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Short Note

5-(1-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-2-phenylethyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione

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Abstract: Multicomponent reactions have been demonstrated as a promising tool for the creation of diverse molecular structures with enhanced efficiency, reduced waste, and a high atom economy. Arylglyoxal monohydrates with two different carbonyl groups are well known as worthwhile synthons in organic synthesis. 2-Pyrone and pyrimidine-2,4,6-trione are versatile building blocks for the synthesis of key intermediates in synthetic organic chemistry as well as in medicinal chemistry. A simple and efficient tandem Knoevenagel–Michael protocol for the synthesis of the previously unknown 5-(1-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-2-phenylethyl)-1,3-dimet-hylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione was elaborated. The suggested method is based on the multicomponent reaction of phenylglyoxal hydrate, 1,3-dimethylbarbituric acid, and 4-hydroxy-6-methyl-2*H*-pyran-2-one. The structure of the synthesized compound was proven by ^{1}H, ^{13}C-NMR, and IR spectroscopy, mass spectrometry, and elemental analysis. A procedure for predicting the possible types of its biological activity was carried out for the title compound.

Keywords: multicomponent reaction; tandem Knoevenagel–Michael process; phenylglyoxal hydrate; 1,3-dimethylbarbituric acid; 4-hydroxy-6-methyl-2*H*-pyran-2-one; ((2*H*-pyran-3-yl)-2-oxo-2-phenylethyl)-1,3-dimethylpyrimidine

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1. Introduction

Multicomponent reactions (MCRs) are reactions that involve the formation of multiple bonds in a single operation. MCRs have been demonstrated as a promising tool for the creation of diverse molecular structures with enhanced efficiency, reduced waste, and high atom economy from easily accessible and inexpensive starting materials by simple mixing of the reactant [1,2]. The ability to obtain the desired compound in "one-pot" with an operationally simple workup without the use of complex purification methods and the avoidance of the isolation of the reaction intermediate is a powerful strategy for green or sustainable synthesis [3].

Arylglyoxal monohydrates with two different carbonyl groups are well known as worthwhile synthons in organic synthesis, especially in the one-pot and multicomponent preparation of heterocyclic frameworks [4]. The presence of an electron-withdrawing ketone group adjacent to the aldehyde caused greater reactivity of the aldehyde group than benzaldehyde. In addition, the presence of the above-mentioned carbonyl groups in the chemical structure of arylglyoxal monohydrates causes superior reactivity and selectivity during the reaction process [5].

2-Pyrone is a versatile building block for the synthesis of key intermediates in synthetic organic chemistry as well as in medicinal chemistry due to the existence of functional groups such as conjugated diene and the ester group [6]. Thus, the development of a

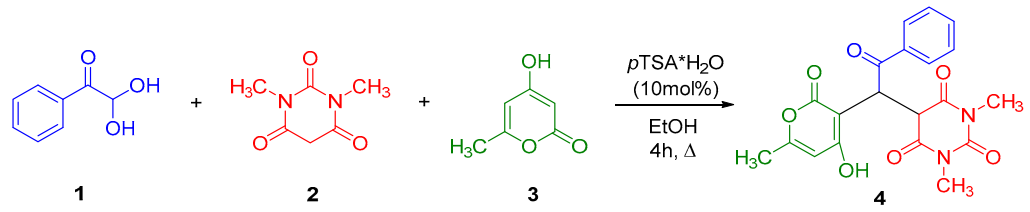
highly efficient synthetic method affording substituted 2-pyrones under mild conditions has attracted considerable attention in organic chemistry [7].

Pyrimidine-2,4,6-trione has been utilized in the design and synthesis of diverse types of compounds and is considered an important building block in organic synthesis [8]. Barbiturates have a special place in pharmaceutical chemistry because of their biological activities such as sedative [9], anticonvulsant [10], antimicrobial [11], and anticancer [12] properties.

Therefore, the elaboration of novel synthetic method based on the multicomponent reaction of arylglyoxals, 2-pyrones, and pyrimidine-2,4,6-triones is of great interest.

2. Results and Discussion

Herein, we develop an efficient tandem Knoevenagel–Michael approach to synthesize 5-(1-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-2-phenylethyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4**) on the basis of the multicomponent reaction of phenylglyoxal hydrate (**1**), 1,3-dimethylbarbituric acid (**2**), and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**3**) (Scheme 1).



Scheme 1. Multicomponent reaction of phenylglyoxal hydrate (**1**), 1,3-dimethylbarbituric acid (**2**), and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**3**).

We have previously demonstrated that the syntheses of such symmetrical and unsymmetrical compounds can be achieved using various techniques and reaction systems [13–18]. In addition, we recently carried out a multicomponent transformation of benzaldehydes, 1,3-dimethylbarbituric acid **2**, and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**3**) by reflux in ethanol for 2 h in the presence of 10 mol% sodium acetate [19].

In this research, the transformation of phenylglyoxal hydrate (**1**), 1,3-dimethylbarbituric acid (**2**), and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**3**) in the presence of *p*-toluenesulfonic acid (*p*TSA) monohydrate in ethanol for 4 h under reflux resulted in 5-(1-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-2-phenylethyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4**).

When the reaction was finished, the reaction mixture was evaporated to dryness in a rotary evaporator vacuum. A small amount of chloroform was added to the resulting residue and stirred for 15 min at ambient temperature. The resulting precipitate of ((2*H*-pyran-3-yl)-2-oxo-2-phenylethyl)-1,3-dimethylpyrimidine **4** in pure form was filtered off and dried in the vacuum of a water jet pump. Final compound **4** was obtained at an 83% yield.

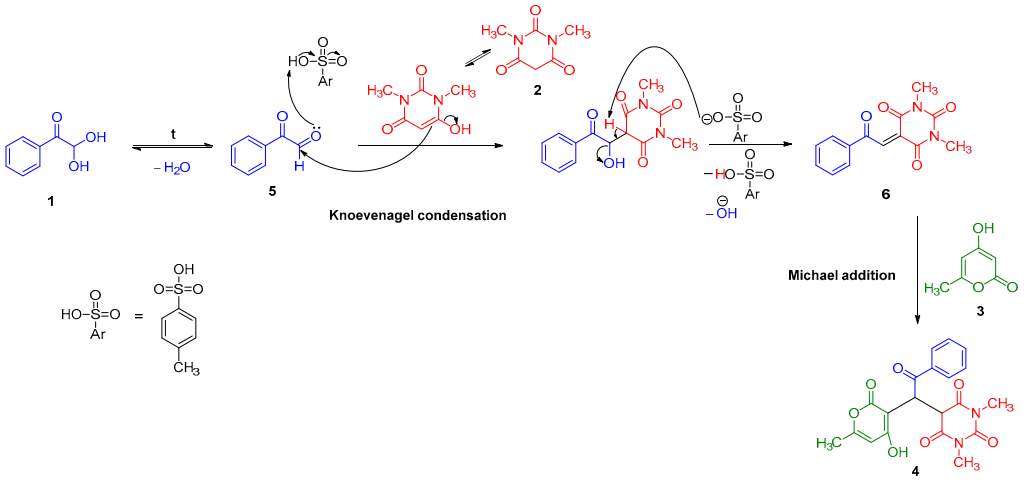
When we carried out the reaction under the conditions described in the article [19], the target compound **4** was obtained with a yield of 75%.

The bond-forming index (BFI) of this process was two, because two new bonds were formed in one stage, namely, two C-C bonds.

The structure of novel ((2*H*-pyran-3-yl)-2-oxo-2-phenylethyl)-1,3-dimethylpyrimi-dine **4** was established using ^{1}H, ^{13}C NMR, and IR spectroscopy, mass spectrometry data, and elemental analysis (see Supplementary Materials).

Taking into consideration the known data on tandem Knoevenagel–Michael reactions [13,19,20], a multicomponent transformation mechanism was proposed (Scheme 2). The process begins with the formation of phenylglyoxal (**5**) from its hydrate **1.** Under these conditions, the condensation of phenylglyoxal (**5**) and 1,3-dimethylbarbituric acid (**2**) results in the formation of the Knoevenagel adduct **6**. The following Michael addition of 4-hydroxy-

6-methyl-2*H*-pyran-2-one **3** affords the formation of 5-(1-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-2-phenylethyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4**).



Scheme 2. A plausible mechanism for the formation of ((2*H*-pyran-3-yl)-2-oxo-2-phenylethyl)-1,3-dimethylpyrimidine **4**.

We did not detect any intermediates during the reaction, so the mechanism was proposed based on the pKa values of C-H acids **2** and **3**. 1,3-Dimethylbarbituric acid (**2**) (pKa 4.68 [21]) has a lower pKa value than 4-hydroxy-6-methyl-2*H*-pyran-2-one (**3**) (pKa 6.83 [22]), so it is a stronger acid and reacts with the carbonyl compound **1** first.

Because the target compound 4 contains two pharmacophore fragments, we carried out a procedure for predicting the possible types of its biological activity. To do this, we used the drug design software PASS (Prediction of Activity Spectra for Substances) [23,24]. Calculations showed that ((2H-pyran-3-yl)-2-oxo-2-phenylethyl)-1,3-dimethylpyri-midine 4 is promising for further research as an anaphylatoxin receptor antagonist, protein CYP2H substrate, platelet aggregation inhibitor, and kidney function stimulant.

3. Materials and Methods

3.1. General Methods

All reagents and solvents were purchased from commercial sources without fur ther purification.

The melting point was taken in open capillary tubes on the Gallenkamp melting-point apparatus (Gallenkamp & Co., Ltd., London, UK). ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AM300 spectrometer (Bruker Corporation, Billerica, MA, USA) at ambient temperature in DMSO-d_6 solution. The correlation of signals in the description of the spectra is not unambiguous. The IR spectrum (KBr pellets) was obtained on a Bruker ALPHA-T FT-IR spectrometer (Bruker Corporation, Billerica, MA, USA). The mass spectrum (EI = 70 eV) was registered on a Kratos MS-30 spectrometer (Kratos Analytical Ltd., Manchester, UK). Elemental analyzer 2400 (Perkin Elmer Inc., Waltham, MA, USA) was applied for elemental analysis.

*3.2. Synthesis of 5-(1-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-2-oxo-2-phenylethyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (**4**)*

Phenylglyoxal hydrate (**1**) (0.152 g, 1 mmol), 1,3-dimethylbarbituric acid (**2**) (0.156 g, 1 mmol), 4-hydroxy-6-methyl-2*H*-pyran-2-one (**3**) (0.126 g, 1 mmol), and *p*-toluenesulfonic acid monohydrate (0.019 g, 0.1 mmol) were refluxed in 5 mL of EtOH for 4 h. After the reaction was finished, the reaction mixture was evaporated to dryness on a rotary evaporator. An amount of 3 mL of chloroform was added to the residue, and this mass was stirred for 15 min at ambient temperature. The precipitate was filtered, washed with

chloroform (2 mL × 2), and dried to isolate pure 5-(1-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-2-phenylethyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4**).

5-(1-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-2-oxo-2-phenylethyl)-1,3-dimeth-ylpyrimidine-2,4,6(1H,3H,5H)-trione (**4**). White crystals; yield 83% (0.330 g); mp = 161–163 °C (from $CHCl_3$); FTIR (KBr) cm^{-1}: 3032 (C-H arom.), 1749 (C=O pyrone), 1677 (C=O b. acid), 1574 (C=C Ar), 1448 (C=C Ar), 1374 (CH_3), 1255 (C-O), 756 (C-H arom.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.18 (s, 3H, CH_3 pyr), 3.15 (s, 6H, 2 N-CH_3), 3.98 (d, 1H, ^3J = 3.9 Hz, CH b.acid), 5.35 (d, 1H, ^3J = 3.9 Hz, C(2)H), 6.00 (s, 1H, CH pyr), 7.46 (t, 2H, ^3J = 7.4 Hz, 2 CH Ph), 7.56 (t, 1H, ^3J = 7.4 Hz, CH Ph), 7.72 (d, 2H, ^3J = 7.4 Hz, 2 CH Ph), 11.92 (s, 1H, OH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 19.2 (CH_3 pyr), 27.9 (N-CH_3), 28.1 (N-CH_3), 46.7 (C(2)H), 47.2 (CH b.acid), 98.7 (CH pyr), 99.7 (C(3) pyr), 127.1 (2C, 2 *o*-CH Ph), 128.6 (2C, 2 *m*-CH Ph), 132.9 (*p*-CH Ph), 136.0 (C Ph), 151.8 (C(2)=O b.acid), 161.8 (C=O pyr), 163.1 (C(6)-CH_3 pyr), 165.7 (C(4)-OH pyr), 166.9 (C(4)=O b.acid), 168.4 (C(6)=O b.acid), 197.2 (C(2)=O gl.) ppm; MS (*m/z*, relative intensity %): 398 $[M]^+$ (100), 271 $[M–H_2O]^+$ (87), 293 $[M–C_7H_5O]^+$ (5), 272 $[M–C_6H_6O_3]^+$ (1), 105 $[C_7H_5O]^+$ (20), 77 $[C_6H_5]^+$ (15); Anal. calcd. for $C_{20}H_{18}N_2O_7$: C, 60.30; H, 4.55; N, 7.03%; found: C, 60.34; H, 4.59; N, 6.94%.

4. Conclusions

In summary, a simple and efficient multicomponent protocol for the synthesis of an earlier unknown 5-(1-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-2-phenylethyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4**) on the basis of the interaction of phenylglyoxal hydrate (**1**), 1,3-dimethylbarbituric acid (**2**), and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**3**) was reported. The presented method may be utilized to synthesize a wide variety of similar substances due to the use of readily available starting materials, atom economy, and a feasible work-up process. The structure of the obtained compound was established by ^{1}H and ^{13}C NMR and IR spectroscopy, mass spectrometry, and elemental analysis.

A procedure for predicting the possible types of its biological activity was carried out for the title compound. ((2*H*-Pyran-3-yl)-2-oxo-2-phenylethyl)-1,3-dimethylpyrimi-dine **4** is promising for further research as an anaphylatoxin receptor antagonist, protein CYP2H substrate, platelet aggregation inhibitor, and kidney function stimulant.

Supplementary Materials: The following are available online. Compound 4 spectra: 1H NMR (Figure S1), 13C NMR (Figure S2), IR (Figure S3), MS (EI) (Figure S4).

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