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Completion of the spectroscopical data for the synthesis of DIMBOA

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Abstract

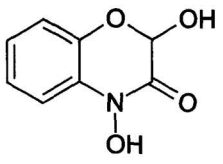
Cyclic hydroxamic acids like 2,4-dihydroxy-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (DIMBOA) and 2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (DIBOA) are found in several plants playing an important role in the defense-system of plants against a variety of enemies. To investigate new mechanism and effects we synthesized the molecules using known synthetic pathways. Since the chemical data of DIMBOA are not complete or even false, we decided to publish the missing ones in this journal.

Keywords

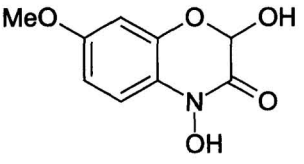
Cyclic hydroxamic acid, DIMBOA, chemical data.

Introduction

Benzoxazinoids are naturally occuring in a variety of plants like *Secale cereale* L. [1], *Triticum aestivum* L. or *Zea mays* L. [2] and especially in many important crop plants of the family *Gramineae*. These compounds are chemical resistance factors against insects, fungi, bacteria and virus in these plants [3], but inhibitory effects on human cancer cells are also reported [4]. The most important cyclic hydroxamic acids are 2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (DIBOA) and 2,4-dihydroxy-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (DIMBOA) and so we synthesized the two molecules following known synthetic pathways [5, 6].



DIBOA

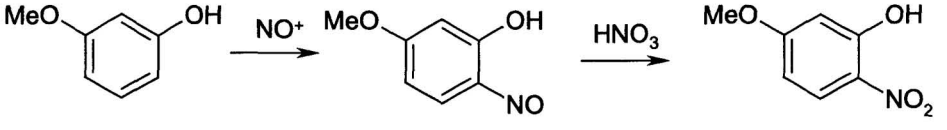


DIMBOA

Results and discussion

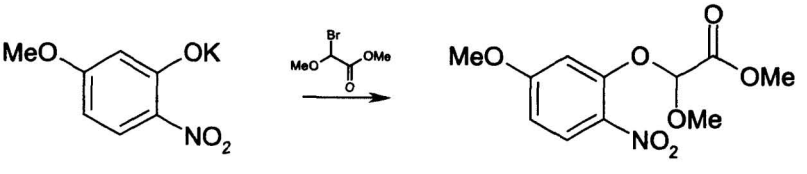
The chemical and physical data of DIBOA are reported complete [5] and are identical to our results. On the other hand the synthesis of DIMBOA is not described fully in the current publications.

The first step is the synthesis of 5-methoxy-2-nitrophenol (**1**) which is also available from commercial suppliers but it is quite expensive and only available in small amounts. *Hartenstein* and *Sicker* [7] describe a convenient method starting from 3-methoxyphenol which was nitrosylated and then oxidized to yield the corresponding nitro-product.



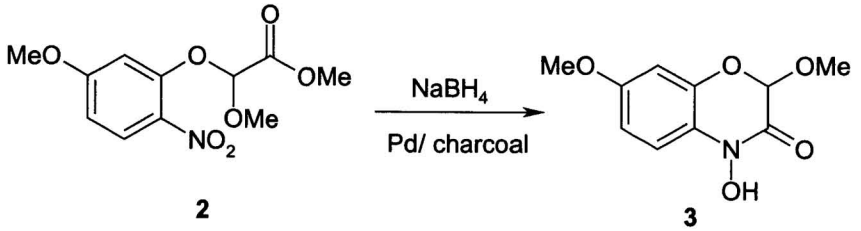
1

The potassium salt of **1** reacted with methyl 2-bromo-2-methoxyacetate *via* S_N-reaction to yield the corresponding acetale **2**. This molecule is quite unstable and only characterized by its melting point in the patent published by *Jernow* and *Rosen* [8]. In our work we present the missing data for compound **2**.



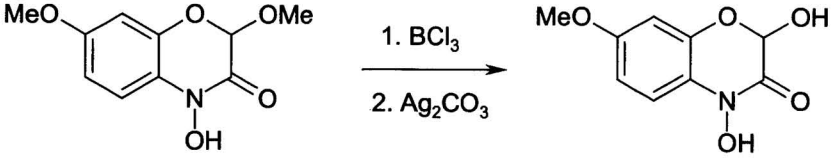
2

The following reduction was easily managed according to literature [6] with $NaBH_4$ and 10% palladium on charcoal in water/ dioxane. The nmr data were completed with ^{13}C nmr values given for the cyclic hydroxamic acid **3**.



2 **3**

The demethylation of the acetale **3** was carried out with BCl_3 in CH_2Cl_2 followed by the reaction with Ag_2CO_3 in water/ THF as proposed in literature [6]. Although the yield was poor the desired molecule **4** (DIMBOA) could be obtained and the chemical data could be completed or corrected, respectively, since the mass spectrum of the compound was published wrong.



3 **4** (DIMBOA)

In conclusion, we could obtain the desired molecules DIBOA and DIMBOA following the literature and we could complete the physical and chemical data for the synthesis of DIMBOA.

Experimental

The melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The ^1H and ^{13}C nmr spectra were recorded on a Bruker Avance DPx200. The ppm-values are related to tetramethylsilane as internal standard. The mass spectra were recorded on a Shimadzu QP-5000 mass spectrometer.

5-Methoxy-2-nitrophenol (**1**) [7]

0.6 mol (74.5 g) 3-methoxyphenol and 0.9 mol (62.1 g) sodium nitrite are solved in three liter water. The solution is stirred at 0 to 2 °C under exclusion of light and 250 ml ice-cold 4N sulfuric acid are added dropwise within 30 minutes. After another 30 minutes the 5-methoxy-2-nitrosophenol formed is filtered off and suspended in a flask containing 1.5 liter water with exclusion of light at 20 °C. Then 1.5 liter nitric acid (50%) is added drop-by-drop within 90 minutes holding the temperatur between 20 and 25 °C. The product formed is filtered off, washed with 100 ml ice-water and recrystallized from methanol yielding 67.2 g (66%) of **1** (mp 93-95 °C). ^{1}H nmr (200 MHz, $CDCl_3$): δ = 11.04 (s, 1H, OH), 8.03 (d, *J* = 10.2 Hz, 1H, phenyl-H), 6.55-6.49 (m, 2H, phenyl-H), 3.88 (s, 3H, OCH_3); ^{13}C nmr (50 MHz, $CDCl_3$): δ = 179.0, 167.0, 157.9, 126.9, 109.4, 101.3, 56.1; ms: *m/e* = 169 (M^+, 100%), 139 (39%), 111 (41%) .

Methyl 2-methoxy-2-(5-methoxy-2-nitrophenoxy)acetate (**2**) [6]

10 mmol (2.07 g) potassium 5-methoxy-2-nitrophenolate are placed without solvent in a dry three-necked flask and 20 mmol (3.32 g) methyl 2-bromo-2-methoxy-acetate are added dropwise. The suspension is stirred at room temperature for 2 hours and then purified by flash column chromatography using toluene/ ethyl acetate 20+1 as eluens yielding 1.8 g (66%) of **2** (mp 81-82 °C). ^{1}H nmr (200 MHz, $CDCl_3$): δ = 7.98 (d, J_{ortho} = 9.1 Hz, 1H, phenyl-H), 6.77 (d, J_{meta} = 2.4 Hz, 1H, phenyl-H), 6.65 (dd, J_{ortho} = 9.1 Hz, J_{meta} = 2.4 Hz, 1H, phenyl-H), 5.57 (s, 1H, acetal-H), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.60 (s, 3H, $OOCH_3$); ^{13}C nmr (50 MHz, $CDCl_3$): δ = 165.8, 164.1, 151.3, 127.9, 107.9, 104.7, 98.6, 55.9, 55.1, 52.9; ms: M^+ not detectable.

2,7-Dimethoxy-4-hydroxy-2H-1,4-benzoxazin-3(4H)-one (**3**) [6]

6.6 mmol (1.79 g) methyl 2-methoxy-2-(5-methoxy-2-nitrophenoxy)acetate (**2**) is solved in 10 ml dioxane and added drop-by-drop to a rapidly stirring suspension of 1 g $NaBH_4$ and 0.1 g 10% palladium on charcoal in 80 ml 1:1 water/ dioxane. The reaction temperature is kept

between 15 and 20 °C. After the complete addition of the ester the mixture is stirred for another 30 minutes, then the catalyst is filtered off and the filtrate is acidified with 1N HCl to pH 4. The solution is extracted immediately three times with ethyl acetate, the combined organic layers are washed with brine, dried with sodium sulfate and evaporated. The raw product is recrystallized from ethanol yielding 0.800 g (53.8%) of **3** (mp 149-150 °C). ^{1}H nmr (200 MHz, $CDCl_3$ + d_6-DMSO): δ = 10.74 (s, broad, 1H, OH), 7.23 (d, J_{ortho} = 9.4 Hz, 1H, phenyl-H), 6.67-6.60 (m, 2H, phenyl-H), 5.38 (s, 1H, acetal-H), 3.78 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3); ^{13}C nmr (50 MHz, $CDCl_3$ + d_6-DMSO): δ = 157.7, 156.2, 140.8, 121.8, 113.7, 107.6, 103.0, 98.4, 55.8, 55.1; ms: *m/e* = 225 (M^+, 12%), 209 (100%), 150 (54%), 149 (49%), 134 (24%).

2,4-Dihydroxy-7-methoxy-2H-1,4-benzoxazin-3(4H)-one (**4**) [6]

3 mmol (0.675 g) 2,7-dimethoxy-4-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**3**) is suspended in 50 ml dry CH_2Cl_2 and cooled to –50 °C under argon with card-ice. 9 mmol (9 ml 1M-solution) boron trichloride is added *via* syringe. The solution is stirred at room temperature for 2.5 hours. After this 8 ml of THF is added and the mixture is given into a seperatory funnel. Then 15 ml water is added, the organic layer is removed, the aqueous layer extracted again with ethyl acetate and the combined organic layers are evaporated without drying to a dark oil. This oil is resolved in 15 ml THF and the solution is added over 10 minutes to a rapidly stirring suspension of 6 mmol (1.6 g) silver carbonate in a 2:1 water-THF mixture and stirred for 20 minutes. The suspension is then filtered and extracted with ethyl acetate until the aqueous layer shows no color with $FeCl_3$. The combined organic layers are washed with brine, dried over sodium sulfate and concentrated to 10 ml. Then 10 ml hexane is added and the mixture is cooled overnight in a refridgerator. The precipitate is filtered off to yield 0.190 g (30%) of **4** (mp 150-155 °C). ^{1}H nmr (200 MHz, d_6-DMSO): δ = 10.82 (s, broad, 1H, OH), 8.14 (s, broad, 1H, OH), 7.15 (d, J_{ortho} = 9.1 Hz, 1H, phenyl-H), 6.69-6.64 (m, 2H, phenyl-H), 5.65 (s, 1H, acetal-H), 3.72 (s, 3H, OCH_3); ^{13}C nmr (50 MHz, d_6-DMSO): δ = 156.8, 156.0, 141.6, 122.4, 113.7,

107.6, 103.4, 92.4, 55.5; ms: *m/e* = 211 (M^+, 7%), 165 (100%), 150 (39%), 106 (17%).

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