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Short Note

1,3-Dimethyl-3′,5-diphenyl-1,5-dihydro-2*H*,5′*H*-spiro[furo[2,3-*d*]pyrimidine-6,4′-isoxazole]-2,4,5′(3*H*)-trione

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Abstract: Michael addition–halogenation–intramolecular ring-closing (MHIRC) reactions are processes in which a halogen atom as a leaving group can attach to substrates or reactants during the reaction, which then undergoes intramolecular ring closure. In this communication the MHIRC transformation of 4-benzylidene-3-phenylisoxazol-5(4*H*)-one and 1,3-dimethylbarbituric acid in the presence of *N*-bromosuccinimide and sodium acetate in EtOH at room temperature was carefully investigated to give novel 1,3-dimethyl-3′,5-diphenyl-1,5-dihydro-2*H*,5′*H*-spiro[furo[2,3-*d*]pyrimidine-6,4′-isoxazole]-2,4,5′(3*H*)-trione in a good yield. The structure of the new compound was confirmed by the results of elemental analysis as well as mass, nuclear magnetic resonance, and infrared spectroscopy.

Keywords: 4-benzylidene-3-phenylisoxazol-5(4*H*)-one; 1,3-dimethylbarbituric acid; spiro[furo[2,3-*d*]pyrimidine]; *N*-bromosuccinimide; MHIRC process

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1. Introduction

One of the most useful methods for the construction of spiro compounds is Michael-initiated ring closure (MIRC) from electron-poor alkenes and halogenated C–H acids [1]. In MIRC reactions a nucleophile with a well-leaving group is added to the substrate, which is necessary for further cyclization [2]. In the Michael addition–halogenation–intramolecular ring-closing (MHIRC) strategy the halogen atom as a leaving group can attach to substrates or reactants during the reaction, which then undergoes intramolecular ring closure [3]. Thus, spirocyclopropanes, spirofurans, as well as non-spirocyclic structures can be obtained.

Nitrogen-containing heterocycles are among the most represented fragments in complicated natural products and bioactive molecules [4].

Barbituric acid has been utilized in the design and synthesis of diverse different types of heterocyclic and carbocyclic compounds, and is considered to be an important building block in organic synthesis [5]. Barbiturates (pyrimidine-2,4,6-triones) have a special place in pharmaceutical chemistry because of their biological activities, such as their sedative [6], anticonvulsant [7], antimicrobial [8], anesthetic [9], anticancer, and antitumor properties [10].

Isoxazole compounds exhibit a wide spectrum of targets and broad biological activities [11]. The integration of an isoxazole ring can offer improved physical, chemical, and biological properties. The inclusion of isoxazole may contribute to increased efficacy, decreased toxicity, and improved pharmacokinetic profiles [12].

In the modern broad range of pharmaceuticals, spiro compounds are not widely used. However, spiro compounds are increasingly being studied as potential drugs for various biomedical applications. The presence of a sterically constrained spiro structure in heterocyclic compounds also adds to the versatility of the properties of spiro compounds [13].

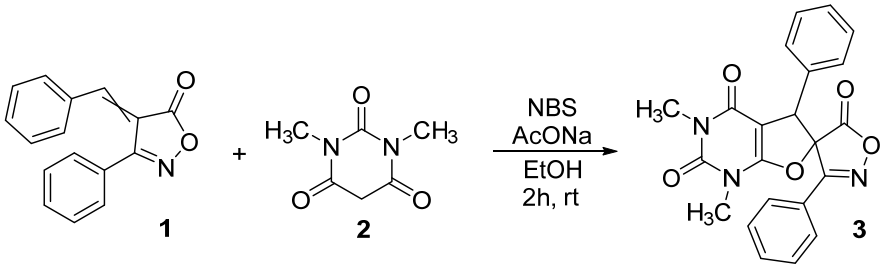
Therefore, the synthesis of new spirofurans with pyrimidine and isoxazole fragments is a prospective area of organic chemistry.

2. Results and Discussion

We previously carried out different MHIRC transformations including electrochemical transformations [14–17]. In these reactions the source of the well-leaving group was molecular bromine, which was either formed during electrolysis or was added directly as a reagent.

Finding a more convenient and non-toxic source of halogen is an important task; studies in this direction are already underway. For example, the use of *N*-halosulfonamides in reactions as sources of halogen has been reported [18].

Now, we wish to report our results on the efficient MHIRC transformation of 4-benzylidene-3-phenylisoxazol-5(4*H*)-one (**1**) and 1,3-dimethylbarbituric acid (**2**) into the previously unknown 1,3-dimethyl-3′,5-diphenyl-1,5-dihydro-2*H*,5′*H*-spiro[furo[2,3-*d*]-pyrimidine-6,4′-isoxazole]-2,4,5′(3*H*)-trione (**3**) in ethanol at room temperature in the presence of *N*-bromosuccinimide (NBS) and sodium acetate for 2 h, as shown in Scheme 1.



Scheme 1. Reaction of 4-benzylidene-3-phenylisoxazol-5(4*H*)-one (**1**) and 1,3-dimethylbarbituric acid (**2**).

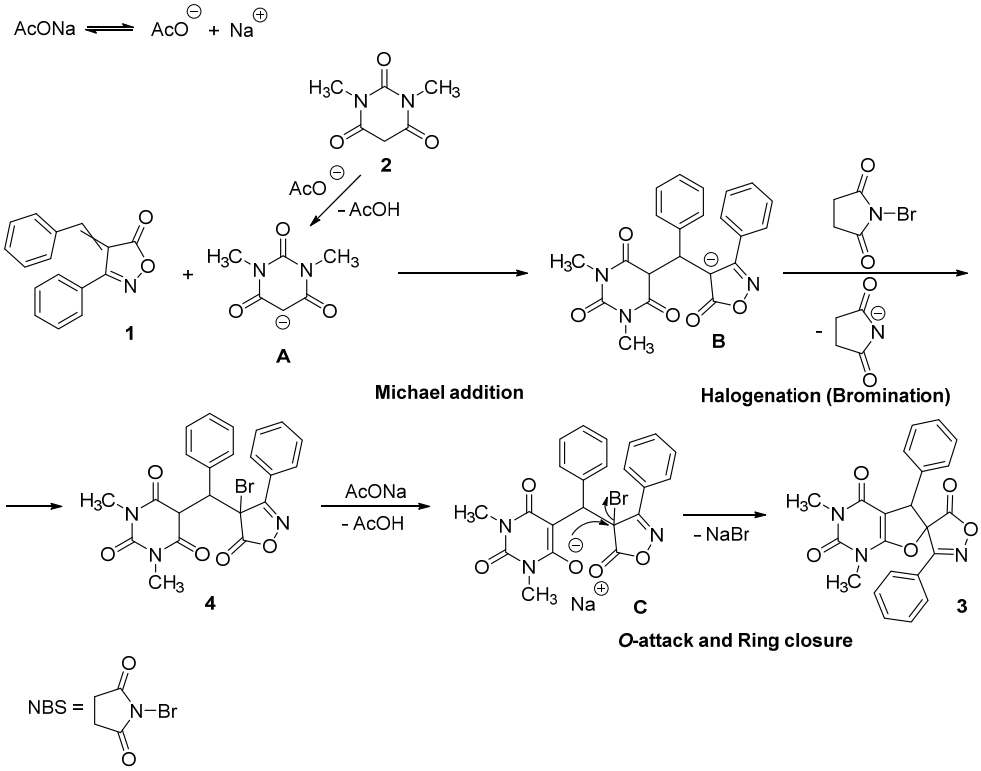
For this process we suggest using NBS as a source of halogen. *N*-Bromosuccinimide is one of the most common and versatile reagents in organic chemistry [19]. It is easy to handle, inexpensive, readily available, non-toxic, and usually more selective than bromine.

A precipitate of the final compound (**3**) is released during the reaction as it proceeds. The final point of the reaction was considered as the complete discoloration of the solution (the color of the solution of the reaction mixture changed from orange to colorless). Compound **3** was synthesized in an 86% yield.

The structure of novel compound **3** was confirmed by ^{1}H and ^{13}C NMR, in addition to IR spectroscopy, mass spectrometry data, and elemental analysis. Only one set of signals was observed in ^{1}H and ^{13}C NMR spectra (Supplementary Materials).

Taking into consideration our previous results [14–17] and data from the literature [18], the following mechanism for the MHIRC transformation of 4-benzylidene-3-phenylisoxazol-5(4*H*)-one (**1**) and 1,3-dimethylbarbituric acid (**2**) was proposed, as shown in Scheme 2.

The first stage of the process is the deprotonation of 1,3-dimethylbarbituric acid (**2**) using an acetate anion in ethanol, which gives the 1,3-dimethylbarbituric acid anion (**A**). Michael addition of the 1,3-dimethylbarbituric acid anion (**A**) to the *β*-carbon position of 4-benzylidene-3-phenylisoxazol-5(4*H*)-one (**1**) as an *α*,*β*-unsaturated compound afforded intermediate **B**. Then, halogenation of the intermediate (**B**) with the use of NBS as a source for electrophilic halogen occurs to give compound **4**. In the presence of a base, the deprotonation of compound **4** takes place, leading to the formation of intermediate **C**. An intramolecular *O*-attack of the hydroxy group to the electrophilic bromosubstituted carbon atom gives 1,3-dimethyl-3′,5-diphenyl-1,5-dihydro-2*H*,5′*H*-spiro[furo[2,3-*d*]-pyrimidine-6,4′-isoxazole]-2,4,5′(3*H*)-trione (**3**).



Scheme 2. Mechanism of 4-benzylidene-3-phenylisoxazol-5(4*H*)-one (**1**) and 1,3-dimethylbarbituric acid (**2**) MHIRC transformation into spiro[furo[2,3-*d*]pyrimidine (**3**).

3. Materials and Methods

3.1. General Methods

The solvents and reagents were purchased from commercial sources and used as received. 4-Benzylidene-3-phenylisoxazol-5(4*H*)-one (**1**) was obtained from benzaldehyde and 3-phenylisoxazol-5(4*H*)-one according to the literature [20].

The melting point was measured with a Gallenkamp melting point apparatus (Gallenkamp & Co., Ltd., London, UK). ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 with a Bruker AM300 spectrometer (Bruker Corporation, Billerica, MA, USA) at ambient temperature. The IR spectrum was registered with a Bruker ALPHA-T FT-IR spectrometer (Bruker Corporation, Billerica, MA, USA) in KBr pellets. The MS spectrum (EI = 70 eV) was obtained directly with a Kratos MS-30 spectrometer (Kratos Analytical Ltd., Manchester, UK). For elemental analysis, a 2400 Elemental Analyzer (Perkin Elmer Inc., Waltham, MA, USA) was used.

3.2. MHIRC Synthesis of 1,3-Dimethyl-3′,5-diphenyl-1,5-dihydro-2H,5′H-spiro[furo[2,3-d]pyrimidine-6,4′-isoxazole]-2,4,5′(3H)-trione 3

4-Benzylidene-3-phenylisoxazol-5(4*H*)-one (**1**) (0.305 g, 1 mmol), 1,3-dimethylbarbituric acid (**2**) (0.156 g, 1 mmol), *N*-bromosuccinimide (0.214 g, 1.2 mmol), and sodium acetate (0.082 g, 1 mmol) were stirred in 3 mL of EtOH for 2 h at room temperature (23 °C). After the reaction was completed the formed solid was filtered, washed with well-chilled ethanol (3 mL × 2), and dried to isolate pure 1,3-dimethyl-3′,5-diphenyl-1,5-dihydro-2*H*,5′*H*-spiro[furo[2,3-*d*]pyrimidine-6,4′-isoxazole]-2,4,5′(3*H*)-trione (**3**).

***1,3-Dimethyl-3′,5-diphenyl-1,5-dihydro-2H,5′H-spiro[furo[2,3-d]pyrimidine-6,4′-isoxazole]-2,4,5′(3H)-trione* (3).** White solid; yield 86% (0.347 g); mp = 218–219 °C (decomp.) (from EtOH); and FTIR (KBr) cm^{-1}: 3035 (C–H Ar), 1817 (C=O izox.), 1716 (C=O), 1683 (C=O), 1664 (C–C Ar), 1504 (C–C Ar), and 1050 (C–O–C). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.18 (s, 3H, N–CH_3), 3.36 (s, 3H, N–CH_3), 5.19 (s, 1H, CH), 7.12–7.20 (m, 2H, C(2)H and C(6)H

Ph), 7.29–7.37 (m, 3H, C(3)H, C(4)H and C(5)H Ph), 7.64 (t, ^{3}J = 7.2 Hz, 2H, C(3)H and C(5)H Ph izox.), 7.73 (t, ^{3}J = 7.2 Hz, 1H, C(4)H Ph izox.), 7.91 (d, ^{3}J = 7.2 Hz, 2H, C(2)H and C(6)H Ph izox.) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.8 (N(3)-Me), 29.7 (N(1)-Me), 53.8 (C(5)H), 85.4 (C spiro), 89.4 (C(4a)), 124.5 (C(1) Ph izox.), 127.1 (2C, C(2)H and C(6)H Ph), 128.4 (2C, C(3)H and C(5)H Ph izox.), 128.6 (2C, C(2)H and C(6)H Ph izox.), 128.7 (C(4)H Ph), 129.9 (2C, C(3)H and C(5)H Ph), 132.1 (C(1) Ph), 133.1 (C(4)H Ph izox.), 134.0 (C-Ph izox.), 158.2 (C(2)=O), 161.5 (C(1a)), 162.4 (C(4)=O), 169.6 (C=O izox.) ppm; MS (*m*/*z*, relative intensity %): 403 $[M]^+$ (23), 358 $[M\text{-}CO_2\text{-}H]^+$ (9), 300 $[M - C_7H_5N]^+$ (18), 284 $[M - C_7H_5NO]^+$ (7), 243 $[M - C_9H_5NO_2 - H]^+$ (25), 142 $[C_9H_4NO]^+$ (27), 77 $[Ph]^+$ (100), 51 $[C_4H_3]^+$ (76); Anal. calcd. for $C_{22}H_{17}N_3O_5$: C, 65.50; H, 4.25; N, 10.42%; found: C, 65.61; H, 4.29; N, 10.36%.

4. Conclusions

The title compound, 1,3-dimethyl-3′,5-diphenyl-1,5-dihydro-2*H*,5′*H*-spiro[furo-[2,3-*d*]pyrimidine-6,4′-isoxazole]-2,4,5′(3*H*)-trione, was synthesized in a good yield by using the simple and efficient MHIRC approach with available equipment and starting compounds. The novel compound was characterized by spectroscopic methods (NMR, IR, and MS-EI) and elemental analysis.

Supplementary Materials: The following are available online. Compound **4** spectra. Figure S1. ^{1}H NMR spectrum of 1,3-dimethyl-3′,5-diphenyl-1,5-dihydro-2*H*,5′*H*-spiro[furo[2,3-*d*]pyrimidine-6,4′-isoxazole]-2,4,5′(3*H*)-trione **3** in DMSO-d_6; Figure S2. ^{13}C NMR spectrum of 1,3-dimethyl-3′,5-diphenyl-1,5-dihydro-2*H*,5′*H*-spiro[furo[2,3-*d*]pyrimidine-6,4′-isoxazole]-2,4,5′(3*H*)-trione **3** in DMSO-d_6; Figure S3. MS (EI) spectrum of 1,3-dimethyl-3′,5-diphenyl-1,5-dihydro-2*H*,5′*H*-spiro[furo[2,3-*d*]pyrimidine-6,4′-isoxazole]-2,4,5′(3*H*)-trione **3**; Figure S4. IR spectrum of 1,3-dimethyl-3′,5-diphenyl-1,5-dihydro-2*H*,5′*H*-spiro[furo[2,3-*d*]pyrimidine-6,4′-isoxazole]-2,4,5′(3*H*)-trione **3**.

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