

Short Note

Methyl 1,4-Benzodioxane-2-Carboxylates Mono-Nitrated at the Aromatic Ring

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Abstract: 2-Substituted 1,4-benzodioxanes bearing one or more substituents at benzene are important templates in the design and synthesis of a large variety of biologically active compounds. One of the most straightforward synthetic strategies to prepare them in racemic form and with a 2-substituent susceptible to further synthetically useful conversions is the condensation of commercially available methyl 2,3-dibromopropionate with already suitably functionalized catechol. Here, we obtain methyl 8- and 5-nitro-1,4-benzodioxane-2-carboxylate by reaction of methyl 2,3-dibromopropionate with 3-nitrocatechol. After separation, the two positional isomers could be unequivocally identified by HMBC NMR analysis.

Keywords: 8-nitro-1,4-benzodioxane-2-carboxylate; 5-nitro-1,4-benzodioxane-2-carboxylate; HMBC NMR; regioisomers; structure elucidation



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1. Introduction

1,4-Benzodioxane has been and is extensively used as a base scaffold to design a large variety of biologically active compounds [1–4]. Substitution at C(2) makes this substructure chiral (Figure 1), and high eudismic ratios are frequently associated with bioactive enantiomeric 2-substituted 1,4-benzodioxanes [1]. 2-Carboxy, 2-hydroxymethyl and 2-aminomethyl-1,4-benzodioxane are their most accessible and versatile synthetic precursors [5]. Indeed, many different preparative approaches have been developed to obtain them in unichiral form, ranging from enantioselective syntheses to any kind of racemate resolution and use of starting C3 synthetic units available from the “chiral pool” [5]. On the other hand, decoration of the benzene ring (Figure 1), a feature of benzodioxane derivatives often critically related to selectivity for biological receptor subtypes or agonist/antagonist profile [6,7], can only be accomplished using two alternative strategies: condensation of a C3 synthetic unit with benzene already bearing the desired substituents or the introduction of the substituents of benzene into the preformed 2-substituted 1,4-benzodioxane. The two strategies are well exemplified by the recently reported condensation of ethyl 2,3-dibromopropionate with 3-methoxycatechol to give ethyl 5- and 8-methoxy-1,4-benzodioxane-2-carboxylate and Friedel–Craft acetylation of ethyl 1,4-benzodioxane-2-carboxylate to give ethyl 6- and 7-acetyl-1,4-benzodioxane-2-carboxylate [8]. Both the strategies suffer drawbacks in terms of the desired regioisomer’s yield and separation, which can be avoided but using purposely prepared polysubstituted benzene intermediates, generally *O*-mono-protected catechol derivatives, such as, for instance, the regioisomers of nitrocatechol monobenzyl ether [6,9].

Weighing up all these issues related to substitutions at dioxane C(2) and free positions of benzene, condensation of largely available methyl 2,3-dibromopropionate and 3-substituted catechol seems the simplest approach to directly obtain 2-carboxy substituted 1,4-benzodioxanes bearing a further substituent at C(8) or C(5), with the only unknowns being the two regioisomers’ separability and certain identification (Scheme 1).

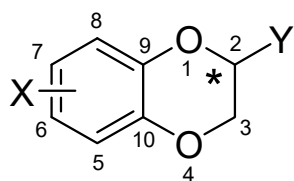
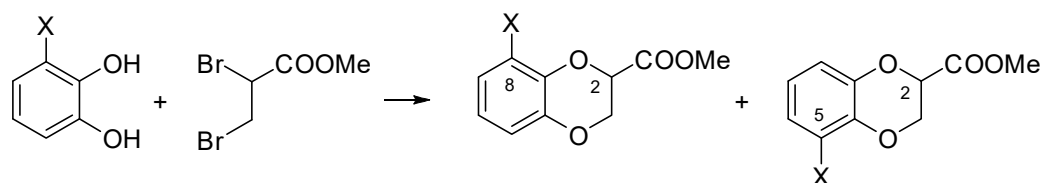


Figure 1. General formula of a chiral 2-substituted 1,4-benzodioxane bearing a substituent at the benzene ring.



Scheme 1. Synthesis of 8- and 5-X substituted methyl 1,4-benzodioxane-2-carboxylates from 3-X substituted catechol and methyl 2,3-dibromopropionate.

Recently, we have reported the unambiguous identification using HSQC and HMBC NMR analyses of methyl 8- and 5-bromo-1,4-benzodioxane-2-carboxylate, **1** and **2** respectively (Figure 2), obtained from methyl 2,3-dibromopropionate and 3-bromocatechol and then chromatographically separated, postulating that structure elucidation of other pairs of 2-substituted 1,4-benzodioxanes bearing an X substituent at the 8 or 5 position would be possible using the same procedure [10]. Here, as a continuation and confirmation of such an approach, we report the preparation of methyl 8- and 5-nitro-1,4-benzodioxane-2-carboxylate, **3** and **4** respectively (Figure 2), from methyl 2,3-dibromopropionate and 3-nitrocatechol and the assignment of the respective structures by analogous analysis of the different patterns of three-bond C-H correlations in the HMBC NMR spectrum.

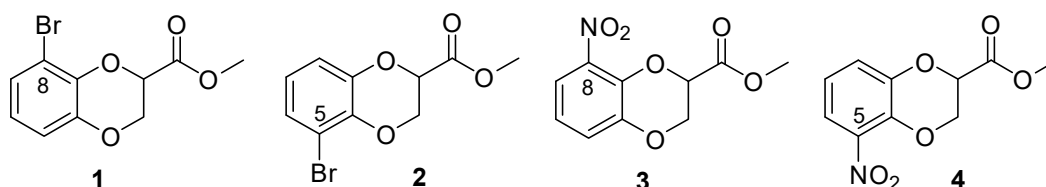


Figure 2. Methyl 8- and 5-bromo-1,4-benzodioxane-2-carboxylates (**1** and **2**) and methyl 8- and 5-nitro-1,4-benzodioxane-2-carboxylates (**3** and **4**).

2. Results and Discussion

Attempts to prepare **3** and **4** by the same procedure previously reported for **1** and **2** [10] were unsuccessful. Indeed, the reaction between methyl 2,3-dibromopropionate and 3-nitrocatechol in boiling acetone in the presence of potassium carbonate gave minimal quantities of the desired products. Therefore, we planned the alternative use of an organic base in a higher boiling solvent. Equimolar amounts of commercially available methyl 2,3-dibromopropionate and 3-nitrocatechol, prepared by nitration of catechol as previously reported [11], were combined in acetonitrile in the presence of diisopropylethylamine and the mixture was heated at reflux temperature overnight. A standard workup provided a mixture of the two regioisomers, with predominance of the isomer quickly moving up the TLC silica gel plate and later identified as that nitrated at C(8) (**3**). This was recovered from the mixture as an insoluble solid by treatment with diethyl ether. Chromatography of the filtrate provided the residual part of **3** and, as a second eluted oily product, the compound was successively identified as 5-nitrated (**4**). The overall yield of **3** was 31% and that of **4** was 20%.

^1H NMR and ^{13}C NMR spectra of both **3** and **4** were consistent with the structure of the methyl ester of 1,4-benzodioxane-2-carboxylic acid nitrated at C(5) or C(8), namely,

the expected products of the reaction (Figure 3). In the aliphatic region of the ^1H NMR spectrum, two double doublets of dioxane CH_2 and, at lower field, the pseudo triplet or double doublet of dioxane CH were recognizable, while, in the aromatic region, the triplet and the two double doublets, from high to low field, could be respectively ascribed to the hydrogen *meta* to the nitro group and the two hydrogens *para* and *ortho* to the nitro group. However, identical patterns of signals and multiplicity with non-decisive chemical shift differences hindered the assignment of the **3** and **4** structures to the first and the second eluted products, respectively, or vice versa. Moreover, the ^{13}C NMR spectra were almost indistinguishable. HSQC NMR further confirmed the structures of 5- or 8-nitrated methyl 1,4-benzodioxane-2-carboxylates, allowing the assignment of the three signals between 118 and 122 ppm, from high to low field, to the three benzene CH *ortho*, *meta* and *para* positioned to NO_2 , respectively, and of the three peaks around 140 ppm to the other three benzene carbons not bearing hydrogen. As for the previously reported regioisomeric brominated benzodioxanes **1** and **2**, HMBC NMR analysis was again resolute for the identification of the signals imputable to C(9) and C(10), the two carbons shared between the two cycles, in **3** and **4** and consequently for the unequivocal identification of the two regioisomers. In the first eluted solid isomer **3**, both the hydrogen *meta* to NO_2 , identified by the triplet, and the methylene hydrogens of dioxane showed a strong $^3J_{\text{H/C}}$ correlation to carbon signaling at 145 ppm. Therefore, this latter was the signal of C(10) and **3** was the 8-nitrated regioisomer (Figure 4). In **4**, the second eluted oily regioisomer nitrated at C(5), the two above correlations took place with two different carbons: the hydrogen *meta* to NO_2 with the carbon signaling at 144 ppm, which is C(9), and the dioxane methylene hydrogens with the carbon signaling at 138 ppm, which is C(10) (Figure 5). These results unequivocally indicated that **3**, the first eluted product, was the isomer nitrated in the 8 position and that **4**, the second eluted product, was the 5-nitrated isomer. The same sequence had been previously observed for **1**, the 8-bromo isomer, and **2**, the 5-bromo isomer [10]. As a consequence of such identification using HMBC NMR, the resonance position of the proton *para* to NO_2 can now be assumed as confidently indicative of the NO_2 position on methyl 1,4-benzodioxane-2-carboxylate: at higher field when NO_2 is at C(8) and the carboxymethyl farther from the *para* proton, at lower field when NO_2 is at C(5) and the carboxymethyl is closer to the *para* proton (Figures 4 and 5). An analogous difference in the chemical shift was previously observed for the proton *para* to bromine in **1** and **2** [10].

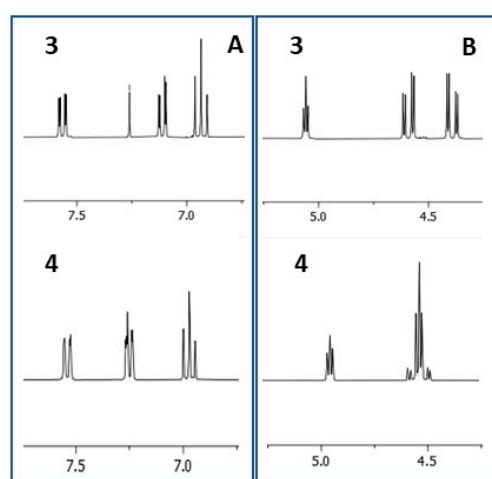


Figure 3. Cont.

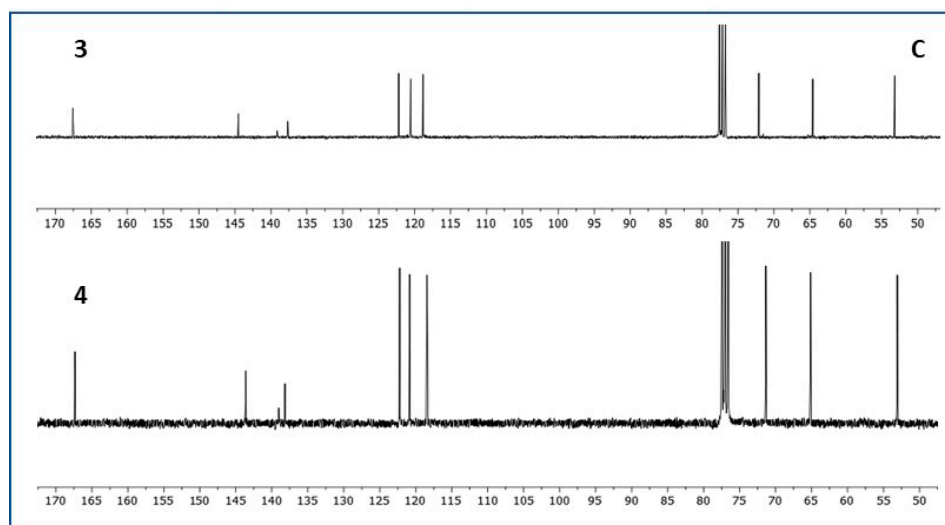


Figure 3. Aromatic region (A) and aliphatic region (B) of the ^1H NMR spectra of **3** and **4** and ^{13}C NMR spectra of **3** and **4** (C). (A) The three adjacent hydrogens of the benzene ring give an analogous sequence of signals: dd, dd and t (from low field to high field). (B) The three hydrogens of the dioxane portion give an analogous sequence of a pseudo triplet and two double doublets or three double doublets. (C) The spectra are indistinguishable. All the spectra were registered in CDCl_3 .

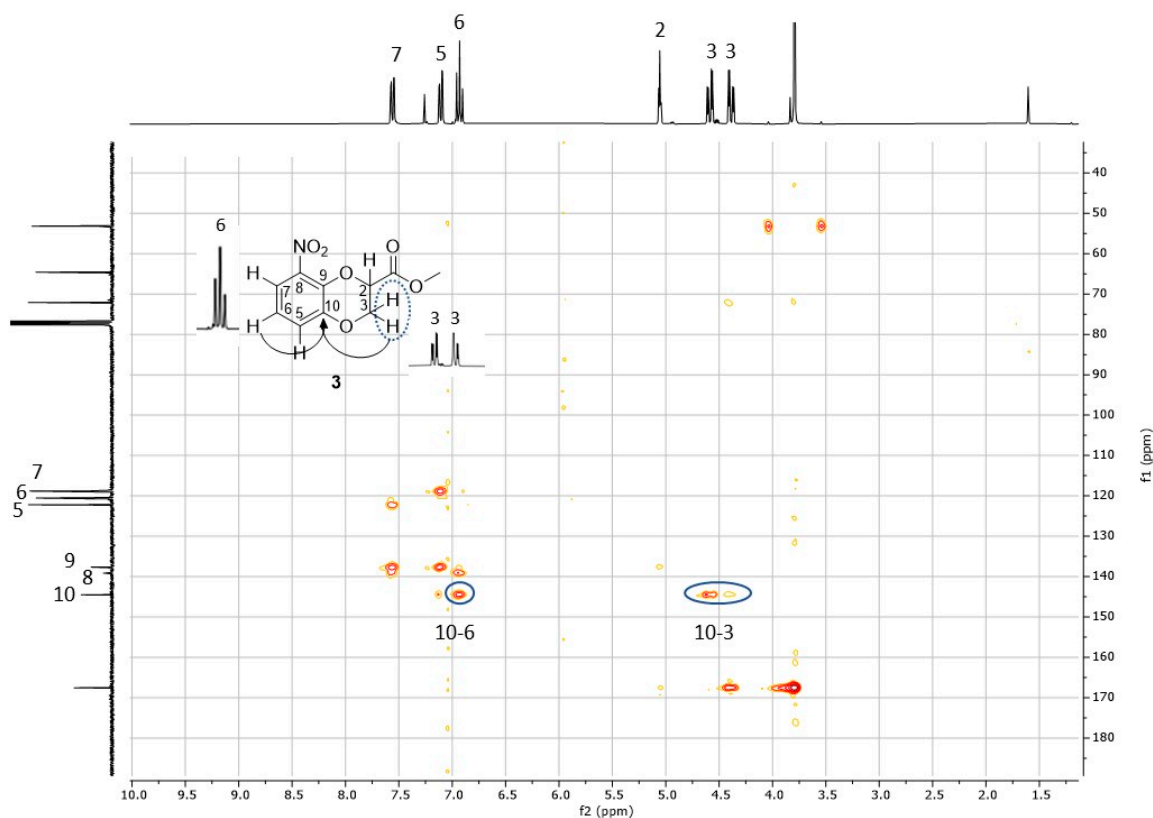


Figure 4. HMBC spectrum of **3** in CDCl_3 displaying important correlations between C(10) and H(6) and between C(10) and H(3).

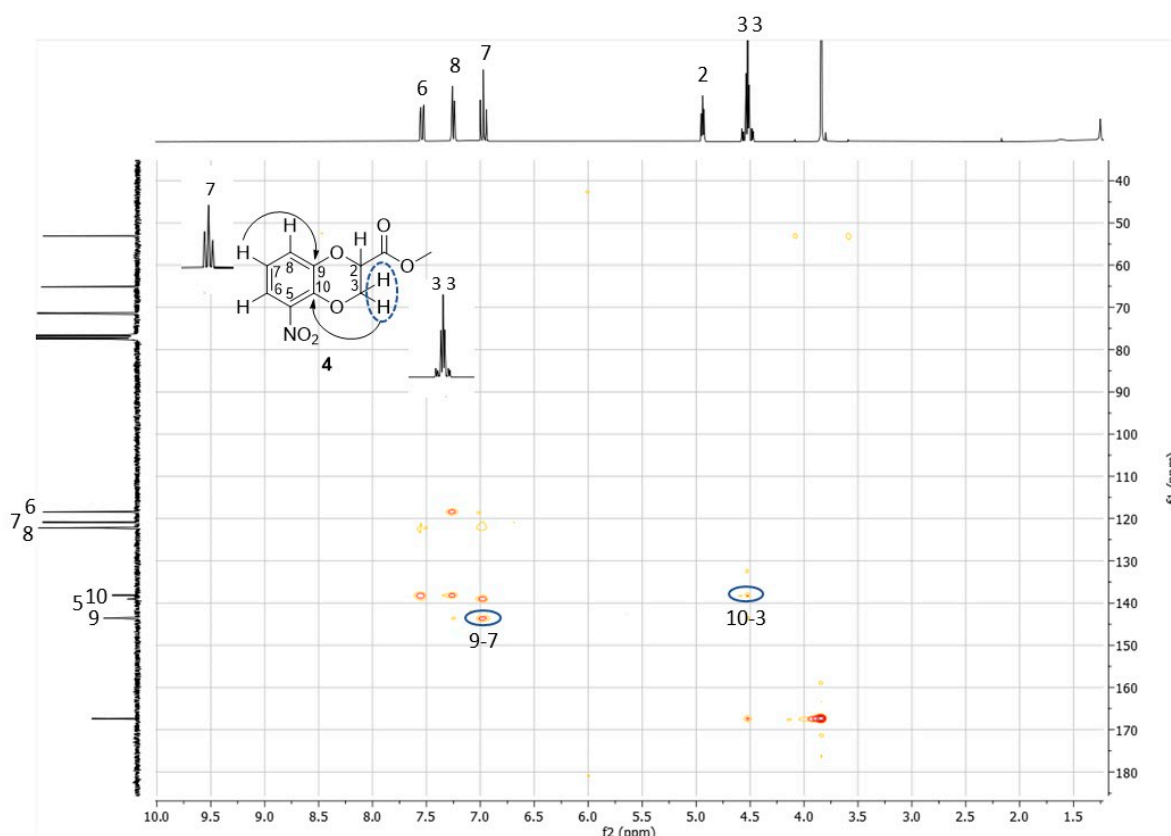


Figure 5. HMBC spectrum of **4** displaying important correlations between C(9) and H(7) and between C(10) and H(3).

3. Materials and Methods

3-Nitrocatechol was prepared from catechol as previously reported [11]. Methyl 2,3-dibromopropionate was purchased from Sigma-Aldrich S.A. (St. Louis, MO, USA). The ^1H and ^{13}C NMR, and two dimensional (2D) (HSQC, and HMBC) spectra were measured on a Varian Mercury 300 FT-NMR spectrometer operating at 300 MHz for ^1H and 75 MHz for ^{13}C . NMR data were recorded in CDCl_3 at 25 °C, with chemical shifts δ reported in parts per million and coupling constants J in Hertz.

Methyl 8-Nitro-1,4-benzodioxane-2-carboxylate (3) and Methyl-5-nitro-1,4-benzodioxane-2-carboxylate (4)

3-Nitrocatechol (2 g, 12.89 mmol) was dissolved into a stirred solution of *N,N*-diisopropylethylamine (6.7 mL, 38.68 mmol) in acetonitrile (35 mL). A solution of methyl 2,3-dibromopropionate (3.17 g, 12.89 mmol) in acetonitrile was added dropwise. The mixture was stirred at reflux overnight and, upon cooling to room temperature, diluted with ethyl acetate, washed with water, then with 1 M aqueous NaOH and, finally, with brine. The organic layer was separated, dried with sodium sulphate and concentrated to give the crude mixture of **3** and **4**. Diethyl ether (7 mL) was added, and the resulting suspension was vigorously stirred for 1 h at room temperature. Upon filtration, **3** was obtained as a white solid (0.47 g, 15.2%): m.p. 90.2 °C, R_f = 0.45 (8/2 diisopropyl ether/petroleum ether); ^1H NMR (300 MHz, CDCl_3) δ 7.56 (dd, J = 8.2, 1.6 Hz, 1H), 7.11 (dd, J = 8.2, 1.6 Hz, 1H), 6.93 (t, J = 8.2 Hz, 1H), 5.06 (pseudo t, J = 3.0 Hz, 1H), 4.59 (dd, J = 11.7, 3.0 Hz, 1H), 4.39 (dd, J = 11.7, 3.0 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 167.5, 144.5, 139.1, 137.7, 122.2, 120.5, 118.8, 72.1, 64.6, 53.2. The filtrate was concentrated, and the resultant crude was purified by flash chromatography on silica gel (gradient elution: from 100% petroleum ether to 80/20 petroleum ether/ethyl acetate) obtaining, in order, **3** (0.49 g, 15.9%) and **4** (0.62 g, 20.1%), which was isolated as a viscous oil. **4**: R_f = 0.37 (8/2 diisopropyl ether/petroleum

ether); ^1H NMR (300 MHz, CDCl_3) δ 7.54 (dd, $J = 8.2, 1.6$ Hz, 1H), 7.25 (dd, $J = 8.2, 1.6$ Hz, 1H), 6.97 (t, $J = 8.2$ Hz, 1H), 4.94 (dd, $J = 4.4, 3.2$ Hz, 1H), 4.59–4.44 (m, 2H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 167.5, 143.7, 139.2, 138.3, 122.4, 121.0, 118.6, 71.5, 65.3, 53.2.

4. Conclusions

In summary, we have obtained the two regioisomeric methyl 1,4-benzodioxane-2-carboxylates nitrated at C(8) (**3**) and C(5) (**4**) by reaction of methyl 2,3-dibromopropionate with 3-nitrocatechol. The complete separation of the two isomers was accomplished by precipitation of pure solid **3** from diethyl ether, followed by chromatography of the filtrate to give, in order, residual **3** and pure **4**, as an oil. The unambiguous identification of their structures was achieved by HMBC NMR, as recently reported for the 8-bromo and 5-bromo analogues. Straightforwardness and easy product separation connote this synthesis, for which, to our knowledge, alternative approaches have not been reported to date.

Supplementary Materials: The following supporting information can be downloaded online: ^1H NMR spectra of **3** and **4** in CDCl_3 ; ^{13}C NMR spectra of **3** and **4** in CDCl_3 ; HSQC spectra of **3** and **4** in CDCl_3 ; HMBC spectra of **3** and **4** in CDCl_3 .

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

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