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Short Note

9,10-Dimethoxy-4-oxo-1-phenyl-1,3,4,6,7,11b-hexahydro-[1,4]thiazino[3,4-a]isoquinoline-1-carboxylic Acid

Valentin Petrov, Teodora Aleksandrova and Aleksandar Pashev *

Department of Chemistry and Biochemistry, Faculty of Pharmacy, Medical University, Pleven, 1 St. Kliment Ohridski Street, 5800 Pleven, Bulgaria; vali.petrov@abv.bg (V.P.); teodora.aleksandrova@mu-pleven.bg (T.A.)
* Correspondence: aleksandar.pashev@mu-pleven.bg

Abstract: The synthesis of the compound 9,10-dimethoxy-4-oxo-1-phenyl-1,3,4,6,7,11b-hexahydro-[1,4]thiazino[3,4-a]isoquinoline-1-carboxylic acid (**4**) was described for the first time using a reaction between 6,7-dimethoxy-3,4-dihydroisoquinoline and phenyl-substituted thiodiacetic anhydride **3**. The reaction proceeded in excellent yield and furnished the compound **4** as a single diastereomer. The structure and relative configuration of **4** was elucidated using a combination of spectroscopic techniques–^{1}H, ^{13}C, COSY, HSQC, HMBC, and NOESY NMR spectra, as well as elemental analysis.

Keywords: 6,7-dimethoxy-3,4-dihydroisoquinoline; thiodiacetic anhydride; [1,4]thiazino[3,4-a]isoquinoline

1. Introduction

The reaction between enolizable anhydrides and different imines is a versatile one-step process that can be used to obtain various nitrogen-containing polycycles with varying substitution patterns and molecular complexity [1–5]. Among the advantages of this synthetic approach are the fact that the process does not require any special catalysts and can be performed in a plethora of organic solvents, sometimes at room temperature. The advancements of synthetic methodologies have given rise to several one-pot varieties of this process [6–10], as well as the application of this reaction in the synthesis of biologically active compounds [2,11] and natural products [7,12].

Our research is focused on the reactions between cyclic imines with monocyclic anhydrides, such as glutaric, diglycolic, thiodiglycolic, and succinic anhydride [13]. This methodology was a previously unexplored approach to the construction of diastereomeric pyrido[2,1-a]isoquinoline derivatives as well as its oxygen and sulfur-containing analogues [13]. When 1-substituted-3,4-dihydroisoquinolines were used in the process, the expected products were obtained only in reaction with thiodiacetic anhydride [13,14]. The obtained sulfur analogues of the tricyclic pyrido[2,1-a]isoquinoline system–[1,4]thiazino[3,4-a]isoquinoline derivatives were found to possess promising DPP-IV inhibitory activity in the sub-micromolar range [15].

In the course of our investigations, we attempted to access more complicated derivatives of the target heterocyclic system. For this reason, we focused on the reaction between 3,4-dihydroisoquinolines and phenyl-substituted monocyclic anhydrides. Among the published substituted monocyclic anhydrides, we chose the 3-phenyl-thiodiacetic anhydride because of its high reactivity even at room temperature [16]. Furthermore, since the reactions of this anhydride have been explored only with acyclic imines, the obtained results could provide useful information about the scope and limitations of the reaction. The

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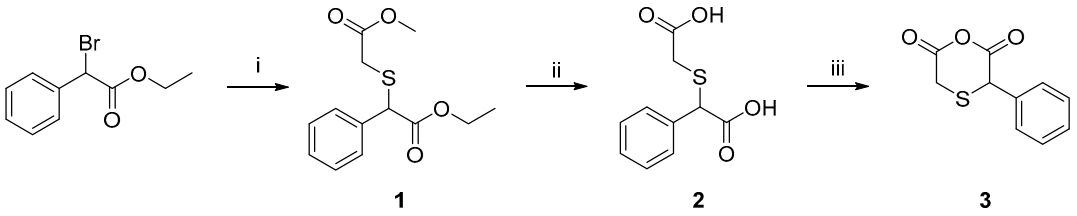
present report outlines the reaction between 6,7-dimethoxy-3,4-dihydroisoquinoline and 3-phenyl-thiodiacetic anhydride. The presented methodology appears to be a valuable and facile synthetic route to previously unreported derivatives of the [1,4]thiazino[3,4-a]isoquinoline ring system.

2. Results and Discussion

2.1. Preparation of 3-Phenyl-thiodiacetic Anhydride

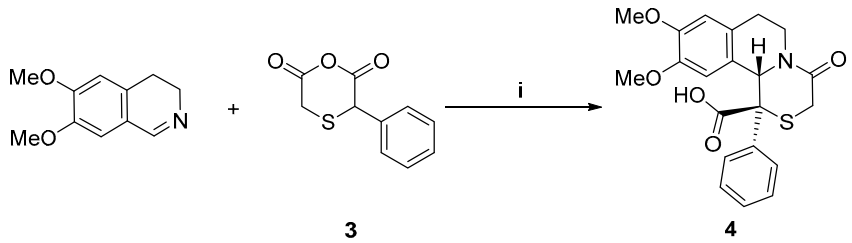
The starting anhydride was prepared using a slightly modified version of the three-step procedure reported by Chizhova et al. [16]. Upon formation of the diester **1** and subsequent hydrolysis, the 2-phenyl-thiodiacetic acid **2** was obtained. TFAA-mediated cyclization in refluxing CH_2Cl_2 gave the 3-phenyl-thiodiacetic anhydride **3** (Scheme 1).



Scheme 1. Reagents and conditions: (i): methyl 2-mercaptoacetate, Et_3N, MeOH, 0 °C to rt, overnight; (ii): 10% aq. NaOH, THF rt, 72 h; (iii): TFAA, dry CH_2Cl_2, reflux, 2 h.

2.2. Reaction with 3,4-Dihydroisoquinoline and Its 1-Substituted Derivatives

The reaction between 6,7-dimethoxy-3,4-dihydroisoquinoline and the substituted anhydride **3** was performed in dry xylene at 110 °C, under inert atmosphere, which is consistent with results from our previous work [13,14]. The anhydride **3** reacted readily because the reaction was completed in under 15 min, as monitored by TLC (Scheme 2).



Scheme 2. Reagents and conditions: (i): xylene, 110 °C, 15 min.

The obtained crude product was recrystallized from ethyl acetate. The structure of **4** was confirmed using a combination of 1D and 2D NMR techniques (^{1}H-, ^{13}C-, COSY, HSQC, HMBC, and NOESY). The product was obtained as a single diastereomer with the carboxy group at C-1 and H-11b being on the same side relative to the heterocyclic ring structure, while the aromatic ring at C-1 was on the opposite side. This corresponds to *rel-(1R,11bS)*-relative configuration. The relative configuration was proven by NOESY-NMR spectra. Spectra can be found in Supplementary Materials.

3. Materials and Methods

Melting points were measured on an automated melting point apparatus SRS EZ-Melt MPA120 (Stanford Research Systems, Sunnyvale, CA, USA) at a ramp rate of 1 °C/min and are presented uncorrected. IR spectra were recorded on a Thermo Fischer Nicolet iS50 FT-IR instrument (Thermo Fisher Scientific, Waltham, MA, USA). NMR spectra were recorded on a Bruker Avance III HD 500 instrument (Bruker Corporation, Billerica, MA, USA) operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. The chemical shifts are given in parts per million (δ)

for the spectra in DMSO-d6 relative to the solvent residual peak [17]. Coupling constants are reported in Hz. Assignments were made using a combination of 1D and 2D spectra (COSY, HSQC, and HMBC). Thin-layer chromatography was performed on Merck 1.05554 silica gel 60F254 aluminum plates, purchased from Sigma Aldrich. Microanalyses were carried out on a Euro Vector EA3000 (Pavia, Italy) elemental analyzer.

3.1. Synthesis of 2-((Carboxymethyl)thio)-2-phenylacetic Acid **2**

The procedure was used as described in the literature [16]. A solution of ethyl 2-bromo-2-phenylacetate (3.6 mL, 20.5 mmol) in methanol (15 mL) was added dropwise to a mixture of methyl thioglycolate (1.85 mL, 20.5 mmol), triethylamine (3.6 mL, 26 mmol), and methanol (25 mL) cooled at 0 °C. The obtained mixture was flushed with dry argon gas and was allowed to reach room temperature, after which the stirring was continued overnight. After evaporation of the volatile products, the mixture was diluted with water (50 mL) and extracted with diethyl ether (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure to yield the ethyl 2-((2-methoxy-2-oxoethyl)thio)-2-phenylacetate **1** as a yellow oil, which slowly solidifies (4.22 g, 90%). The obtained **1** was dissolved in THF (4.3 mL), and then 10% NaOH (16 mL) was added slowly to the solution. The reaction mixture was stirred at room temperature for 72 h. After that the reaction mixture was acidified with concentrated HCl to pH around 1–2. The mixture was extracted with ethyl acetate (2 × 50 mL). The organic phase was washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to afford the acid **2** (3.21 g, 76%) as off-white crystals. Mp 130–131 °C. ^{1}H NMR (DMSO-d_6): 3.1 (1H, d, *J* = 15.2 Hz); 3.25 (1H, d, *J* = 15.1 Hz); 4.79 (1H, s); 7.29–7.42 (5H, m); 12.87 (1H, br.s.). The melting point and the ^{1}H-NMR spectrum were identical with the literature data [16], and the acid **2** was used without further purification in the preparation of the anhydride **3**.

3.2. Synthesis of 3-Phenyl-1,4-oxathiane-2,6-dione **3**

The acid **2** (3.21 g, 14.18 mmol) was dissolved in dry CH_2Cl_2 (15 mL), and the trifluoroacetic anhydride (2.17 mL, 15.6 mmol) was added. The mixture was flushed with dry argon gas and was refluxed for 3 h. After that the mixture was concentrated under reduced pressure, and the crude product (2.78 g, 94%) was recrystallized from dry toluene. After cooling, the anhydride **3** crystallizes promptly as a white solid (2.6 g, 88%). Mp 97–98 °C. Anal. Calcd. for $C_{10}H_8O_3S$: C 57.68%, H 3.87%, S 15.4%; found C 57.97%; H 4.01%; S 15.29%.

3.3. Synthesis of Rel-(1R,11bS)-9,10-dimethoxy-4-oxo-1-phenyl-1,3,4,6,7,11b-hexahydro-[1,4]thiazino[3,4-a]isoquinoline-1-carboxylic Acid **4**

To a suspension of 6,7-dimethoxy-3,4-dihydroisoquinolinium perchlorate (1.1 mmol, 0.320 g) in water (10 mL), a 25% NaOH (5 mL) solution was added. The mixture was stirred for 15 min at room temperature and was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The obtained 6,7-dimethoxy-3,4-dihydroisoquinoline free base (0.19 g, 1 mmol) was dissolved in dry xylene (2 mL), and the anhydride **3** (0.208 g, 1 mmol) was added. The mixture was flushed with dry argon gas and was stirred at 110 °C until the starting imine reacted completely. The course of the reaction was monitored by TLC (ethyl acetate:hexane:formic acid = 3:2:0.1). After completion, the reaction mixture was diluted with ethyl acetate (10 mL) and was extracted with 10% sodium carbonate solution (2 × 10 mL). The combined aqueous layers were acidified to pH 1–2 with concentrated HCl upon which the product **4** separates as yellowish crystals (0.324 g, 81%). The crude product was recrystallized from ethyl acetate (0.289 g, 70%). Mp 120.2–120.8 °C. IR (KBr): 3400–2200 (OH), 1717 (CO), 1635 (CON) cm^{-1}. ^{1}H NMR (DMSO-d_6): 2.57 (1H, dt, H-7,

J = 3.1, 15.6 Hz); 2.67 (1H, m, H-7); 2.84 (1H, m, H-6); 3.72 (1H, d, H-3, *J* = 12.2 Hz); 3.73 (3H, s, OCH_3); 3.74 (1H, d, H-3, *J* = 12.1 Hz); 3.75 (3H, s, OCH_3); 4.46 (1H, d, H-11b, *J* = 3 Hz); 6.69 (1H, s, H-7); 7.11 (1H, d, H-11, *J* = 2.9 Hz); 7.31 (1H, m, 1-phenyl H-4); 7.34 (1H, m, 1-phenyl H-3 and H-5); 7.35 (1H, m, 1-phenyl H-2 and H-6); 12.56 (1H, br.s., COOH). ^{13}C NMR (DMSO-d_6): 28.06 (1C, C-6); 28.63 (1C, C-3); 37.6 (1C, C-6); 47.86 (1C, C-11b); 55.39 (1C, OCH_3); 56.11 (1C, OCH_3); 62.42 (1C, C-1); 110.1 (1C, C-11); 111.46 (1C, C-8); 127.69 (1C, C-7a); 128.33 (1C, C-11a); 128.58 (2C, 1-phenyl C-2 and C-6); 129.21 (2C, 1-phenyl C-3 and C-5); 130.96 (1C, 1-phenyl C-4); 138.72 (1C, 1-phenyl C-1); 147.41 (1C, C-9); 147.46 (1C, C-10); 165.44 (1C, C-4); 170.13 (1C, COOH).

Anal. Calcd. for $C_{10}H_8O_3S$: C 63.14%, H 5.30%, N 3.51%, S 8.03%; found C 63.37%, H 5.41%, N 3.66%, S 8.20%.

Supplementary Materials: The following supporting information can be downloaded, ^{1}H-NMR spectra of compounds **2** and **4**, as well as ^{13}C-NMR spectrum of compound **4.**

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

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