molbank

MDPI

Short Note

(2*R*,6′*R*,*E*)-3′-(1-Aminoethylidene)-7-chloro-4,6-dimethoxy-6′-methyl-3*H*-spiro[benzofuran-2,1′-cyclohexane]-2′,3,4′-trione

Boris V. Lichitsky *, Andrey N. Komogortsev and Valeriya G. Melekhina

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Science, Leninsky Pr., 47, 119991 Moscow, Russia
* Correspondence: blich2006@mail.ru

Abstract: A novel synthesis approach for griseofulvin derivatives was developed. The presented method is based on a two-stage process that includes preliminary acetylation of *griseofulvic* acid followed by condensation with ammonium acetate. The advantages of this protocol include readily available starting materials and a simple target product isolation procedure. The structure of the synthesized polycyclic compound was approved by ^{1}H, ^{13}C-NMR spectroscopy, high-resolution mass spectrometry with electrospray ionization (ESI-HRMS), and X-ray diffraction.

Keywords: *griseofulvic* acid; enaminone; acylation

check for updates

Citation: Lichitsky, B.V.; Komogortsev, A.N.; Melekhina, V.G. (2*R*,6′*R*,*E*)-3′-(1-Aminoethylidene)-7-chloro-4,6-dimethoxy-6′-methyl-3*H*-spiro[benzofuran-2,1′-cyclohexane]-2′,3,4′-trione. *Molbank* **2023**, *2023*, M1590. https://doi.org/10.3390/M1590

Academic Editor: Bartolo Gabriele

Received: 22 December 2022
Revised: 16 January 2023
Accepted: 11 February 2023
Published: 16 February 2023

1. Introduction

Griseofulvin is a well-known drug, first isolated from the soil fungus *Penicillium griseofulvum*, which was used in medicine due to its wide range of biological activity [1–5] (Figure 1). It was shown that griseofulvin possessed significant antifungal properties and was employed for the treatment of various types of dermatophytosis [6–10]. However, its remarkable side effects impede its broad use in medicinal practice [11]. At the same time, the preparation of griseofulvin derivatives allows one to minimize negative action and extend the area of pharmacological application of this compound. For example, the antibacterial activity of griseofulvin analogs on a panel of Gram-positive and Gram-negative microorganisms is described in the literature [12]. Thus, modification of the griseofulvin core is of great interest and opens up access to a wide variety of biologically active compounds. A convenient synthon for the preparation of numerous derivatives of this class is *griseofulvic* acid (Figure 1), which can be easily obtained by acid hydrolysis of commercially available griseofulvin [13]. In this case, the presence of a β-diketone fragment in the structure creates opportunities for extensive synthetic applications.

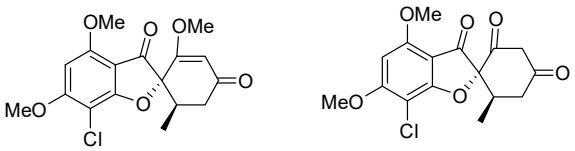
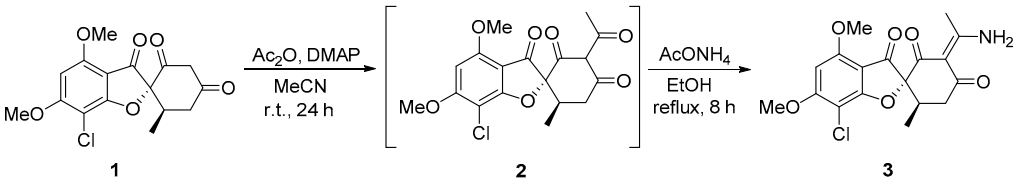


Figure 1. The structures of Griseofulvin and *Griseofulvic* acid.

2. Results

Previously, we elaborated a general route for the preparation of griseofulvin analogs based on a multicomponent reaction of *griseofulvic* acid with aldehydes and Meldrum's acid [3]. In the present communication, we continue to employ the well-studied chemistry of cyclic 1,3-diketones for the modification of *griseofulvic* acid. Initially, we carried out C-acetylation of the starting compound **1**. It should be noted that similar acylation of cyclic β-diketones is well documented in the literature [14–16]. In the considered case, acetic

anhydride was used as an acylating agent. The process was performed at room temperature for 24 h in the presence of DMAP, which was utilized as a base. At the same time, the obtained acylated derivative **2** was applied at the next stage without additional purification. Subsequent reactions with ammonia generated in situ from ammonium acetate made it possible to synthesize the target enaminodiketone **3** in a 63% total yield. The process was carried out by refluxing ethanol for 8 h (Scheme 1).



Scheme 1. Synthesis of enaminodiketone **3**.

The synthesized product **3** is the solid crystalline compound, whose structure was confirmed by ^{1}H, ^{13}C-NMR spectroscopy, and high-resolution mass spectrometry (see Supplementary Materials, Figures S1–S3). ^{1}H NMR spectra of the product contain two broad signals of the protons of the amino group in the region δ 11.63 and 9.60 ppm. The presence of conjugation of the amino group with the unsaturated β-diketone moiety appears to cause hindered rotation around the C–N bond and, as a consequence, nonequivalence of the protons in the NH_2 fragment. At the same time, the intramolecular hydrogen bond of one of the protons with the oxygen atom results in a significant difference in chemical shifts. Note that similar spectral data are described in the literature for other cyclic enaminodiketones [17]. The structure of the synthesized compound was confirmed by X-ray diffraction (Figure 2 and see Supplementary Materials, Tables S1–S7). The results of the X-ray analysis unambiguously indicate the *E*-configuration of the enaminodiketone fragment.

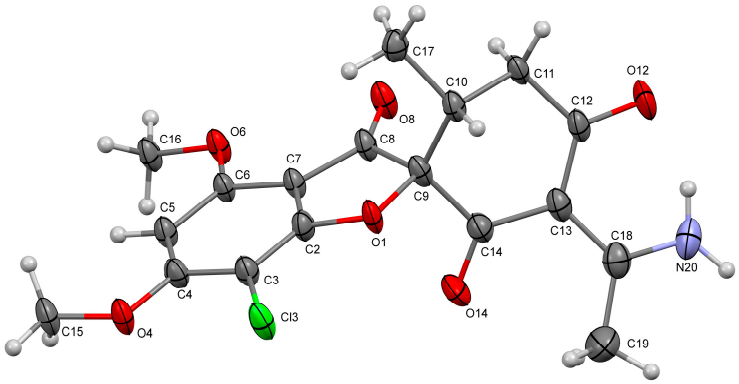
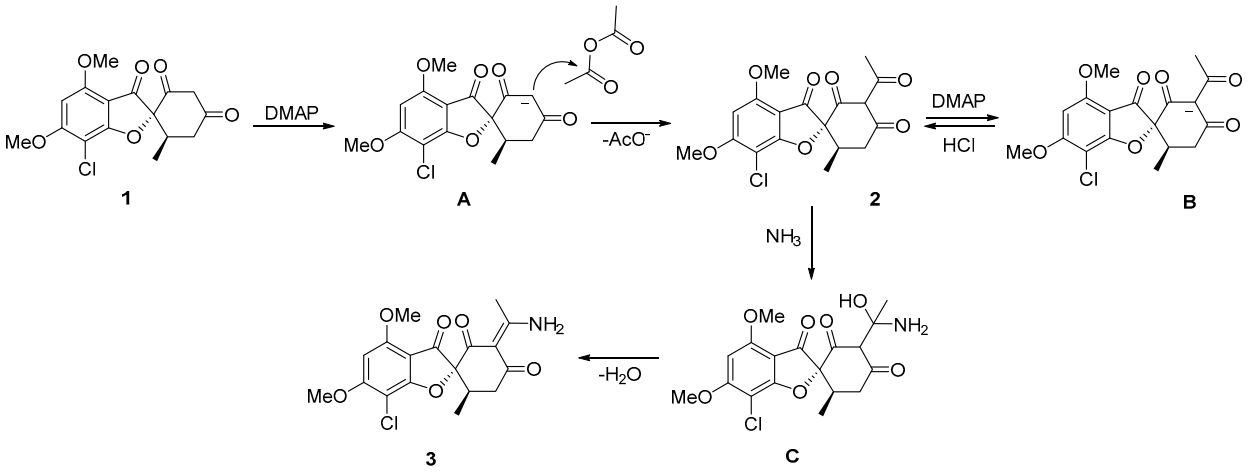


Figure 2. The X-ray crystal structure of compound **3** (CCDC 2240675).

The plausible mechanism of the considered process is presented in Scheme 2. The anion **A** is generated initially with *griseofulvic* acid **1**. Next, the interaction of anion **A** with acetic anhydride leads to acylated product **2**, which, under the action of DMAP, transforms into anion **B**. Further acidification results in acetylated griseofulvin derivative **2**. Subsequent addition of ammonia to the acetyl group and elimination of water leads to the target product **3**. Note that the second stage of the process proceeds regiospecifically, and the interaction with ammonia occurs exclusively with the participation of the acetyl fragment. This appears to be due to the low steric availability of other carbonyl units in the polycyclic spiro-system. It should be emphasized that similar results were described in the literature for other acylated cyclic 1,3-diketones [17].



Scheme 2. Proposed reaction mechanism.

3. Materials and Methods

Griseofulvic acid **1** was synthesized from griseofulvin by the known procedure [18]. All starting chemicals and solvents were commercially available and were used as received NMR spectra were recorded with Bruker Avance 300 (300 MHz) spectrometer (Billerica, MA, USA) in DMSO-d_6. Chemical shifts (ppm) were given relative to solvent signals (DMSO-d_6: 2.50 ppm (^{1}H NMR) and 39.52 ppm (^{13}C NMR)). High-resolution mass spectrum (HRMS) was obtained on a Bruker microTOF II instrument (Bruker Daltonik Gmbh, Bremen, Germany) using electrospray ionization (ESI). Optical rotations were measured on a polarimeter, JASCO P-2000 (JASCO Corporation, Tokyo, Japan), and calibrated with a pure solvent as a blank. The melting point was determined on a Kofler hot stage (Dresden, Germany). X-ray diffraction data were collected at 100K using graphite monochromatized Cu Kα-radiation on a four-circle Rigaku Synergy S diffractometer equipped with a HyPix6000HE area-detector (kappa geometry, shutterless ω-scan technique) (See SI, Table S1–S7). The intensity data were integrated and corrected for absorption and decay by the CrysAlisPro program [19]. The structure was solved by direct methods using SHELXT [20] and refined on F^2 using SHELXL-2018 [21] in the OLEX2 program [22]. The Mercury program suite [23] was used for molecular graphics.

Experimental Procedure for the Synthesis of the (2R,6′R,E)-3′-(1-Aminoethylidene)-7-chloro-4,6-dimethoxy-6′-methyl-3H-spiro[benzofuran-2,1′-cyclohexane]-2′,3,4′-trione 3

Griseofulvic acid **1** (1 mmol, 0.34 g) and DMAP (2.2 mmol, 0. 27 g) were dissolved in MeCN (4 mL). Then acetic anhydride (2.2 mmol, 0.22 g) was added and kept at room temperature for 24 h. The resulting mixture was evaporated in vacuo. The obtained residue was dissolved in MeOH (3 mL) and acidified with HCl_{conc} (0.4 mL). Then, 3 mL of H_2O was added, and the mixture was stirred for 3 h and left overnight. The precipitate formed was filtered off and washed with 30% aqueous MeOH (3 × 6 mL). The obtained crude acylated product **2** was dissolved in EtOH (3 mL), $AcONH_4$ (5 mmol, 0.39 g) was added, and the solution was refluxed for 8 h. Finally, 9 mL of H_2O was added to the mixture, and the precipitate formed was filtered off and washed with 20% aqueous EtOH (3 × 5 mL). White powder; yield 63% (0.24 g); mp 159–161 °C, $[\alpha]_D^{25}$ = +11.9° (c 0.94, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6) (Figure S1) δ 11.63 (br.s, 1H), 9.60 (br.s, 1H), 6.45 (s, 1H), 4.03 (s, 3H), 3.90 (s, 3H), 3.03–2.88 (m, 1H), 2.77–2.64 (m, 1H), 2.48–2.33 (m, 4H), 0.82 (d, J = 6.5 Hz, 3H). ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6) (Figure S2) δ 195.12, 192.09, 186.32, 175.63, 169.09, 164.01, 157.38, 105.16, 104.64, 95.10, 94.88, 90.72, 57.45, 56.40, 40.33, 32.26, 24.29, 14.54. HRMS (ESI-TOF) (Figure S3) *m/z*: $[M + H]^+$ Calcld for $C_{18}H_{18}ClNO_6$ + H^+: 380.0895; Found: 380.0881.

4. Conclusions

In summary, a novel method for the preparation of a griseofulvin derivative was elaborated. The described approach consists of the preliminary acetylation of *griseofulvic* acid and the final interaction with ammonium acetate. The advantages of this method are the application of readily available starting materials and a simple isolation procedure, which avoids chromatographic purification. The structure of the obtained griseofulvin derivative was confirmed by ^{1}H, ^{13}C-NMR spectroscopy, high-resolution mass spectrometry with electrospray ionization (ESI-HRMS), and X-ray diffraction analysis.

Supplementary Materials: The following supporting information can be downloaded online: copies of ^{1}H, ^{13}C-NMR, mass spectra, and X-ray crystallographic data for compound **3**. Figure S1: ^{1}H NMR spectrum (300 MHz) of compound **3** in DMSO-d_6; Figure S2: ^{13}C {^{1}H} NMR spectrum (75 MHz) of compound **3** in DMSO-d_6; Figure S3: HRMS for compound **3**; Tables S1–S7: X-ray crystallographic data for compound **3**.

Author Contributions: Supervision, B.V.L.; conceptualization and methodology B.V.L. and A.N.K.; writing—original draft preparation, B.V.L., A.N.K. and V.G.M.; writing—review and editing, V.G.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: The data for the compounds presented in this study are available in the Supplementary Materials of this article.

Acknowledgments: Crystal structure determination was performed in the Department of Structural Studies of Zelinsky Institute of Organic Chemistry, Moscow.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study, in the collection, analysis, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

References

1. Harris, C.M.; Roberson, J.S.; Harris, T.M. Biosynthesis of griseofulvin. *J. Am. Chem. Soc.* **1976**, *98*, 5380–5386. [CrossRef] [PubMed]
2. Petersen, A.B.; Rønnest, M.H.; Larsen, T.O.; Clausen, M.H. The Chemistry of Griseofulvin. *Chem. Rev.* **2014**, *114*, 12088–12107. [CrossRef] [PubMed]
3. Kartsev, V.; Geronikaki, A.; Petrou, A.; Lichitsky, B.; Kostic, M.; Smiljkovic, M.; Soković, M.; Sirakanyan, S. Griseofulvin Derivatives: Synthesis, Molecular Docking and Biological Evaluation. *Curr. Top. Med. Chem.* **2019**, *19*, 1145–1161. [CrossRef] [PubMed]
4. Aris, P.; Wei, Y.; Mohamadzadeh, M.; Xia, X. Griseofulvin: An Updated Overview of Old and Current Knowledge. *Molecules* **2022**, *27*, 7034. [CrossRef] [PubMed]
5. Ko, B.-S.; Oritani, T.; Yamashita, K. Synthesis and Biological Activities of Griseofulvin Analogs. *Agric. Biol. Chem.* **1990**, *54*, 2199–2204. [CrossRef] [PubMed]
6. Brescini, L.; Fioriti, S.; Morroni, G.; Barchiesi, F. Antifungal Combinations in Dermatophytes. *J. Fungi* **2021**, *7*, 727. [CrossRef] [PubMed]
7. Lana, A.J.D.; Pippi, B.; Carvalho, A.R.; Moraes, R.C.; Kaiser, S.; Ortega, G.G.; Fuentefria, A.M.; Silveira, G.P. In Vitro additive effect on griseofulvin and terbinafine combinations against multidrug-resistant dermatophytes. *Braz. J. Pharm. Sci.* **2018**, *54*, e17149. [CrossRef]
8. Shehabeldine, A.; El-Hamshary, H.; Hasanin, M.; El-Faham, A.; Al-Sahly, M. Enhancing the Antifungal Activity of Griseofulvin by Incorporation a Green Biopolymer-Based Nanocomposite. *Polymers* **2021**, *13*, 542. [CrossRef] [PubMed]
9. Bai, Y.-B.; Gao, Y.-Q.; Nie, X.-D.; Tuong, T.-M.-L.; Li, D.; Gao, J.-M. Antifungal Activity of Griseofulvin Derivatives against Phytopathogenic Fungi in Vitro and in Vivo and Three-Dimensional Quantitative Structure–Activity Relationship Analysis. *J. Agric. Food Chem.* **2019**, *67*, 6125–6132. [CrossRef]
10. El-Nakeeb, M.A.; McLellan, W.L.; Lampen, J.O. Antibiotic Action of Griseofulvin on Dermatophytes. *J. Bacteriol.* **1965**, *89*, 557–563. [CrossRef]
11. Hamdy, A.K.; Sheha, M.M.; Abdel-Hafez, A.A.; Shouman, S.A. Design, Synthesis, and Cytotoxicity Evaluation of Novel Griseofulvin Analogues with Improved Water Solubility. *Int. J. Med. Chem.* **2017**, *2017*, 7386125. [CrossRef] [PubMed]
12. Geronikaki, A.; Kartsev, V.; Petrou, A.; Akrivou, M.G.; Vizirianakis, I.S.; Chatzopoulou, F.M.; Lichitsky, B.; Sirakanyan, S.; Kostic, M.; Smiljkovic, M.; et al. Antibacterial activity of griseofulvin analogues as an example of drug repurposing. *Int. J. Antimicrob. Agents* **2020**, *55*, 105884. [CrossRef] [PubMed]

13. Arkley, V.; Attenburrow, J.; Gregory, G.I.; Walker, T. 241. Griseofulvin Amlogues. Part I. Modification of the aromatic ring. *J. Chem. Soc.* **1962**, 1260–1268. [CrossRef]
14. Crowe, L.B.; Hughes, P.F.; Alcorta, D.A.; Osada, T.; Smith, A.P.; Totzke, J.; Loiselle, D.R.; Lutz, I.D.; Gargesha, M.; Roy, D.; et al. A Fluorescent Hsp90 Probe Demonstrates the Unique Association between Extracellular Hsp90 and Malignancy in Vivo. *ACS Chem. Biol.* **2017**, *12*, 1047–1055. [CrossRef]
15. Goodwin, D.; Simerska, P.; Chang, C.-H.; Mansfeld, F.M.; Varamini, P.; D'Occhio, M.J.; Toth, I. Active immunisation of mice with GnRH lipopeptide vaccine candidates: Importance of T helper or multi-dimer GnRH epitope. *Bioorg. Med. Chem.* **2014**, *22*, 4848–4854. [CrossRef] [PubMed]
16. Hughes, P.F. Indazolyl- and Indolyl-Benzamide Derivatives. WIPO Patent WO2016040809 A1, 17 March 2016.
17. Chu, D.T.W.; Huckin, S.N. Chemistry of hexamethyldisilazane. Silylation of β-diketones and amination of β-triketones. *Can. J. Chem.* **1980**, *58*, 138–142. [CrossRef]
18. Rønnest, M.H.; Harris, P.; Gotfredsen, C.H.; Larsen, T.O.; Clausen, M.H. Synthesis and single crystal X-ray analysis of two griseofulvin metabolites. *Tetrahedron Lett.* **2010**, *51*, 5881–5882. [CrossRef]
19. *CrysAlisPro*, Version 1.171.41.106a; Rigaku Oxford Diffraction: Warriewood, NSW, Australia, 2021.
20. Sheldrick, G.M. SHELXT-Integrated space-group and crystal-structure determination. *Acta Cryst.* **2015**, *A71*, 3–8. [CrossRef]
21. Sheldrick, G.M. Crystal structure refinement with SHELXL. *Acta Cryst.* **2015**, *C71*, 3–8. [CrossRef]
22. Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. OLEX2: A complete structure solution, refinement and analysis program. *J. Appl. Cryst.* **2009**, *42*, 339–341. [CrossRef]
23. Macrae, C.F.; Sovago, I.; Cottrell, S.J.; Galek, P.T.A.; McCabe, P.; Pidcock, E.; Platings, M.; Shields, G.P.; Stevens, J.S.; Towler, M.; et al. Mercury 4.0: From visualization to analysis, design and prediction. *J. Appl. Cryst.* **2020**, *53*, 226–235. [CrossRef] [PubMed]