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Органічна хімія

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SYNTHESIS OF NOVEL SUBSTITUTED 3-(5-ARYL-1,3,4-OXADIAZOL-2-YL)THIOPHEN-2-AMINES VIA GEWALD REACTION

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By the multicomponent Gewald reaction of an activated nitrile, a carbonyl component and elemental sulphur in the presence of morpholine as a catalyst, novel substituted 3-(5-aryl-1,3,4-oxadiazol-2-yl)thiophen-2-amines were obtained.

Key words: 1,3,4-oxadiazole, Gewald reaction, multicomponent reactions, 2-aminothiophenes.

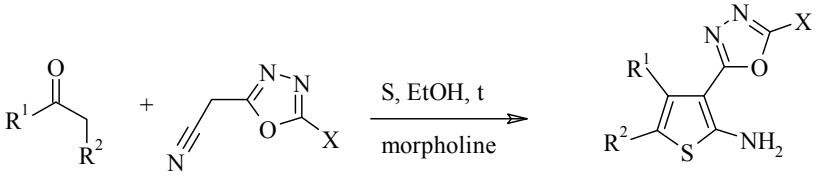
1,3,4-Oxadiazoles are the important group of heterocyclic compounds [1] due to their wide spectrum of bioactivities including anti-inflammatory and hypotensive [2], antibacterial [3], hypoglycemic [4], anticancer [5], antifungal [6], insecticidal [7] activities, and inhibition of HIV replication [8]. Likewise 1,3,4-oxadiazoles are useful in medical chemistry as surrogates of carboxylic acids, esters, and carboxamides [9]. In addition, 1,3,4-oxadiazole derivates were used to create such drugs as Vadrin, Eudormil, SC27166 [10]. 2-Aminothiophenes have also received considerable attention due to their wide range of pharmaceutical and biological activities [11–14]. A series of 1,3,4-oxadiazole derivatives carrying the thiophene unit have been synthesized recently. It has been reported that such compounds were potentially electron-transporting electroluminescent materials [15]. From this point of view it is interesting to combine both fragments in one molecule.

In this paper such compounds were prepared in a well-established classical Gewald method [11, 16], which involves multicomponent condensation of an activated nitrile, a carbonyl component and elemental sulphur in the presence of morpholine as a catalyst.

It is well-known that one of the most convenient methods of the synthesis of substituted 2-aminothiophenes is one-pot Gewald reaction. This synthesis initially involves the Knoevenagel condensation of an activated nitrile and carbonyl component, followed by a sulphur mediated cyclization to afford desired 2-aminothiophenes. It was shown that heterocyclic 2-aminothiophenes **3a-f** can be easily prepared *via* Gewald reaction under classical conditions with good yields (Scheme 1, Table). In this case, we can prove that the 1,3,4-oxadiazole ring is a good acceptor, which is suitable for condensation. To obtain the 1,3,4-oxadiazole fragment in the third position we used nitrile with the 1,3,4-oxadiazole ring. Such reagents were obtained from 2-cyanoacetohydrazide, corresponding substituted benzoyl chloride and phosphoric trichloride. According to this method, compounds **2a–d** were synthesized. We tried to involve heterocyclic compounds **2a–d** into Gewald reaction

with the following carbonyl components: cyclohexanone **1a**, ethyl 3-oxobutanoate **1b**, pentane-2,4-dione **1c**. The experiment showed that these conversations were performed in very good yields.

The products **3a–f** are crystalline compounds. Their structures were confirmed by ^{1}H NMR spectroscopy.



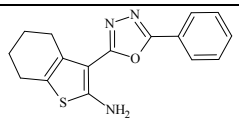
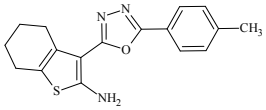
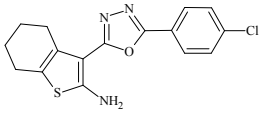
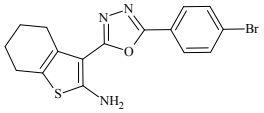
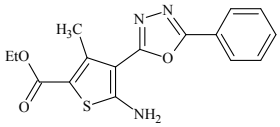
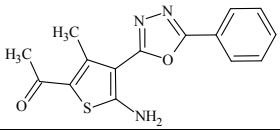
1a-c **2a-d** **3a-f**

R^1+R^2 = -$(CH_2)_4$- (**a,b,c,d**)
R^1= Me (**e,f**)
R^2= COOEt (**e**), C(O)Me (**f**)

X = Ph (**a,e,f**), 4-MeC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-BrC_6H_4 (**d**)

Scheme 1

Substituted 3-(5-aryl-1,3,4-oxadiazol-2-yl)thiophen-2 amines

Number	Product	Yield, %	Melting point, °C
3a		83	178-179
3b		81	174-175
3c		85	169-170
3d		86	154-155
3e		78	216-217
3f		77	214-215

Therefore, for the first time substituted 3-(5-aryl-1,3,4-oxadiazol-2-yl)thiophen-2-amines were easily obtained via Gewald reaction.

Experimental

The ^{1}H NMR spectra were recorded on a Varian Mercury 400 instrument (400 MHz for ^{1}H). The ^{1}H chemical shifts are reported in parts per million relative to tetramethylsilane. Mass spectra were run using Agilent 1100 series LC/MSD. All melting points are uncorrected.

General Procedure for the synthesis of 2-aminothophenes 3a–f:

Elemental sulphur (0,01 mol) and morpholine (0,8 ml) was added to a solution of carbonyl component **1a–c** (0,01mol) and activated with oxadiazole ring nitrile **2a–d** (0,01mol) in EtOH. The mixture was stirred and heated to 50-60°C at reflux for 3 h. The reaction mixture was cooled to the room temperature and the formed solid was filtered off and recrystallized from ethanol.

3-(5-Phenyl-1,3,4-oxadiazol-2-yl)-4,5,6,7-tetrahydro-1-benzothiophen-2-amine 3a: This compound was isolated as a white powdered solid, m.p. 178–179°C (ethanol) in 83% yield. ^{1}H NMR (400 MHz, DMSO-d_6) ppm: δ 1.84 (br. s, 4H, CH_2), 2.54 (br. s, 2H, CH_2), 2.84 (br. s, 2H, CH_2), 7.17 (br. s, 2H, NH_2), 7.50–7.57 (m, 3H, H_{Ph}-3,4,5), 7.97–8.03 (m, 2H, H_{Ph}-2,6). MS m/z: 298 (M^++1). Anal. requires for $C_{16}H_{15}N_3OS$ (297.37) calcd./found: C, 64.62/64.58; H, 5.08/5.19; N, 14.13/14.24.

3-[5-(4-Methylphenyl)-1,3,4-oxadiazol-2-yl]-4,5,6,7-tetrahydro-1-benzothiophen-2-amine 3b: This compound was isolated as white powdered solid, m.p. 174–175°C (ethanol) in 81% yield. ^{1}H NMR (400 MHz, DMSO-d_6) ppm: δ 1.86 (br. s, 4H, CH_2), 2.24 (s, 3H, CH_3), 2.53 (br. s, 2H, CH_2), 2.84 (br. s, 2H, CH_2), 7.15 (br. s, 2H, NH_2), 7.49 (d, 2H, J 7.8, H_{Ar}-3,5), 8.05 (d, 2H, J 7.8, H_{Ar}-2,6). MS m/z: 312 (M^++1). Anal. requires for $C_{17}H_{17}N_3OS$ (311.40) calcd./found: C, 65.57/65.65; H, 5.50/5.38; N, 13.49/13.37.

3-[5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl]-4,5,6,7-tetrahydro-1-benzothiophen-2-amine 3c: This compound was isolated as a white powdered solid, m.p. 169–170°C (ethanol) in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$) ppm: δ 1.81–1.89 (m, 4H, CH_2), 2.53–2.64 (m, 2H, CH_2), 2.79–2.91 (m, 2H, CH_2), 5.46 (br. s, 2H, NH_2), 7.63 (d, 2H, *J* 8.5, H_{Ar}-3,5), 8.12 (d, 2H, *J* 8.5, H_{Ar}-2,6). MS m/z: 332 (M^++1). Anal. requires for $C_{16}H_{14}ClN_3OS$ (331.82) calcd./found: C, 57.91/57.83; H, 4.25/4.31; N, 12.66/12.42.

3-[5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl]-4,5,6,7-tetrahydro-1-benzothiophen-2-amine 3d: This compound was isolated as a white powdered solid, m.p. 154–155°C (ethanol) in 86% yield. ^{1}H NMR (400 MHz, DMSO-d_6) ppm: δ 1.83–1.91 (m, 4H, CH_2), 2.51–2.63 (m, 2H, CH_2), 2.80–2.89 (m, 2H, CH_2), 7.20 (br. s, 2H, NH_2), 7.87 (d, 2H, *J* 8.4, H_{Ar}-3,5), 8.05 (d, 2H, *J* 8.4, H_{Ar}-2,6). MS m/z: 376, 378 (M^++1). Anal. requires for $C_{16}H_{14}BrN_3OS$ (376.27) calcd./found: C, 51.07/51.19; H, 3.75/3.81; N, 11.17/11.28.

Ethyl 5-amino-3-methyl-4-(5-phenyl-1,3,4-oxadiazol-2-yl)thiophene-2-carboxylate 3e: This compound was isolated as a white powdered solid, m.p. 216–217°C (ethanol) in 78% yield. ^{1}H NMR (300 MHz, $CDCl_3$) ppm: δ 1.36 (t, 3H, *J* 7.1, Me), 2.89 (s, 3H, Me), 4.30 (q, 2H, *J* 7.1, CH_2), 5.76 (br. s, 2H, NH_2), 7.52–7.58 (m, 3H, H_{Ph}-3,4,5), 8.07–8.11 (m, 2H, H_{Ph}-2,6). MS m/z: 330 (M^++1). Anal. requires for $C_{16}H_{15}N_3O_3S$ (329.37) calcd./found: C, 58.34/58.27; H, 4.59/4.45; N, 14.57/14.83.

1-[5-Amino-3-methyl-4-(5-phenyl-1,3,4-oxadiazol-2-yl)thiophen-2-yl] ethanone 3f: This compound was isolated as a white powdered solid, m.p. 214–215°C (ethanol) in 77% yield. ^{1}H NMR (400 MHz, DMSO-d_6) ppm: δ 2.49 (s, 3H, Me), 2.98 (s, 3H, Me), 7.16 (br. s, 2H, NH_2), 7.54–7.59 (m, 3H, H_{Ph}-3,4,5), 8.03–8.09 (m, 2H, H_{Ph}-2,6). MS m/z: 300 (M^++1). Anal. requires for $C_{15}H_{13}N_3O_2S$ (299.35) calcd./found: C, 60.18/60.11; H, 4.38/4.57; N, 14.04/13.87.

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СИНТЕЗ НОВИХ ЗАМІЩЕНИХ 3-(5-АРИЛ-1,3,4-ОКСАДІАЗОЛ-2-ІЛ)-2-АМІНОТІОФЕНІВ РЕАКЦІЄЮ ҐЕВАЛЬДА

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Мультикомпонентну реакцію Ґевальда використано для синтезу нових заміщених 3-(5-арил-1,3,4-оксадіазол-2-іл)-2-амінотіофенів. Вони утворюються під час взаємодії (5-арил-[1,3,4]оксадіазол-2-іл)ацетонітрилів з метиленактивними карбонільними сполуками і сіркою за наявності морфоліну як каталізатора.

Ключові слова: 1,3,4-оксадіазол, реакція Ґевальда, мультикомпонентні реакції, 2-амінотіофени.

СИНТЕЗ НОВЫХ ЗАМЕЩЕННЫХ 3-(5-АРИЛ-1,3,4-ОКСАДИАЗОЛ-2-ИЛ)-2-АМИНОТИОФЕНОВ РЕАКЦИЕЙ ГЕВАЛЬДА

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С помощью мультикомпонентной реакции Гевальда получено новые замещенные 3-(5-арил-1,3,4-оксадиазол-2-ил)-2-аминотиофены. Они образуются при взаимодействии (5-арил-[1,3,4]оксадиазол-2-ил) ацетонитрила с метиленактивными карбонильными соединениями и серой в присутствии морфолина как катализатора.

Ключевые слова: 1,3,4-оксадиазол, реакция Гевальда, мультикомонентные реакции, 2-аминотиофены.

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