

Short Note

4-Benzoyl-2-(4-bromophenyl)-1-(4-methoxyphenyl)-1,2-dihydropyrimidino[4,3-*c*][1,4]benzoxazine-3,5-dione

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Abstract: The reaction of 3-benzoylpyrrolo[2,1-*c*][1,4]benzoxazin-1,2,4-trione with *N*-(4-bromophenyl)-1-(4-methoxyphenyl)methanimine under thermolytical conditions afforded 4-benzoyl-2-(4-bromophenyl)-1-(4-methoxyphenyl)-1,2-dihydropyrimidino[4,3-*c*][1,4]benzoxazine-3,5-dione in a good yield. The reaction proceeded via in situ generation of a reactive intermediate, acyl(imidoyl)ketene. The compound was fully characterized.

Keywords: 1,4-oxazine; pyrimidine; pyrimidino[4,3-*c*][1,4]benzoxazine; Schiff base; thermolysis

1. Introduction

Pyrimidino[4,3-*c*][1,4]benzoxazines are oxygen-nitrogen heterocycles interesting for medical applications. For example, potential pharmaceutical substances, bearing pyrimidino[4,3-*c*][1,4]benzoxazine core, were developed for treatment of cancer [1], tumors [2,3], cardiovascular disorders [1] and neurological disorders [1] (Figure 1).



Citation: Khramtsova, E.E.; Dmitriev, M.V.; Maslivets, A.N. 4-Benzoyl-2-(4-bromophenyl)-1-(4-methoxyphenyl)-1,2-dihydropyrimidino[4,3-*c*][1,4]benzoxazine-3,5-dione. *Molbank* **2023**, *2023*, M1583. <https://doi.org/10.3390/M1583>

Academic Editor: Fawaz Aldabbagh

Received: 28 December 2022

Revised: 9 January 2023

Accepted: 6 February 2023

Published: 8 February 2023



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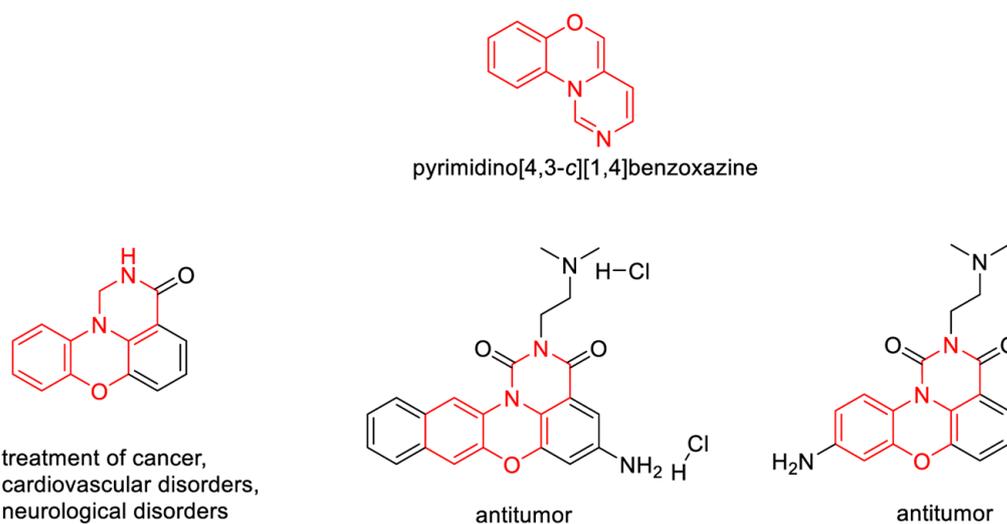
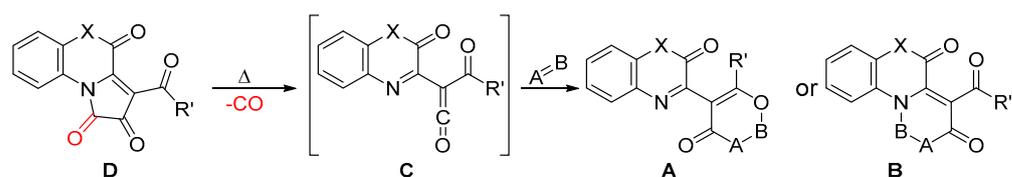


Figure 1. Potential pharmaceutical substances, bearing pyrimidino[4,3-*c*][1,4]benzoxazine core.

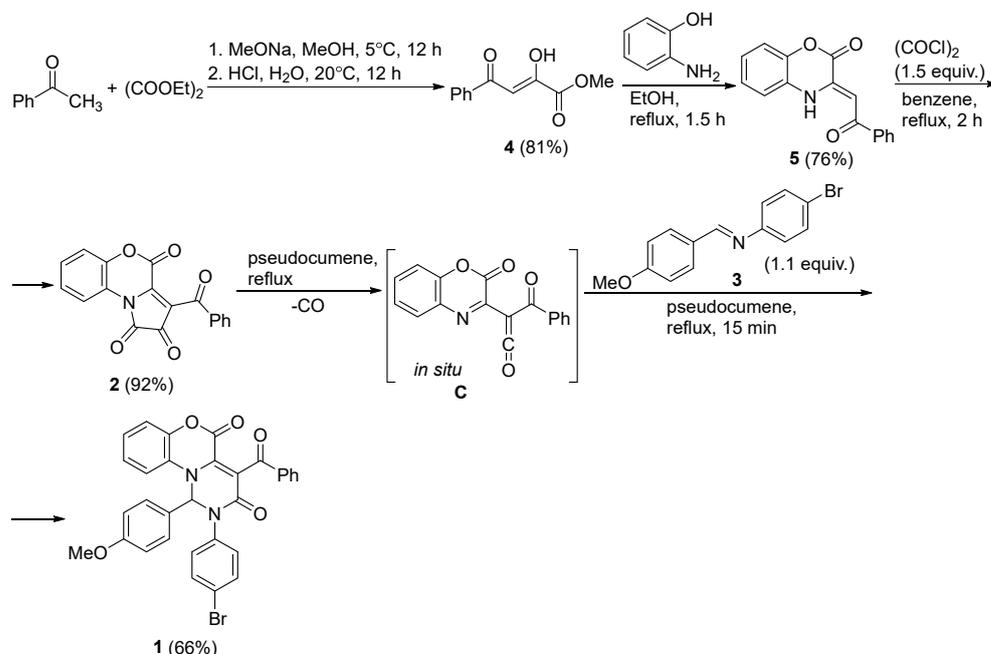
As a continuation of our study on the syntheses of fused heterocycles **A** or **B** via reactions of acyl(imidoyl)ketenes **C**, generated by the thermolysis of [*e*]-fused 1*H*-pyrrolo-2,3-diones **D** [4] (Scheme 1), we synthesized a novel representative of 4-aryloyl-1,2-diaryl-1,2-dihydropyrimidino[4,3-*c*][1,4]benzoxazine-3,5-diones (type **B** heterocycles on the Scheme 1) [5]-4-benzoyl-2-(4-bromophenyl)-1-(4-methoxyphenyl)-1,2-dihydropyrimidino[4,3-*c*][1,4]benzoxazine-3,5-dione **1** [6], by the reaction of 3-benzoylpyrrolo[2,1-*c*][1,4]benzoxazin-1,2,4-trione **2** with *N*-(4-bromophenyl)-1-(4-methoxyphenyl)methanimine **3** under thermolysis conditions.



Scheme 1. Synthesis of fused heterocycles **A** and **B** via reactions of acyl(imidoyl)ketenes **C**.

2. Results and Discussion

The title compound **1** was synthesized in several steps (Scheme 2). Initially, methyl benzoylpyruvate **4** was obtained by the Claisen condensation of acetophenone and diethyl oxalate [7]. Next, the reaction of compound **4** and *o*-aminophenol afforded benzoxazine-2-one **5** [7]. After that, acylation of compound **5** by oxalyl chloride resulted in [*e*]-fused 1*H*-pyrrole-2,3-dione **2** [8]. Finally, thermolysis of compound **2** in the presence of Schiff base **3** gave the target compound **1** in a good yield [6]. The final transformation proceeded one-pot through two steps. Firstly, pyrrolobenzoxazinetrione **2** underwent thermal decomposition to form in situ highly reactive acyl(imidoyl)ketene **C**. Secondly, ketene **C** was involved in a [4+2] cycloaddition reaction with Schiff base **3** to afford the target compound **1**.



Scheme 2. Synthesis of 4-benzoyl-2-(4-bromophenyl)-1-(4-methoxyphenyl)-1,2-dihydropyrimidino[4,3-*c*][1,4]benzoxazine-3,5-dione **1**.

Structure of compound **1** was unambiguously confirmed by the single crystal X-ray analysis (CCDC 2047333, CCDC Refcode = FADPUZ) [6].

It should also be mentioned that compound **1** shows fluorescent properties in solid state (Figure 2) and in a solution.

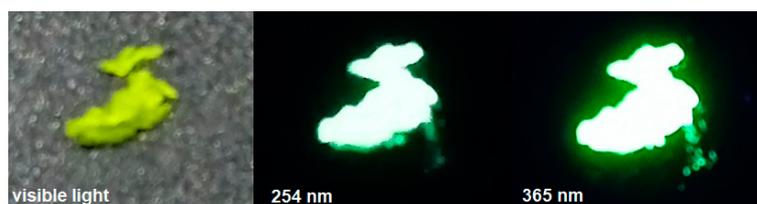


Figure 2. Solid state fluorescence of compound **1**.

3. Materials and Methods

3.1. General Information

^1H and ^{13}C NMR spectra (Supplementary Materials) were acquired on a Bruker Avance III 400 HD spectrometer (Fällanden, Switzerland) (at 400 and 100 MHz, respectively) in $\text{DMSO-}d_6$ using the solvent residual signal (in ^1H NMR, 2.50 for $\text{DMSO-}d_6$; in ^{13}C NMR, 39.51 for $\text{DMSO-}d_6$) as an internal standard. IR spectrum was recorded on an FSM-1201 spectrometer (LOMO, St Petersburg, Russia) from a mull in mineral oil. The melting point was measured on a Khimlabpribor PTP apparatus (USSR). Elemental analysis was carried out on a Vario MICRO Cube analyzer (Langensfeld, Germany). Solid state fluorescence of compound **1** was photographed with Xiaomi Redmi 9A 32 Gb main camera (13 MP) (Beijing, China) in the light of a TLC viewing cabinet Petrolaser TLC-254/365 Thin Layer Chromatography Dark Room (Petrolaser, St Petersburg, Russia). The single crystal X-ray analysis of compound **1** was performed on an Xcalibur Ruby diffractometer (Agilent Technologies, Cheshire, UK). The empirical absorption correction was introduced by multi-scan method using SCALE3 ABSPACK algorithm [9]. Using WinGX [10], the structure was solved with the SHELXS [11] program and refined by the full-matrix least-squares minimization in the anisotropic approximation for all non-hydrogen atoms with the SHELXL [12] program. The hydrogen atoms were positioned geometrically and refined using a riding model. Thin-layer chromatography (TLC) was performed on Silufol (Czechoslovakia) plates using EtOAc/benzene, 1:5 *v/v*, benzene, EtOAc as eluents. CO was indicated by gas detector tubes Gazoopredelitel GH-4 (specifications 12.43.20-76, USSR). The starting compounds **2–5** were obtained according to the reported procedures [7,8,13] from commercially available reagents. All procedures with compound **2** were performed in an oven-dried glassware. Benzene and pseudocumene for procedures with compound **2** were distilled over Na before the use. All other solvents and reagents were purchased from commercial vendors and used as received.

3.2. 4-Benzoyl-2-(4-bromophenyl)-1-(4-methoxyphenyl)-1,2-dihydropyrimidinol[4,3-*c*][1,4]benzoxazine-3,5-dione **1**

A suspension of 1 g (3.1 mmol) of 3-benzoylpyrrolo[2,1-*c*][1,4]benzoxazin-1,2,4-trione **2** and 1 g (3.4 mmol) of *N*-(4-bromophenyl)-1-(4-methoxyphenyl)methanimine **3** in 50 mL of anhydrous pseudocumene was refluxed for 15 min (until evolution of CO stopped). Next, the reaction mixture was cooled to room temperature. The formed precipitate was filtered off and recrystallized from toluene to yield the title compound **1**. Yield: 1.19 g (66%); yellow solid; mp 233–236 °C (decomp.). ^1H NMR ($\text{DMSO-}d_6$, 400 MHz): δ = 8.04–8.00 (m, 1 H), 7.80–7.52 (m, 5 H), 7.42–7.29 (m, 7 H), 7.24–7.17 (m, 3 H), 7.06–7.00 (m, 2 H), 3.79 (s, 3 H) ppm. ^{13}C NMR ($\text{DMSO-}d_6$, 100 MHz): δ = 55.2, 70.8, 113.9, 114.3 (2 C), 117.3, 118.9, 122.4, 123.6, 125.2, 125.7, 127.6 (2 C), 127.8 (2 C), 128.1, 128.2 (2 C), 128.6 (2 C), 130.4, 131.5, 131.7 (2 C), 132.8, 137.1, 138.7, 140.6, 154.6, 160.0, 160.6, 190.6 ppm. IR (mineral oil): 1766, 1660 cm^{-1} . Anal. Calcd (%) for $\text{C}_{31}\text{H}_{21}\text{BrN}_2\text{O}_5$: C 65.67; H 4.18; N 4.19. Found: C 65.94; H 4.13; N 4.11. Crystal structure of compound **1** was deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 2047333, CCDC Refcode = FADPUZ [6].

Supplementary Materials: The following supporting information can be downloaded online, copies of NMR spectra for new compound.

Author Contributions: Conceptualization, A.N.M.; methodology, E.E.K. and A.N.M.; validation, E.E.K. and A.N.M., investigation, E.E.K. (synthetic chemistry), M.V.D. (X-ray analysis); writing—original draft preparation, E.E.K.; writing—review and editing, E.E.K. and M.V.D.; visualization, E.E.K.; supervision, A.N.M.; project administration, A.N.M.; funding acquisition A.N.M. All authors have read and agreed to the published version of the manuscript.

Funding: This study was performed under financial support by the Perm Research and Educational Center “Rational subsoil use”.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The presented data are available in this article.

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

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