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The synthesis of 3-methyl-6-R-[1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazole derivatives

Aim. To conduct the synthesis and confirm the structure of 3-methyl-6-R-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole derivatives as potential biologically active compounds.

Results and discussion. It has been shown that the heterocyclization reaction of 4-amino-5-methyl-4*H*-1,2,4-triazole-3-thiol with carboxylic acids in the excess of phosphorus oxychloride yields 3-methyl-6-R-[1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazoles.

Experimental part. The reaction of 4-amino-5-methyl-4*H*-1,2,4-triazole-3-thiol with the corresponding carboxylic acids was carried out in the excess of phosphorus oxychloride. The mixture was heated for 5 h with subsequent cooling and neutralization to pH 7 using ammonia solution. ^{1}H NMR spectra of the compounds synthesized were recorded on a Varian Mercury VX-200 spectrometer operating at a frequency of 200 MHz, in DMSO-d_6, using tetramethylsilane (TMS) as an internal standard. Melting points were measured using a MPA100 device. The elemental analysis was performed on a Elementar Vario EL Cube elemental analyzer. Agilent 1260 Infinity HPLC System equipped with Agilent 6120 mass spectrometer were used for registering LC-MS data.

Conclusions. As a result of this study 10 new compounds of the 3-methyl-6-R-[1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazole series have been obtained. The structure and purity of the products have been confirmed using ^{1}H NMR spectroscopy, LC-MS and elemental analysis.

Key words: synthesis; 1,2,4-triazoles; physicochemical properties

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Синтез похідних 3-метил-6-R-[1,2,4]триазоло[3,4-*b*][1,3,4]тіадіазолу

Мета. Синтезувати та підтвердити структуру похідних 3-метил-6-R-[1,2,4]триазоло[3,4-*b*][1,3,4]тіадіазолу – потенційних біологічно активних сполук.

Результати та їх обговорення. Показано, що взаємодія 4-аміно-5-метил-4*H*-1,2,4-триазол-3-тіолу з карбоновими кислотами у присутності надлишку фосфору оксихлориду перебігає з утворенням 3-метил-6-R-[1,2,4]триазоло[3,4-*b*][1,3,4]тіадіазолів.

Експериментальна частина. Взаємодію 4-аміно-5-метил-4*H*-1,2,4-триазол-3-тіолу з карбоновими кислотами проводили у надлишку фосфору оксихлориду при нагріванні впродовж 5 годин з подальшим охолодженням та нейтралізацією до pH 7 розчином амоніаку. ^{1}H ЯМР-спектри синтезованих сполук було записано на спектрометрі Varian Mercury VX-200, робоча частота – 200 МГц, в ДМСО-d_6, з використанням тетраметилсилану (TMS) як внутрішнього стандарту. Температури плавлення вимірювали за допомогою пристрою MPA100. Елементний аналіз виконували на елементному аналізаторі Elementar Vario EL Cube. Систему HPLC Agilent 1260 Infinity з мас-спектрометром Agilent 6120 використано для реєстрації LC-MS-даних.

Висновки. В результаті дослідження синтезовано 10 нових сполук з ряду похідних 3-метил-6-R-[1,2,4]-триазоло[3,4-*b*][1,3,4]тіадіазолу. Структуру та чистоту синтезованих сполук підтверджено методами ^{1}H ЯМР-спектроскопії, LS-MS та елементним аналізом.

Ключові слова: синтез; 1,2,4-триазоли; фізико-хімічні властивості

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Синтез производных 3-метил-6-R-[1,2,4]триазоло[3,4-*b*][1,3,4]тиадиазола

Цель. Синтезировать и подтвердить структуру производных 3-метил-6-R-[1,2,4]триазоло[3,4-*b*][1,3,4]-тиадиазола – потенциальных биологически активных соединений.

Результаты и их обсуждение. Показано, что взаимодействие 4-амино-5-метил-4*H*-1,2,4-триазол-3-тиола с карбоновыми кислотами в присутствии избытка оксихлорида фосфора протекает с образованием 3-метил-6-R-[1,2,4]триазоло[3,4-*b*][1,3,4]тиадиазолов.

Экспериментальная часть. Взаимодействие 4-амино-5-метил-4H-1,2,4-триазол-3-тиола с карбоновыми кислотами проводили в избытке оксихлорида фосфора при нагревании в течении 5 часов с последующим охлаждением и нейтрализацией до pH 7 раствором аммиака. ^{1}H ЯМР-спектры синтезированных соединений были записаны на спектрометре Varian Mercury VX-200, рабочая частота – 200 МГц, в ДМСО-d_6, с использованием тетраметилсилана (TMS) в качестве внутреннего стандарта. Температуры плавления измеряли с помощью устройства MPA100. Элементный анализ выполняли на элементном анализаторе Elementar Vario EL Cube. Система HPLC Agilent 1260 Infinity с масс-спектрометром Agilent 6120 использована для регистрации LC-MS-данных.

Выводы. В результате исследования синтезированы 10 новых соединений из ряда производных 3-метил-6-R-[1,2,4]триазоло[3,4-*b*][1,3,4]тиадиазола. Структура и чистота соединений подтверждены методами ^{1}H ЯМР-спектроскопии, LS-MS и элементным анализом.

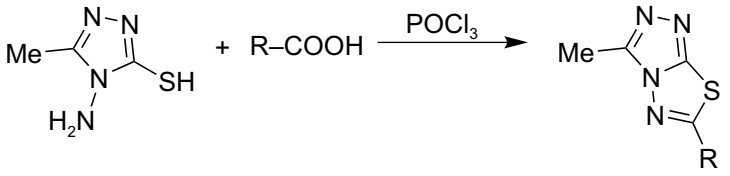
Ключевые слова: синтез; 1,2,4-триазолы; физико-химические свойства

The derivatives of 1,2,4-triazole have been attractive for research for many years, particularly due to their reactivity and synthetic capabilities, whereas the search for new potential biologically active compounds among them remains one of the priorities of modern medicinal, pharmaceutical, and organic chemistry [1–4]. Specifically, the 1,2,4-triazole moiety can be found in various pharmaceutical substances that are available at the market today [5], for instance, ribavirin used as antiviral substance, estazolam and triazolam used to treat sleep disorders and insomnia, anastrozole, vorozole and letrozole applied for breast cancer management [5–7].

Biological activities of functionalized 1,2,4-triazoles are being intensively studied [8–12]. At the same time, many of these compounds have already been used as anti-inflammatory, antibacterial, and antifungal products [5, 6]. Development of new synthetic approaches for obtaining 1,2,4-triazole derivatives that may be used in medical and biological studies is of great significance for synthetic chemists [13, 14]. Therefore, the aim of this work was to synthesize and confirm the structure of new potentially biologically active derivatives of the 3-methyl-6-R-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole series.

To attain the aim 4-amino-5-methyl-4*H*-1,2,4-triazole-3-thiol **1** was used as an initial compound [17]. Heterocyclization of compound **1** with carboxylic acids **2a–j** was carried out in the excess of phosphorus oxychloride, yielding 3-methyl-6-R-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **3a–j** (Scheme).

The structure of 3-methyl-6-R-[1,2,4]-triazolo[3,4-*b*]-[1,3,4]thiadiazoles **3a–j** was confirmed using elemental analysis (Table 1), ^{1}H NMR-spectroscopy, and LC-MS analysis (Table 2).



1 **2a–j** **3a–j**

a: R = 2-F-Ph; **b: R** = 2-MeO-Ph; **c: R** = 4-*t*Bu-Ph; **d: R** = 2-Cl-4-NO_2-Ph;
e: R = 2-Cl-5-NO_2-Ph; **f: R** = furan-2-yl; **g: R** = thiophen-2-yl;
h: R = 5-bromothiophen-2-yl; **i: R** = pyridin-2-yl; **j: R** = adamantan-1-yl

Scheme. The synthesis of 3-methyl-6-R-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **3a–j**

Table 1

Physicochemical properties and the elemental composition of 3-methyl-6-R-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **3a–j** synthesized

Compound	R	M. p., °C	Molecular formula	Yield, %	Calculated, % / Found, %			
					C	H	N	S
3a	2-F-Ph	143–145	$C_{10}H_7FN_4S$	82	51.27 / 51.35	3.01 / 3.02	23.92 / 23.95	13.69 / 13.73
3b	2-MeO-Ph	122–124	$C_{11}H_{10}N_4OS$	84	53.64 / 53.84	4.09 / 4.07	22.75 / 22.79	13.02 / 13.06
3c	4-*t*Bu-Ph	121–123	$C_{14}H_{18}N_4S$	82	61.74 / 61.34	5.92 / 5.90	20.57 / 20.43	11.77 / 11.70
3d	2-Cl-4-NO_2-Ph	118–120	$C_{10}H_6ClN_5O_2S$	86	40.62 / 40.66	2.05 / 2.06	23.68 / 23.75	10.84 / 10.82
3e	2-Cl-5-NO_2-Ph	166–168	$C_{10}H_6ClN_5O_2S$	82	40.62 / 40.29	2.05 / 2.09	23.68 / 23.53	10.84 / 10.75
3f	furan-2-yl	159–161	$C_8H_6N_4OS$	89	46.59 / 46.46	2.93 / 2.90	27.17 / 27.28	15.55 / 15.59
3g	thiophen-2-yl	137–139	$C_8H_6N_4S_2$	89	43.23 / 43.17	2.72 / 2.71	25.20 / 25.23	28.85 / 28.80
3h	5-bromothiophen-2-yl	154–156	$C_8H_5BrN_4S_2$	88	31.90 / 31.64	1.67 / 1.60	18.60 / 18.42	21.29 / 21.35
3i	pyridin-2-yl	152–154	$C_9H_7N_5S$	90	49.76 / 49.65	3.25 / 3.24	32.24 / 32.34	14.76 / 14.71
3j	adamantan-1-yl	150–152	$C_{14}H_{18}N_4S$	90	61.28 / 61.35	6.61 / 6.64	20.42 / 20.44	11.69 / 11.71

Table 2

^{1}H NMR spectra and LC-MS data for 3-methyl-6-R-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **3a–j**

Compound	^{1}H NMR (200 MHz, DMSO-d_6), δ, ppm	LC-MS, m/z [M+1]
3a	7.94–7.86 (1H, m, C_6H_4), 7.47–7.43 (1H, m, C_6H_4), 7.33 (2H, dtd, J_1 = 8.2 Hz, J_2 = 7.5 Hz, J_3 = 1.6 Hz, C_6H_4), 2.54 (3H, s, CH_3)	235.25
3b	7.79–7.73 (1H, m, C_6H_4), 7.57–7.48 (1H, m, C_6H_4), 7.17 (1H, td, J_1 = 7.5 Hz, J_2 = 1.5 Hz, C_6H_4), 7.11 (1H, dd, J_1 = 7.5 Hz, J_2 = 1.5 Hz, C_6H_4), 4.01 (3H, s, OCH_3), 2.53 (3H, s, CH_3)	247.06
3c	7.92–7.84 (2H, m, C_6H_4), 7.60–7.53 (2H, m, C_6H_4), 2.54 (3H, s, CH_3), 1.35 (9H, s, C_4H_9)	273.38
3d	8.30–8.21 (2H, m, C_6H_3), 7.98 (1H, d, J = 7.4 Hz, C_6H_3), 2.49 (3H, s, CH_3)	297.70
3e	8.46 (1H, d, J = 1.5 Hz, C_6H_3), 8.24 (1H, dd, J_1 = 7.5 Hz, J_2 = 1.5 Hz, C_6H_3), 7.77 (1H, d, J = 7.5 Hz, C_6H_3), 2.49 (3H, s, CH_3)	297.70
3f	7.79–7.76 (1H, m, furan-2-yl), 7.28–7.24 (1H, m, furan-2-yl), 6.69–6.65 (1H, m, furan-2-yl), 2.56 (3H, s, CH_3)	207.22
3g	7.83–7.75 (2H, m, thiophen-2-yl), 7.19 (1H, t, J = 7.5 Hz, thiophen-2-yl), 2.54 (3H, s, CH_3)	223.29
3h	7.58 (1H, d, J = 7.5 Hz, 5-bromothiophen-2-yl), 7.15 (1H, d, J = 7.5 Hz, 5-bromothiophen-2-yl), 2.52 (3H, s, CH_3)	302.19
3i	8.76–8.73 (1H, m, pyridin-2-yl), 7.98–7.95 (1H, m, pyridin-2-yl), 7.62–7.54 (1H, m, pyridin-2-yl), 7.47–7.41 (1H, m, pyridin-2-yl), 2.59 (3H, s, CH_3)	218.25
3j	2.52 (3H, s, CH_3), 2.14 (3H, dddd, J_1 = 13.6 Hz, J_2 = 6.8 Hz, J_3 = 6.3 Hz, J_4 = 0.7 Hz, adamantan-1-yl), 2.06 (6H, dd, J_1 = 6.8 Hz, J_2 = 0.8 Hz, adamantan-1-yl), 1.83–1.72 (6H, m, adamantan-1-yl)	275.38

The LC-MS analysis revealed individual peaks of the compounds synthesized on chromatograms, while the mass-to-charge ratios corresponded to the molecular masses of the compounds (Table 2).

The data of the elemental analysis confirmed the structures of 3-methyl-6-R-[1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazoles **3a–j** (Table 1).

Finally, ^{1}H NMR spectra for the compounds **3a–j** synthesized indicated that these compounds had the predicted structures (Table 2). For example, obtaining 6-(2-fluorophenyl)-3-methyl-[1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazole **3a** was confirmed by the signals of the corresponding 2-fluorophenyl and methyl groups attached to the 1,2,4-triazole nucleus. The ^{1}H NMR spectrum for compound **3a** was characterized by a chemical shift in a strong field appearing as a triple proton singlet of the methyl group bound with 1,2,4-triazole ring at 2.54 ppm. Protons of the 2-fluorophenyl moiety appeared as two single proton multiplets and double proton signal at 7.91 ppm, 7.45 ppm and 7.33 ppm, respectively.

Experimental part

The chemical reagents were obtained from "Ukrorgsyntez Ltd (UOS)" with the entire set of quality certificates. The physicochemical characterization of the compounds synthesized was performed according to methods and approaches provided by the State Pharmacopoeia of Ukraine (SPhU). An automatic MPA100 apparatus was used for determining melting points. The elemental analysis was conducted using an Elementar Vario EL Cube elemental analyzer. ^{1}H NMR spectra were recorded using a Varian Mercury VX-200 spectrometer operating at a frequency of 200 MHz, DMSO-d_6 was used as a solvent and tetramethylsilane (TMS) was used as an internal standard. The spectra interpretation was performed using SpinWorks software. The LC-MS data were recorded by Agilent 1260 Infinity HPLC System equipped with Agilent 6120 mass spectrometer in the electrospray ionization mode (ESI) [15, 16].

The procedure for the synthesis of 3-methyl-6-R-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles 3a–j. Into a 100 mL round-bottomed flask containing a triple excess of phosphorus oxychloride add 4-amino-5-methyl-4*H*-1,2,4-triazole-3-thiol **1** (0.01 mol) and the corresponding acid (0.01 mol) when heating. Heat the mixture on a water bath for 5 h. Then allow it to cool and pour the mixture onto ice. When the ice is melted, neutralize the mixture to pH = 7 with ammonia solution, rinse the precipitate formed thoroughly with water and filter. The compounds synthesized are yellow (**3a**, **3d**, **3i**), green (**3b, 3g**), and brown (**3c, 3e, 3f, 3h, 3j**) crystals. For analytical purposes, recrystalize the compounds from 2-propanol (**3a, 3f**), acetic acid (**3d, 3e, 3g, 3h**), 1-butanol (**3b, 3c, 3i**), and methanol (**3j**).

Conclusions

As a result of this study 10 new substances of the 3-methyl-6-R-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole series have been obtained. The structure and purity of the products have been confirmed using ^{1}H NMR spectroscopy, LC-MS and elemental analysis.

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

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