


Short Note

3-Ethoxycarbonyl-1,4-benzodioxin-2-carboxylic Acid

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Abstract: 3-Ethoxycarbonyl-1,4-benzodioxin-2-carboxylic acid, a novel 2,3-disubstituted benzodioxin, was prepared from readily available 1,4-benzodioxin-2-carboxylic acid by lithiation at C(3) and a reaction with the electrophile ethyl chloroformate. The analytical characterization of the product was performed via IR, ¹H-NMR, ¹³C-NMR, HRMS, and HPLC-UV. Due to the unsymmetrically disubstituted unsaturation, the obtained monoester of 1,4-benzodioxin-2,3-dicarboxylic acid is a building block of great potential in the synthesis of a variety of compounds containing the benzodioxin or benzodioxane scaffold.

Keywords: 3-ethoxycarbonyl-1,4-benzodioxin-2-carboxylic acid; 1,4-benzodioxin; ethyl chloroformate; lithiation; ethoxycarbonylation

1. Introduction

The 1,4-benzodioxane motif has wide application in a variety of compounds, many of which exert bioactivity and have therapeutic potential [1–4]. Two main structural features critically condition the interaction capabilities of 1,4-benzodioxane-based compounds with biological targets, namely the substitutions at dioxane C(2), resulting in chirality and, frequently, high eudismic ratios, [1] and decoration of the benzene ring, mainly involved in receptor subtype selectivity [5,6]. Whilst many methods, based on different approaches, have been developed to prepare 1,4-benzodioxanes 2-substituted [7] and/or substituted at the benzene ring [8–10], the 2,3-disubstitution has received less attention from the literature, possibly due to lower demand by medicinal chemists. In this respect, unsaturation between C(2) and C(3) can be synthetically strategic in order to access symmetrically and unsymmetrically 2,3-disubstituted 1,4-benzodioxins and hence 1,4-benzodioxanes. Such an approach, exploiting the presence of the 2,3-unsaturation, is exemplified by the preparation reported here, in which 1,4-benzodioxin-2-carboxylic acid (**2**) is converted into the unsymmetrically 2,3-disubstituted benzodioxin 3-ethoxycarbonyl-1,4-benzodioxin-2-carboxylic acid (**3**) (Figure 1) and (Scheme 1). The dicarboxylic acid monoester **3** is a synthon of great potential due to the presence of unsaturation and two substituents, both susceptible to many useful chemical transformations, which can be selectively performed thanks to the differentiating mono-esterification.

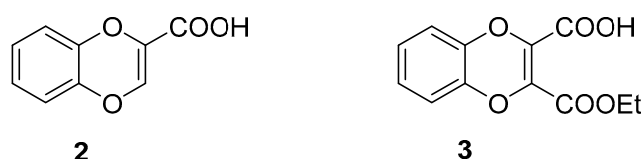


Figure 1. Chemical structures of 1,4-benzodioxin-2-carboxylic acid and 3-ethoxycarbonyl-1,4-benzodioxin-2-carboxylic acid.



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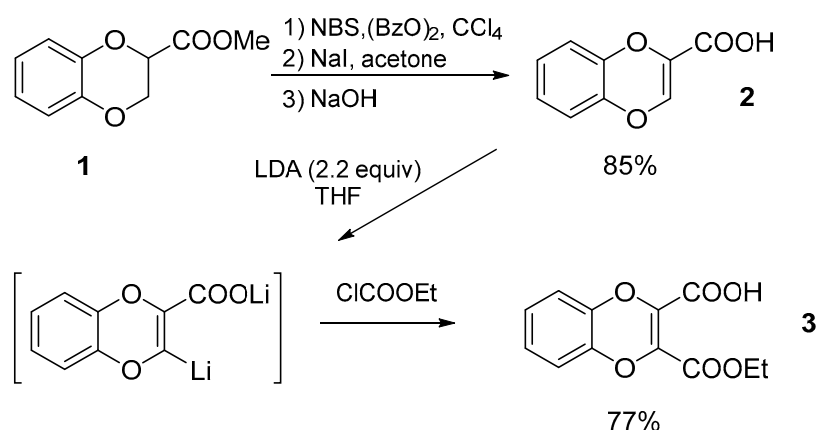
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Scheme 1. Synthesis of 3-ethoxycarbonyl-1,4-benzodioxin-2-carboxylic acid.

2. Results and Discussion

The starting α,β -unsaturated carboxylic acid **2** was easily prepared from readily accessible methyl ester of 1,4-benzodioxan-2-carboxylate (**1**) [11] with an almost quantitative yield according to previously reported procedures involving, in sequence, 2,3-dibromination with NBS, debromination to methyl 1,4-benzodioxin-2-carboxylate with NaI in acetone, and ester saponification [11,12].

To convert **2** into the 2,3-dicarboxylic acid monoester **3**, we exploited the possibility of regioselective dioxin ring metalation by reaction with lithium diisopropylamide (LDA) to give the bis-anionic intermediate species lithium 3-lithio-1,4-benzodioxin-2-carboxylate, which reacts well with the electrophile ethyl chloroformate providing **3**. In the literature, the lithiation of oxygenated heterocycles, followed by condensation with an electrophile, was first described for furan, 3-furoic acid, and 2-furoic acid which gave the nucleophiles 2-furyllithium, lithium 2-lithio-3-furoate, and lithium 5-lithio-2-furoate, respectively [13,14]. Shortly thereafter, the procedure was successfully applied to **2**, and the resulting dianion condensed with several carbonyl compounds [15]. On the other hand, the use of ethyl chloroformate is reported in the ethoxycarbonylation of a wide variety of nucleophiles [16]. In our case, the lithiation/ethoxycarbonylation of **2**, performed in THF at $-78\text{ }^{\circ}\text{C}$ under anhydrous conditions, provided **3**, after standard work-up and purification by flash chromatography, with a high 77% yield.

The novel benzodioxindicarboxylic acid monoester was characterized by IR and NMR spectroscopy and high-resolution mass spectroscopy. The ¹H NMR showed the disappearance of the singlet of the starting material, located at 7.09 ppm and ascribable to the olefinic hydrogen of **2**, and the appearance of the signals of the ethyl ester group, due to the ethoxycarbonylation of the benzodioxin C(3), namely, a quartet at 4.45 and a triplet at 1.43. The ¹³C NMR showed twelve singlets in agreement with the number of unique carbon environments. The high-resolution mass spectrum confirmed the identity of the product.

3. Materials and Methods

1,4-benzodioxin-2-carboxylic acid (**2**) was prepared from methyl 1,4-benzodioxan-2-carboxylate (**1**), in turn obtained from methyl 2,3-dibromopropionate and catechol as previously reported [11,12]. Methyl 2,3-dibromopropionate and catechol were purchased from Sigma-Aldrich S.A. (St. Louis, MO, USA). ATR-FT-IR spectra were acquired with a Perkin Elmer Spectrum One FT-IR (Perkin Elmer, Waltham, MA, USA), equipped with a Perkin Elmer Universal ATR sampling accessory consisting of a diamond crystal. The ¹H and ¹³C NMR spectra were measured on a Varian Mercury 300 FT-NMR spectrometer operating at 300 MHz for ¹H and 75 MHz for ¹³C. NMR data were recorded in CDCl₃ at 25 $^{\circ}\text{C}$, with chemical shifts reported in parts per million (ppm) and coupling constants *J* in Hertz. Melting points were recorded with a Buchi B-540 apparatus (Flawil, Switzerland). An HRMS analysis was performed on a Sciex QTOF X500b system. The purity

of the title compound was assessed by HPLC-UV analysis using an HP1050 system. A chromatographic run was performed with a Vision HT C18 Classic column (particle size 5 μm , 250 \times 4.6 mm dimensions) using a solvent gradient elution (flux rate 1.5 mL/min) with a mobile phase consisting of A = 0.1% TFA in water and B = 0.1% TFA in acetonitrile; the linear gradient started with a 30% B and rose to 50% in 9 min. The detection wavelength was set to 280 nm.

3-Ethoxycarbonyl-1,4-benzodioxin-2-carboxylic Acid (**3**)

A stirred solution of **2** (4 g, 22.45 mmol) in anhydrous THF (40 mL) was cooled at $-78\text{ }^{\circ}\text{C}$ under an inert atmosphere. Then, a 2 M solution of LDA in THF (24.7 mL, 49.39 mmol) was slowly added, and the obtained solution was stirred for 4 h at $-78\text{ }^{\circ}\text{C}$. Ethyl chloroformate (2.6 mL, 26.94 mmol) was added, and the mixture was stirred for an additional 4 h at $-78\text{ }^{\circ}\text{C}$, then warmed to room temperature and added to a saturated solution of NH_4Cl (30 mL). The suspension was extracted with diethyl ether ($3 \times 40\text{ mL}$), and the collected organic layers were dried over sodium sulphate and filtered and concentrated under vacuum. The resulting crude was purified by flash chromatography on silica gel (gradient elution: from 9/1 to 8/2 DCM/MeOH) to give **3** as a white solid (4.30 g, 77%): m.p. $100\text{ }^{\circ}\text{C}$; $R_f = 0.45$ (8/2 DCM/MeOH); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 6.94 (m, 3H), 6.81 (m, 1H), 4.47 (q, $J = 7.1\text{ Hz}$, 2H), 1.45 (t, $J = 7.1\text{ Hz}$, 3H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) ppm 163.38, 160.97, 141.11, 140.86, 135.96, 134.68, 125.95, 125.68, 116.86, 116.35, 64.09, 13.87. FTIR (ATR): $\nu = 3420, 2985, 1742, 1666\text{ cm}^{-1}$. HRMS (ESI-) m/z calcd. for $\text{C}_{12}\text{H}_9\text{O}_6$ $[\text{M}-\text{H}]^-$ 249.0405, found 249.0403. HPLC-UV purity: 94.02%.

4. Conclusions

In summary, we have developed an efficient and simple procedure to prepare 3-ethoxycarbonyl-1,4-benzodioxin-2-carboxylic acid with high yield from the readily available 1,4-benzodioxin-2-carboxylic acid. The title compound is an intermediate of great interest because the two substituents are susceptible to selective transformations, paving the way to other 2,3-substituted benzodioxin and benzodioxane derivatives and benzodioxins and benzodioxanes 2,3-fused with lactones, anhydrides, and lactams.

Supplementary Materials: The following supporting information can be downloaded online: IR, $^1\text{H NMR}$ and $^{13}\text{C NMR}$ spectra of **3**, HRMS spectrum of **3**.

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