Ethyl (E)-4-(2,4-Dimethoxyphenyl)-6-(2,4dimethoxystyryl)-2-oxo-1,2,3,4-tetrahydropyrimidine5-carboxylate

by Alfinda Novi Kristanti

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Short Note

Ethyl (*E*)-4-(2,4-Dimethoxyphenyl)-6-(2,4-dimethoxystyryl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Hery Suwito [1,*], Lutfan Zulianto [1], Kautsar Ul Haq [1], Erwanto Erwanto [1], Abdulloh Abdulloh [1], Alfinda Novi Kristanti [1] and Indriani Indriani [2]

[1] Department of Chemistry, Faculty of Science and Technology, Airlangga University, Surabaya 60115, Indonesia; lutfan.zulianto-2016@fst.unair.ac.id (L.Z.); kautsar.ul.haq-2016@fst.unair.ac.id (K.U.H.); erwanto-2015@fst.unair.ac.id (E.E.); abdulloh@fst.unair.ac.id (A.A.); alfinda-n-k@fst.unair.ac.id (A.N.K.)

[2] Department of Chemistry, Tadulako University, Palu 94118, Indonesia; indri.2707@gmail.com

* Correspondence: herys08032002@yahoo.com; Tel.: +62-31-5922-427

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Abstract: A new compound belonging to the "heterostilbene" derivative, namely ethyl (*E*)-4-(2,4-dimethoxyphenyl)-6-(2,4-dimethoxystyryl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2**), has been successfully synthesized as an unprecedented side product of the Biginelli reaction between 2,4-dimethoxybenzaldehyde, ethyl acetoacetate and urea, employing PTSA as catalyst in reflux conditions and using ethanol as solvent. The molecular structure of compound (**2**) was established by FTIR, HRESIMS, 1D and 2D NMR.

Keywords: multicomponent reaction; Biginelli reaction; side product

1. Introduction

The Biginelli reaction is a multicomponent reaction used to synthesize dihydropyrimidinone (DHPM) derivatives in a one-step reaction from three components—an aldehyde, a carbonyl compound possessing the acidic C-H moiety, and urea or its derivatives—under acidic reaction conditions [1,2]. Although this reaction normally produces DHPM derivatives, there are similar reactions, usually called Biginelli-*type* reactions, that produce different pyrimidine derivatives, such as spiropyrimidinone [3,4] and arylidinepyrimidinone [5–11].

In this paper, we report a compound which differs from the product generated from both of the Biginelli-*type* reactions mentioned above. Despite the similarity of its reaction pattern to the Biginelli-*type* reaction producing arylidenepyrimidinone, there is a difference in the carbonyl component used. The aforementioned Biginelli-*type* reaction uses a cyclic mono carbonyl component that has two kinds of acidic C-H with equivalent reactivity, such as cyclopentanone [5–10], cyclohexanone [9–11] and cyclooctanone [9], so that it yields a bicyclic arylidenepyrimidinone. Interestingly, in our experiment, we used an acyclic 1,3-dicarbonyl component that possessed two acidic C-H moieties with different reactivities, namely ethyl acetoacetate. Consequently, we obtained a DHPM derivative attaching styryl moiety at C-6 (**2**).

2. Results and Discussion

Compound **2** was isolated as a side product from the Biginelli reaction between 2,4-dimethoxybenzaldehyde, ethyl acetoacetate and urea using PTSA as catalyst in reflux condition in ethanol (Figure 1). Separation of compound **2** from the main product, namely ethyl 4-(2,4-dimethoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1**), was conducted by column chromatography. Under our reaction conditions, we obtained more product **2** than product **1**,

although compound **2** is a side product. We got 152 mg (15.6%) of compound **1** and 402 mg (28.6%) of compound **2**. Both compounds were successfully separated, their purity analyzed by TLC, and their structure then determined using spectroscopic evidence. In this paper, we do not discuss compound **1**, because it has been reported previously [12].

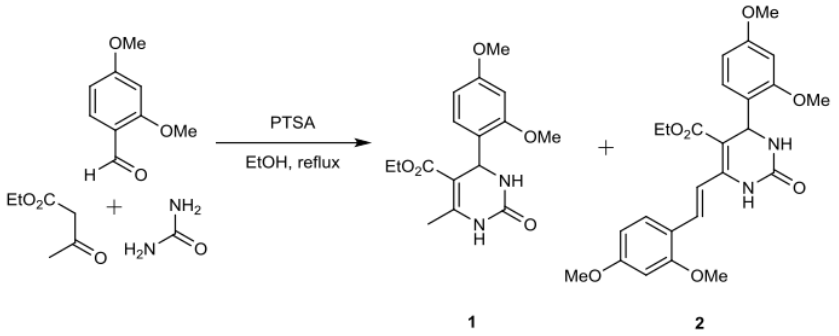

Figure 1. Biginelli reaction producing compound **2**.

The usage of the catalyst PTSA for the Biginelli reaction has often been reported. This catalyst can be used under various reaction conditions, such as reflux in ethanol [13], grindstone [14], microwave [15] and ultrasonic irradiation [16]. However, these reaction conditions give only the main product, and do not provide side products such as compound **2**. Seemingly, the amount of catalyst used has an effect on the formation of side products. The reaction condition mentioned used PTSA in a relatively low amount (<15%). In contrast with our experiment based on ethyl acetoacetate, we used 33 mol% of the catalyst. The reaction between compound **1** and 2,4-dimethoxybenzaldehyde using 33% PTSA as catalyst gave no product. This observation led to the argument that compound **2** was formed through a one-step multicomponent reaction, competing with the formation reaction of compound **1**. Therefore, we propose a reaction pathway which starts with an aldol condensation between ethyl acetoacetate and 2,4-dimethoxybenzaldehyde to produce intermediate 5, which is a γ,δ-unsaturated dicarbonyl compound. A subsequent Biginelli reaction then generates compound **2** (see Figure 2).

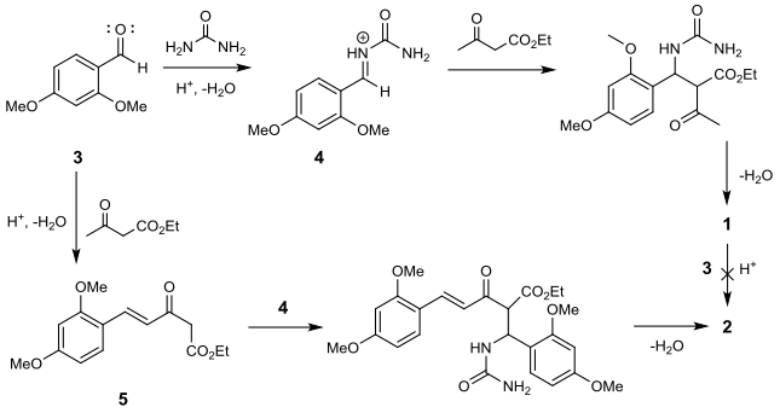

Figure 2. Proposed reaction pathway of compound **2**.

This reaction pathway differs from the pathway suggested by Zhang et al. (2015), who proposed that product **1** is an intermediate in the reaction that was conducted using the Lewis acid catalyst, $FeCl_3 \cdot 6H_2O$ [17]. Besides the different catalyst, the 1,3-dicarbonyl component used by Zhang was an acetoacetanilide derivative. However, our proposed reaction pathway requires further proof, because we did not verify the existence of intermediate **5** during the reaction process. In addition, the nucleophilicity of ethyl acetoacetate at the γ position is relatively low, except under strongly basic conditions, where a dianion can be formed [18,19].

Ethyl (E)-4-(2,4-dimethoxyphenyl)-6-(2,4-dimethoxystyryl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5- carboxylate (**2**): pale yellow solid (402 mg, 28,6%); Rf = 0.57 (*n*-hexane: ethyl acetate = 1:2); HRESIMS $[M - H]^-$ calcd for $C_{25}H_{27}N_2O_7$ 467.1818, found 467.1815; IR (DRS, KBr, cm^{-1}): 3266, 3104 (str, NH amide), 2927 (m, CH aliphatic), 1685 (str, C=O amide, 1607 (str, C=C conjugated), 1503 (str, C=C aromatic) dan 1270 (str, C_{aryl}-O-C_{alkyl}); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H (ppm) 8.09 (d, J = 17.0 Hz, 1H), 7.59 (d, J = 8.6 Hz, 1H), 7.30 (d, J = 17.0 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.83 (s, 1H), 6.51 (dd, J = 8.6, 2.3 Hz, 1H), 6.46 (d, J = 2.2 Hz, 1H), 6.44 (d, J = 2.3 Hz, 1H), 6.36 (dd, J = 8.4, 2.2 Hz, 1H), 5.73 (d, J = 2.8 Hz, 1H), 5.67 (s, 1H), 4.09 (m, 2H), 3.85 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C (ppm) 165.8, 162.2, 160.7, 158.9, 157.9, 153.1, 145.2, 128.2, 127.7, 127.5, 122.4, 117.6, 117.4, 105.6, 103.9, 99.9, 98.9, 98.4, 60.2, 55.6, 55.6, 55.5, 55.5, 50.0, 14.3.

The HRESIMS displayed a negative molecular ion peak at m/z 467.1815, indicating a molecular formula of $C_{25}H_{27}N_2O_7$ and 13 degrees of unsaturation (see Supplementary Material, Figure S1). From the IR spectrum following groups N-H, the amide bond types C-H aliphatic, C=O amide type, conjugated C=C, and C-O-C alkyl-aryl ether were identified, respectively, and are exhibited by absorption band at υ_{max} (cm^{-1}) 3266, 2927, 1685, 1607, 1503 and 1270 (see Supplementary Material, Figure S2). Analysis of ^{1}H-NMR (Table 1) indicating two aromatic protons with *orto* coupling [δ_H 7.59 (d, J = 8.6 Hz) and 7.01 (d, J = 8.4 Hz], two aromatic protons showing *orto* and *meta* coupling [δ_H 6.51 (dd, J = 8.6, 2.3 Hz) dan 6.36 (dd, J = 8.4, 2.2 Hz)], and two aromatic protons showing *meta* coupling [δ_H 6.46 (d, J = 2.2 Hz) and 6.44 (d, J = 2.3 Hz)]. This evidence indicated two aromatic rings, each possessing three protons with ABX systems. The signal of two olefinic protons, shown as two doublet signals at 8.09 and 7.30 ppm with J = 17.0 Hz, indicated the existence of an *E* geometric alkene. The signal at 5.73 ppm showed a benzylic or allylic proton closed to electronegative atom (nitrogen). The presence of four methoxy groups is shown by four singlet signals with an integration value of 12 at δ_H 3.85–3.77 ppm. The presence of multiplet signal at 4.09 ppm with an integration value of 2 and a triplet signal at 1.14 ppm with an integration value of 3 showed the existence of an ethoxy moiety possessing diastereotopic protons at CH_2 moiety (see Supplementary Materials, Figures S3 and S4). In ^{13}C-NMR (Table 1), the 25 signals shown represent all carbon atoms of compound **2** (see Supplementary Materials, Figure S5).

Table 1. NMR data of compound **2** in $CDCl_3$.

No. Atom	δ_H (mult, J Hz)	δ_C (ppm)	HMBC
1	6.83 (s, 1H)		C-5, C-7
2		153.1	
3	5.67 (s, 1H)		C-5
4	5.73 (d, J = 2.8 Hz, 1H)	50.0	C-2, C-5, C-6, C-15, C-16, C-20, C-21
5		99.9	
6		145.2	
7	7.30 (d, J = 17.0 Hz, 1H)	117.4	C-6, C-8, C-9
8	8.09 (d, J = 17.0 Hz, 1H)	127.7	C-5, C-6, C-9
9		117.6	
10		162.2	
10′	3.83 (s, 3H)	55.5–55.6	C-10

Table 1. *Cont.*

No. Atom	δ_H (mult, *J* Hz)	δ_C (ppm)	HMBC
11	6.44 (d, *J* = 2.3 Hz, 1H)	98.9	C-9, C-10
12		158.9	
12′	3.85 (s, 3H)	55.5–55.6	C-12
13	6.51 (dd, *J* = 8.6, 2.3 Hz, 1H)	105.6	C-9, C-11
14	7.59 (d, *J* = 8.6 Hz, 1H)	128.2	C-8, C-10, C-12
15		122.4	
16		157.9	
16′	3.85 (s, 3H)	55.5–55.6	C-16
17	5.46 (d, 1H)	98.4	C-15, C-16, C-18, C-19
18		160.7	
18′	3.77 (s, 3H)	55.5–55.6	C-18
19	6.36 (dd, *J* = 8.4, 2.2 Hz, 1H)	103.9	C-15, C-17, C-18
20	7.01 (d, *J* = 8.4 Hz, 1H)	127.5	C-4, C-16, C-18
21		165.8	
22	4.09 (m, 2H)	60.2	C-21, C-23
23	1.14 (t, *J* = 7.1 Hz, 3H)	14.3	C-22

Based on the results of the HMQC experiment, we observed two protons forming no correlation with carbon atoms, namely singlet proton signal at δ_H at 6.83 and 5.67 ppm. This indicated that both protons were attached to a heteroatom, namely nitrogen. Furthermore, it was observed that a proton at δ_H 5.73 ppm attached to a carbon atom at δ_H 50.0 ppm (see Supplementary Materials, Figure S6). This showed that the proton is a benzylic-allylic attached to nitrogen, which is characteristic for 3,4-dihydropyrimidinone with aryl substituent at C-4. In addition, the existence of the 3,4-dihydropyrimidinone scaffold was also supported by the results of the HMBC experiment, which showed a correlation between the proton at C-4 with conjugated olefinic carbon (δ_C 99 ppm (C-5) and 145.2 ppm (C-6) the and urea carbonyl type (δ_C 153.1, C-2). The presence of the aryl group at C-4 is proved by a long-range correlation of the C-4 proton with three aromatic protons [δ_C 122.4 (C-15), 157.9 (C-16), and 127.5 (C-20)]. Long-range correlation of the C-4 proton with the carbon atom δ_C 165.8 ppm indicated that the conjugated carbonyl ester was attached to C-5. The position of styryl moiety at C-6 is proved by the long-range correlation of proton H-1 (δ_H 6.83 ppm) with olefinic carbon (δ_C 117.4. C-7). In addition, both olefinic protons [7.30 (H-7) and 8.09 (H-8)] built long-range correlations with C-6. The long-range correlations of the HMBC experiment that are possible with the structure of compound **2** are displayed in Figure 3 and in Figure S7 in the Supplementary Materials. Based on the structure elucidation, it can be concluded that compound **2** is a new compound, and it has not been previously identified in the literature.

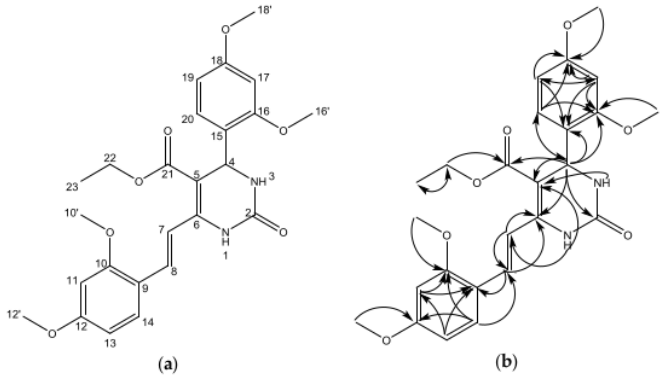

Figure 3. (**a**) Numbering of the structure, and (**b**) Selected HMBC correlations for compound **2**.

3. Materials and Methods

3.1. General

All reagents and solvents (E.Merck (Darmstadt, Germany) or Sigma Aldrich (St. Louis, MO, USA)) were used without further purification. Reaction progress was monitored by TLC on silica gel GF254 aluminum sheets (0.25 mm) using various developing systems. Spots were detected under UV light (λ 254 nm). Column chromatography was carried out using silica gel 60 G. The IR spectrum was recorded in KBr powder with the Diffuse Reflectance method on spectrophotometer IRTracer100 (Shimadzu, Kyoto, Japan). The mass spectrum was recorded using an HR mass spectrometer Waters LCT Premier XE (Waters, Santa Clara, CA, USA). The NMR spectrum (^{1}H-, ^{13}C-NMR, HMQC and HMBC) was recorded using JEOL 400 ECA spectrometer (JEOL, Tokyo, Japan) with $CDCl_3$ as solvent and internal standard.

3.2. Synthesis of Compound **2**

The mixture of 2,4-dimethoxybenzaldehyde (5 mmol), ethyl acetoacetate (3 mmol), urea (5 mmol), PTSA (1 mmol), and 3 mL ethanol was refluxed in a round bottom flask. The progress of the reaction was monitored by TLC. After 6 h, the reaction mixture was cooled down to room temperature, and precipitated by the addition of water. The orange precipitate (mixture of compounds **1** and **2**) was then filtered off, dried, and then subjected to a silica gel 60 G column chromatography using a mixture of chloroform:ethyl acetate (3:1) as mobile phase.

4. Conclusions

A new "Heterostilbene-*type*" compound, namely (*E*)-4-(2,4-dimethoxyphenyl)-6-(2,4-dimethoxystyryl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, is an unprecedented side product of the Biginelli reaction between 2,4-dimethoxybenzaldehyde, ethyl acetoacetate, and urea using PTSA as catalyst under reflux conditions.

Supplementary Materials: The following are available online at http://www.mdpi.com/1422-8599/2017/3/M946, HRESIMS, FTIR, ^{1}H-NMR, ^{13}C-NMR, HMQC, HMBC and spectra are reported in the supplementary materials as Figures S1–S7 and structure refinement parameters as Table S1.

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Author Contributions: H.S. brought out the ideas, managed the research, and wrote the manuscript, L.Z. and E.E. performed the synthesis, K.U.H. analyzed the data and wrote the draft. I.I. analyzed the data, A.A. and A.N.K. correct the draft.

Conflicts of Interest: The authors declare no conflicts of interest.

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