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Juliya V. Kharchenko, Oleksandr S. Detistov, and Valeriy D. Orlov

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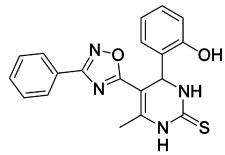
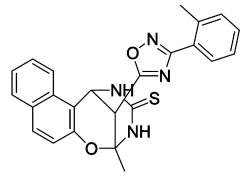
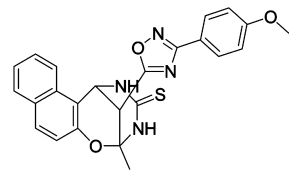


1Ak



7Bl



7Dl

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Synthesis of Substituted 5-(1,2,4-Oxadiazol-5-yl)-3,4-dihydropyrimidine-2(1*H*)-thiones

Juliya V. Kharchenko, Oleksandr S. Detistov,* and Valeriy D. Orlov

Chemical Department, V.N. Karazin Kharkiv National University, 4 Svoboda Sq., Kharkiv 61077, Ukraine

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We have developed a liquid-phase route for combinatorial synthesis of novel substituted 5-(1,2,4-oxadiazol-5-yl)-3,4-dihydropyrimidine-2(1*H*)-thiones. Biginelli-type three-component condensation of 1-(3-aryl-1,2,4-oxadiazol-5-yl)acetones, thiourea, and benzaldehydes is shown to result in new 5-(1,2,4-oxadiazol-5-yl)-3,4-dihydropyrimidine-2(1*H*)-thione heterocyclic system. If salicylaldehydes are used in this reaction, a mixture of 5-(1,2,4-oxadiazol-5-yl)-3,4-dihydropyrimidine-2(1*H*)-thiones and 11-(1,2,4-oxadiazol-5-yl)-2,3,5,6-tetrahydro-4*H*-2,6-methano-1,3,5-benzoxadiazocine-4-thiones is formed.

Introduction

Multicomponent reactions (MCRs) are in general of increasing importance in organic and medicinal chemistry.[1] Now, when the drug discovery strongly requires speed, diversity, and efficiency, MCR strategies offer significant advantages over conventional linear-type syntheses.[2] The Biginelli protocol is particularly attractive because the resulting dihydropyrimidine (DHPM) scaffold displays a wide range of biological activities, which has led to the development of a number of leading compounds based on that structural core.[3] Recent publications on Biginelli-type reactions describe the use of different catalysts,[4,5] microwave,[6] and ultrasound[7] irradiations. On the other hand, substances containing a disubstituted 1,2,4-oxadiazoles fragment are frequently used in drug discovery as an important bioisostere for esters and amides to improve pharmacokinetic properties of drug candidates.[8] Oxadiazoles have been being the subject of investigation in a number of different therapeutic areas, usually as a replacement for ester or amide functional groups. 1,2,4-Oxadiazoles have been proposed as muscarinic receptor agonist,[9,10] benzodiazepine receptor agonist,[11] histamine H3 receptor antagonist,[12] and antiviral compounds.[13] This paper presents a new library of 5-(1,2,4-oxadiazol-5-yl)-3,4-dihydropyrimidine-2(1*H*)-thiones; it includes 70 substances obtained by the three-component condensation of the Biginelli type.

Results and Discussion

Below we describe a new liquid-phase parallel synthesis of the library of compounds **1** (Figure 1).

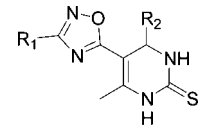
Our approach is based on the condensation of 1-(3-aryl-1,2,4-oxadiazol-5-yl)acetones **2**, thiourea **3** and aromatic aldehydes **4**, which is carried out under the classic Biginelli reaction conditions.

We started with chemsets **2A**−**G** obtained by the reaction of arylamidoximes **5A**−**G** with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **6** (Scheme 1). Chemsets **5A-G** were obtained using the reported method.[14]

The synthesis of building blocks **2A**−**G** was carried out in dioxane with triethylamine as the catalyst. Yields of target products are satisfactory (32−64%) (Figure 2, Table 1).

In ^{1}H NMR spectra of compounds **2A**−**G**, the signals of methyl and methylene groups are observed at 2.20−2.30 and 4.40−4.55 ppm correspondingly. All other proton signals are observed at their usual positions.

Biginelli-type three-component condensation of building blocks **2A**−**G**, thiourea **3**, and benzaldehydes **4a-j** (Figure 3) leads to the formation of dihydropyrimidines **1A**−**G**,**a**−**j**



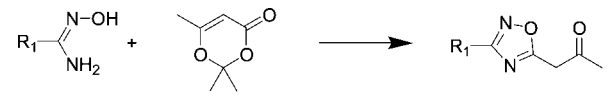
1

Figure 1. 5-(1,2,4-Oxadiazol-5-yl)-3,4-dihydropyrimidine-2(1*H*)-thiones, **1**.

Table 1. Yields of Building Blocks **2A**−**G**

substance	yield, %
2A	32
2B	41
2C	39
2D	47
2E	51
2F	64
2G	56

Scheme 1. Synthesis of 1-(3-Aryl-1,2,4-oxadiazol-5-yl)acetones, **2A**−**G**



5A-G **6** **2A-G** Yields: 32-64%

* To whom correspondence should be addressed. E-mail: DeAS@INBOX.ru.

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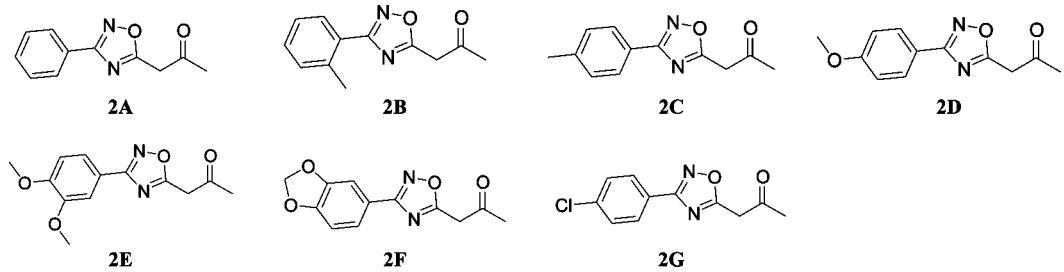


Figure 2. Selected 1-(3-aryl-1,2,4-oxadiazol-5-yl)acetones **2A**−**G** for library design.

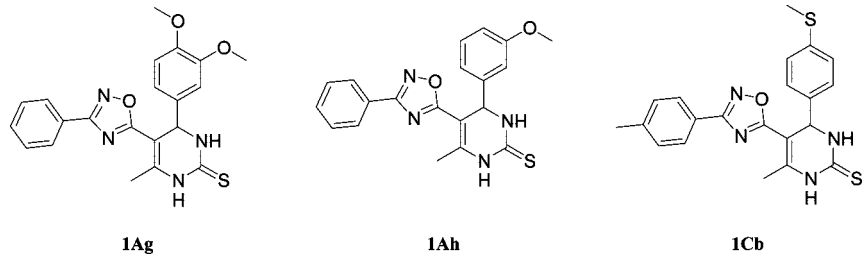


Figure 3. Selected benzaldehydes **4a**−**j** for library design.

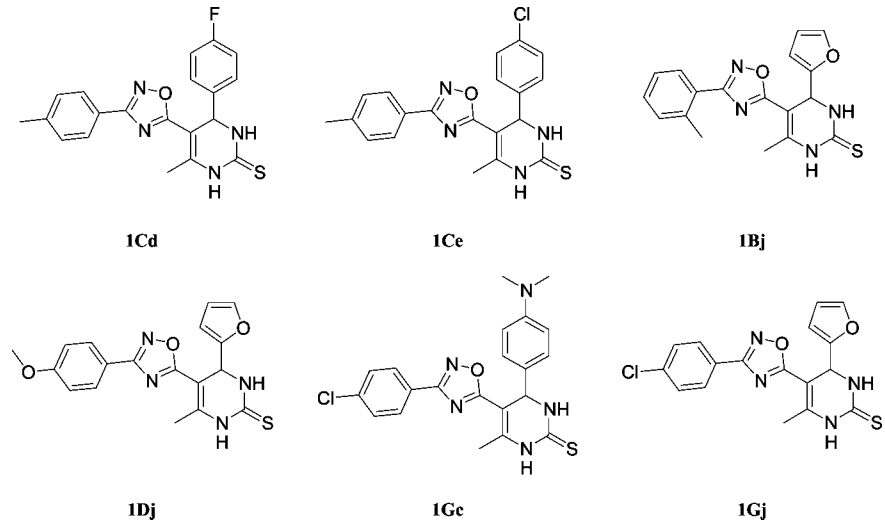


Figure 4. Examples of 5-(1,2,4-oxadiazol-5-yl)-3,4-dihydropyrimidine-2(1*H*)-thiones synthesized, **1**.

(Scheme 2, Figure 4). The yields of products are different depending on the structure of initial reagents. Thus, if electron-releasing groups are in para-positions of R_1 and R_2 substitutes in scaffold **1,** the yields of the target products are high. If, alternatively, R_1 and R_2 substitutes have no electron-releasing groups or if positions of these groups are different, yields of products decrease to good and seldom to satisfactory.

Dihydropyrimidines **1** were characterized by ^{1}H NMR, ^{13}C NMR, DEPT, and LC/MS analysis. The ^{1}H, ^{13}C NMR, and DEPT spectra confirm the suggested structures. According to the LC/MS data, all the synthesized compounds were more than 90% pure. Results of the element analysis are in accordance with theoretical considerations. This complex of experimental data proofs the purity of obtained substances. In ^{1}H NMR spectra the proton H4 in 3,4-dihydropyrimidine-2(1*H*)-thione structures **1** is clearly observed as singlet in the range of δ 5.35−5.55 ppm. The protons NH are observed as singlets in two ranges of δ 10.60−10.80 and 9.60−9.90 ppm. All other proton signals are observed in their usual resonance areas.

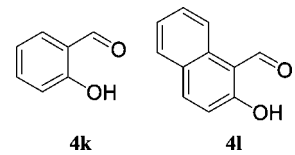
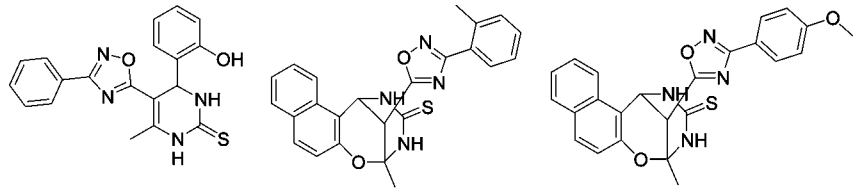


Figure 5. Salicylaldehyde inputs **4k**, **l**.

We also studied the three-componentcondensation of chemset **2A**−**G**, thiourea **3**, and salicylaldehydes **4k**, **l** (Figure 5). As a rule, thin-layer chromatography (TLC) showed the formation of mixtures of dihydropyrimidines **1** and methanobenzoxadiazocines **7** under the reaction conditions (Scheme 3).

Sporadically pure dihydropyrimidines **1** and methanobenzoxadiazocines **7** were formed. Thus, in the case of salicylaldehyde **4k** and building block **2A**, pure compound **1Ak** was formed; in the case of salicylaldehyde **4l** and building blocks **2B**, **D**, pure compounds **7Bl**, **7Dl** were formed (Figure 6).

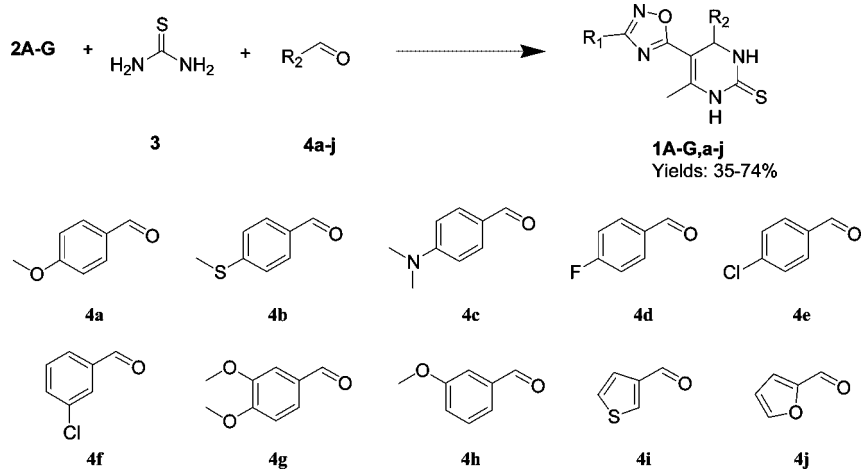
The formation of methanobenzoxadiazocine heterocyclic system was proved for compound **7Bl** by ^{1}H NMR, ^{13}C NMR, and DEPT analysis. In ^{1}H NMR spectra of this substance, the signals of 4 protons of methanobenzoxadia-



1Ak **7Bl** **7Dl**

Figure 6. Examples of pure 4-(2-hydroxyphenyl)-5-(1,2,4-oxadiazol-5-yl)-3,4-dihydropyrimidine-2(1*H*)-thiones, **1Ak**, and 11-(1,2,4-oxadiazol-5-yl)-2,3,5,6-tetrahydro-4*H*-2,6-methano-1,3,5-benzoxadiazocine-4-thiones synthesized, **7Bl**, **7Dl**.

Scheme 2. Synthesis of 5-(1,2,4-Oxadiazol-5-yl)-3,4-dihydropyrimidine-2(1*H*)-thiones, **1A−G**,**a−j**

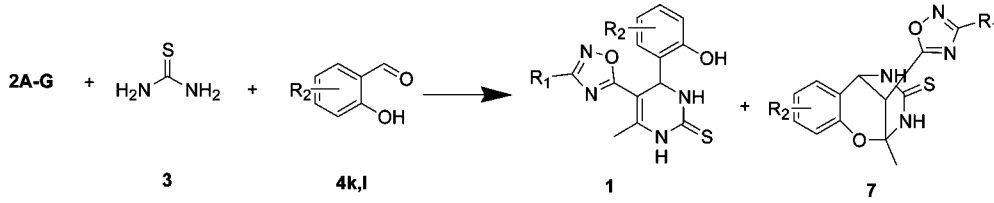


3 **4a-j** **1A-G,a-j** Yields: 35-74%

4a **4b** **4c** **4d** **4e**

4f **4g** **4h** **4i** **4j**

Scheme 3. Three-Component Condensation of Chemsets **2A−G**, Thiourea **3**, and Salicylaldehydes **4k**, **l**



3 **4k,l** **1** **7**

zocine moiety were observed: two protons NH in the ranges of δ 9.30−9.40 and 9.55−9.65 ppm, the proton H6 in the range 5.40−5.45 ppm, and the proton H11 in the range 4.30−4.35 ppm. The signal of proton H11 is characteristic for methanobenzoxadiazocine heterocyclic system: it is absent in ^{1}H NMR spectra of dihydropyrimidine with 2-hydroxyphenyl substitute **1Ak**, whereas proton OH is observed as singlet in the range of δ 9.25−9.30 ppm. ^{1}H NMR spectra of all other substances of this series show complex signals of both proton H11 of methanobenzoxadiazocine heterocyclic system and proton OH of substitutes at dihydropyrimidines core. The ^{1}H, ^{13}C NMR, and DEPT spectra of substances **7Bl** and **1Ak** confirm the offered structures.

Conclusions

An efficient synthetic route has been developed for the combinatorial synthesis of novel 5-(1,2,4-oxadiazol-5-yl)-3,4-dihydropyrimidine-2(1*H*)-thione library in solution. It is based on the Biginelli-type three-component condensation of 1-(3-aryl-1,2,4-oxadiazol-5-yl)acetones, thiourea, and aromatic aldehydes. Substances with low levels of impurities were obtained using a simple crystallization from the reaction mixtures. Product yields varied depending on the reactant structures, but in most cases, the desired products were obtained with high and good yields. The three-component condensation of 1-(3-aryl-1,2,4-oxadiazol-5-yl)acetones, thiourea and salicylaldehydes was also studied. As a rule, the mixture of 5-(1,2,4-oxadiazol-5-yl)-3,4-dihydropyrimidine-2(1*H*)-thiones and 11-(1,2,4-oxadiazol-5-yl)-2,3,5,6-tetrahydro-4*H*-2,6-methano-1,3,5-benzoxadiazocine-4-thiones was formed under reaction conditions.

Supporting Information Available. Experimental procedures, spectroscopic data, references for known compounds, ^{1}H NMR, ^{13}C NMR, and ^{13}C NMR DEPT spectra, and LC/MS data of synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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