradhan, M. Patra // Ind. J. Chem. – 2006. – Vol. 45B. – P. 933–942.
8. Green Synthesis and Urease Inhibitory Activity of Spiro–Pyrimidinethiones / Spiro–Pyrimidinones-Barbituric Acid Derivatives / M. Ziarani, S. Asadi, S. Faramarzi, M. Amanlou // Iran. J. Pharm. Res. – 2015. – Vol. 14 (4). – P. 1105–1114.
9. Synthesis and CNS depressant of newer spirobarbiturates / B. Goel, S. Sharma, K. Bajaj et al. // Ind. J. Pharm. Sci. – 2005. – Vol. 67. – P. 194–199.
10. Cope, A. Spirobarbituric Acids Containing a Six–membered Carbocyclic Ring / A. Cope, P. Kovacic, M. Burg // J. Am. Chem. Soc. – 1949. – Vol. 71 (11). – P. 3658–3662. https://doi.org/10.1021/ja01179a023
11. Kotha, S. Spiro-annulation of barbituric acid derivatives and its analogs by ring–closing metathesis reaction / S. Kotha, A. Deb, R. Kumar // Bioorg. Med. Chem. Lett. – 2005. – Vol. 15 (4). – P. 1039–1043. https://doi.org/10.1016/j.bmcl.2004.12.034
12. Kotha, S. Design and synthesis of spiro-heterocycles by ring–closing metathesis / S. Kotha, A. Deb // Ind. J. Chem. – 2008. – Vol. 47B. – P. 1120–1134.
13. Synthesis of new *N,N'*–disubstituted 5–spirocyclopenten–3–yl 2,4,6–trioxyhexahydropy–rimidines / N. I. Kobyzhcha, V. M. Holovatiuk, Yu.V. Bezugly, V. I. Kashkovsky // J. of Org. and Pharm. Chem. – 2013. – Vol. 11 (4). P. 42–47. https://doi.org/10.24959/ophcj.13.770
14. Synthesis of mono– and *N,N*–disubstituted thioureas and *N*–acylthioureas / A. R. Katritzky, N. Kirichenko, B. V. Rogovoy et al. // Synthesis. – 2004. – Vol. 11. – P. 1799–1805. https://doi.org/10.1055/s-2004-829127
15. A Recyclable Ru–Based Metathesis Catalyst / J. S. Kingsbury, J. P. Harrity, P. J. Bonitatebus, A. H. Hoveyda // J. Am. Chem. Soc. –1999. – Vol. 121 (4). – P. 791–799. https://doi.org/10.1021/ja983222u

References

1. Girgis, A. S., Farag, H., Ismail, N. S. M., & George, R. F. (2011). Synthesis, hypnotic properties and molecular modeling studies of 1,2,7,9–tetraaza–spiro[4.5] dec–2–ene–6,8,10–triones. *European Journal of Medicinal Chemistry, 46 (10),* 4964–4969. https://doi.org/10.1016/j.ejmech.2011.07.058
2. Cope, Arthur C. (1955). Spiro barbituric acids. *US Pat.* Appl., 2725380 A ; declared 13.08.1949 ; published 29.11.1955.
3. Lee, W. C. (1953). Comparative depression of several short acting barbiturates and spiro–barbiturates. *The Japanese Journal of Pharmacology, 2,* 123–126. https://doi.org/10.1254/jjp.2.123
4. Osman, A. N., Kandeel, M. M., Saidand, M. M., Ahmed, E. M. (1996). Synthesis and anticonvulsant activity of certain spiro compounds derived from barbituric and thiobarbituric acids. *Ind. J. Chem, 35B,* 1073–1078. https://doi.org/10.1002/chin.199652179
5. Behera, R. K., Behera, A., Pradhan, K., Pati, R. A., Patra, M. (2006). Studies on spiroheterocycles Part–II : Heterocyclization of the spiro compounds containing cyclohexanone and thiobarbituric acid with different bidentate nucleophilic reagents. *Synth. Commun, 36,* 3729–3742. https://doi.org/10.1080/00397910600946231
6. Bhaskarachar, R. K., Revanasiddappa, V. G., Hegde, S., Balakrishna, J. P., Reddy, S. Y. (2015). Design, synthesis and anticancer activity of functionalized spiro–quinolines with barbituric and thiobarbituric acids. *Med. Chem. Res., 24,* 3516–3528. https://doi.org/10.1007/s00044-015-1408-7

7. Behera, R. K., Behera, A. K., Pradhan, R., Patra, M. (2006). Studies on spiroheterocycles part–I : Installation of biologically active heterocyclic nuclei into spiro compounds derived from cyclohexanone and diphenyl thiobarbituric acid. *Ind. J. Chem., 45B,* 933–942.
8. Ziarani, M., Asadi, S., Faramarzi, S., Amanlou M. (2015). Green Synthesis and Urease Inhibitory Activity of Spiro–Pyrimidinethiones / Spiro–Pyrimidinones–Barbituric Acid Derivatives. *Iran. J. Pharm. Res., 14 (4),* 1105–1114.
9. Goel, B., Sharma, S., Bajaj, K., Bansal, D., Singh, T., Malik, N., … Kumar, A. (2005). *Synthesis and CNS depressant of newer spirobarbiturates,* 67, 194–199.
10. Cope, A., Kovacic, P., Burg, M. (1949). Spirobarbituric Acids Containing a Six–membered Carbocyclic Ring. *J. Am. Chem. Soc., 71 (11),* 3658–3662. https://doi.org/10.1021/ja01179a023
11. Kotha, S., Deb, A., Kumar, R. (2005). Spiro–annulation of barbituric acid derivatives and its analogs by ring–closing metathesis reaction. *Bioorg. Med. Chem. Lett., 15 (4),* 1039–1043. https://doi.org/10.1016/j.bmcl.2004.12.034
12. Kotha, S. and Deb, A. (2008). Design and synthesis of spiro–heterocycles by ring–closing metathesis. *Ind. J. Chem., 47B,* 1120–1134.
13. Kobyzhcha, N. I., Holovatiuk, V. M., Bezugly, Yu.V., Kashkovsky, V. I. (2013). Synthesis of new *N,N'*–disubstituted 5–spirocyclopenten–3–yl 2,4,6–trioxyhexahydropy–rimidines. *Journal of Organic and Pharmaceutical Chemistry, 11 (4),* 42–47. https://doi.org/10.24959/ophcj.13.770
14. Katritzky, A. R., Kirichenko, N., Rogovoy, B. V., Kister, J., Tao, H. (2004). Synthesis of mono– and *N,N*–disubstituted thioureas and *N*–acylthioureas. *Synthesis, 11,* 1799–1805. https://doi.org/10.1055/s-2004-829127
15. Kingsbury, J. S., Harrity, J. P., Bonitatebus, P. J., Hoveyda, A. H. (1999). A Recyclable Ru–Based Metathesis Catalyst. *J. Am. Chem. Soc, 121 (4),* 791–799. https://doi.org/10.1021/ja983222u

Надійшла до редакції 22.01.2019 р.