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Short Note

(Z)-*N*-Carbamothioyl-4-hydroxy-2-oxo-4-(*p*-tolyl)but-3-enamide

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Abstract

The reaction of 5-(*p*-tolyl)furan-2,3-dione with thiourea in a 1:1 ratio when refluxed in 1,4-dioxane gives (*Z*)-*N*-carbamothioyl-4-hydroxy-2-oxo-4-(*p*-tolyl)but-3-enamide with a good yield. This compound was fully characterized.

Keywords: furandione; aroylpyruvic thioureide; biological activity; thiourea

1. Introduction

Structural modifications in 2-thioxo-4-imidazolidinone (2-thiohydantoin) produce compounds with a wide spectrum of pharmacological and biological activities, including antibacterial, antifungal, anticonvulsant, anti-human immunodeficiency virus (HIV), anti-cancer, antitumor, antidiabetic, and anti-inflammatory activities [1–4]. This scaffold is also included in the structures of medicinal products such as Enzalutamide and Apalutamide, which have been FDA-approved as nonsteroidal antiandrogens, or Necrostatin-1, an inhibitor of necroptosis [1,5,6] (Figure 1). Thus, the development of new synthetic approaches to compounds bearing a 2-thioxo-4-imidazolidinone core is in demand.

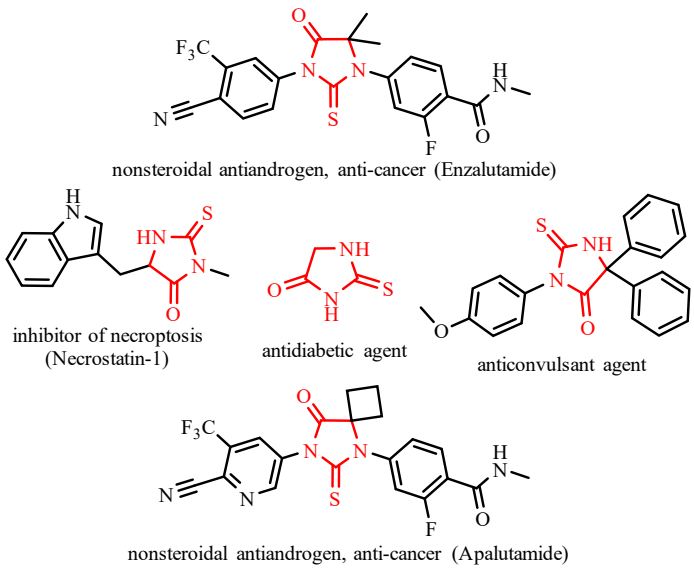


Figure 1. Potential pharmaceutical substances bearing a 2-thiohydantoine core.

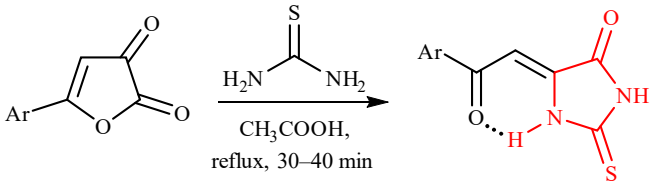
Earlier, the formation of 2-thioxoimidazolidin-4-ones was described by refluxing 5-arylfuran-2,3-diones with thiourea in 15 mL of anhydrous acetic acid for 30–40 min (Scheme 1) [7].

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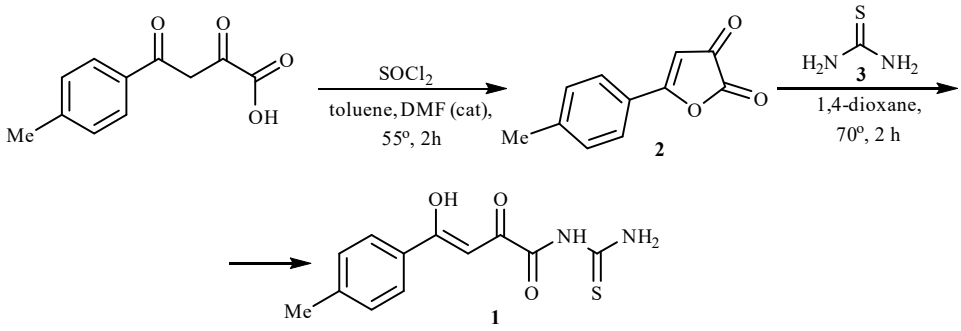


Scheme 1. Synthesis of 2-thioxoimidazolidin-4-ones via a reaction of 5-arylfuran-2,3-diones and thiourea.

Pursuing the development of a synthetic protocol for enaminones under milder conditions [8] than used in [7], we synthesized an intermediate of the reaction, (Z)-N-carbamothioyl-4-hydroxy-2-oxo-4-(p-tolyl)but-3-enamide 1, whose synthesis and characteristics are reported herein.

2. Results and Discussion

The title compound **1** was synthesized in several stages (Scheme 2). Initially, 5-(*p*-tolyl)furan-2,3-dione **2** was obtained in the reaction of 2,4-dioxo-4-(*p*-tolyl)butanoic acid with thionyl chloride [9]. Then, as a result of the reaction of compound **2** and thiourea **3**, (*Z*)-*N*-carbamothioyl-4-hydroxy-2-oxo-4-(*p*-tolyl)but-3-enamide **1**, the target compound, was obtained for the first time.



Scheme 2. Synthesis of (*Z*)-*N*-carbamothioyl-4-hydroxy-2-oxo-4-(*p*-tolyl)but-3-enamide **1**.

The structure of compound **1** was unambiguously confirmed by X-ray diffraction analysis of a single crystal (CCDC 2503066) (Figure 2).

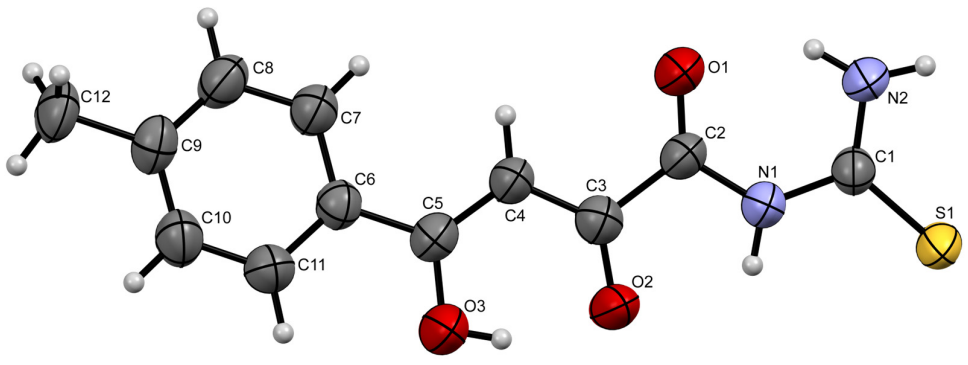


Figure 2. Structure of compound **1,** obtained by X-ray diffraction analysis.

3. Materials and Methods

3.1. General Information

^{1}H and ^{13}C NMR spectra (Supplementary Materials) were obtained on a Bruker Avance III 400 HD spectrometer (Fällanden, Switzerland) (at 400 and 100 MHz, respectively) in $CDCl_3$ using the solvent residual signal (in ^{1}H NMR, 7.27 for $CDCl_3$; in ^{13}C NMR, 77.00 for

$CDCl_3$) as an internal standard. IR spectrum was recorded on a Perkin Elmer Spectrum Two Spectrometer (Shelton, CT, USA) as mulls in mineral oil. The melting point was measured on a Khimlabpribor PTP (USSR) device. The single crystal X-ray analysis of compound **1** was performed on an Xcalibur Ruby diffractometer (Agilent Technologies, Wroclaw, Poland). An empirical absorption correction was introduced via the multi-scan method using the SCALE3 ABSPACK algorithm [10]. Using OLEX2 [11], the structure was solved with the SHELXT [12] program and refined by full-matrix least-squares minimization in the anisotropic approximation of all non-hydrogen atoms with the SHELXL [13] program. Hydrogen atoms bound to carbon were positioned geometrically and refined using a riding model. Hydrogen atoms of OH, NH, and NH_2 groups were refined independently with isotropic displacement parameters. Elemental analysis was carried out on a Vario MICRO Cube analyzer. The compound 4-(4-Methylphenyl)-2,4-dioxobutanoic acid was obtained according to reported procedures [14] from commercially available reagents. The starting compound **2** was obtained according to reported procedures from commercially available reagents [9]. All procedures with compound **2** were performed in oven-dried glassware. All other solvents and reagents were purchased from commercial vendors and used as received.

*3.2. (Z)-N-Carbamothioyl-4-hydroxy-2-oxo-4-(p-tolyl)but-3-enamide **1***

A suspension of 0.63 g (3.33 mmol) of 5-(*p*-tolyl)furan-2,3-dione **2** was added to a solution of 0.25 g (3.33 mmol) of thiourea **3** in 25 mL of anhydrous 1,4-dioxane and refluxed for 2 h. Next, the reaction mixture was cooled to room temperature, and after full evaporation of the solvent on a rotovap, the formed precipitate was recrystallized from chloroform to yield the title compound **1**. Yield: 0.75 g (86%); yellow solid; m.p. 155–156 °C (decomp.). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.46 (s, 3H), 7.05 (br.s, 1H), 7.16 (s, 1H), 7.33 (d, 2H, *J* = 8.3 Hz), 7.93 (d, 2H, *J* = 8.3 Hz), 9.62 (br.s, 1H), 9.85 (s, 1H), 15.56 (br.s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.0, 94.5, 128.2 (2C), 130.0 (2C), 130.8, 145.8, 160.5, 175.2, 181.6, 187.4. IR (mineral oil): 3342, 3245, 3162, 3062, 1708, 1604 cm^{-1}. Anal.Calcd (%) for $C_{12}H_{12}N_2O_3S$: C 54.53; H 4.58; N 10.60; S 12.13. Found: C 54.81; H 4.48; N 10.63; S 11.82.

Crystal data of compound **1**. $C_{12}H_{12}N_2O_3S$, *M* = 264.30, triclinic, space group *P*–1, *a* = 5.8383(10) Å, *b* = 7.8011(14) Å, *c* = 13.859(3) Å, α = 96.197(15)°, β = 98.548(15)°, γ = 96.606(15)°, *V* = 615.00(19) $Å^3$, *T* = 295(2) K, *Z* = 2, μ(Mo Kα) = 0.265 mm^{-1}. The final refinement parameters: R_1 = 0.0860 (for observed 1490 reflections with $I > 2\sigma(I)$); wR_2 = 0.2623 (for all independent 2822 reflections, R_{int} = 0.0390), *S* = 1.040. The largest diff. peak and hole were 0.796 and −0.290 $eÅ^{-3}$. The crystal structure of compound **1** was deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 2503066.

Supplementary Materials: The following supporting information (copies of the NMR spectra and checkCIF of compound **1**) can be downloaded online.

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

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

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

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