Reaction of 4-hydroxycoumarin or its *O*-substituted derivatives with diatomic interhalogens: ICl and IBr

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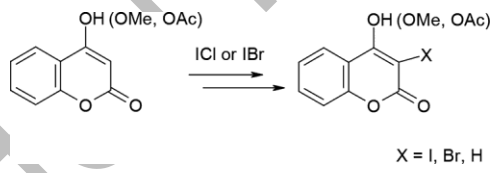
Abstract

Herein we present some aspects regarding the iodination/bromination of 4-hydroxycoumarin or its *O*-methyl or *O*-acetyl derivatives with iodine monochloride or iodine monobromide as halogenation reagents. Also the investigation of photochemical transformation of the three 3-iodocoumarins was investigated for the first time.

Graphical Abstract



KEYWORDS: 4-hydroxycoumarin, 4-hydroxy-3-iodocoumarin, iodine monochloride, iodine monobromide, photochemistry

INTRODUCTION

Coumarin is one of the most intensively studied molecules, its derivatives both from natural or synthetic sources possessing valuable biological activities.[1] In particular, 4-hydroxycoumarin and its derivatives are found as building blocks of important bioactive molecules[2,3] such as warfarin[4] and as an important synthetic tool in obtaining a large

class of bioactive heterocycles.[2] In particular 3-substituted coumarins with nitrogen heterocycles[5] are valuable compounds for their properties such as fluorescence.[6]

The halogenation of 4-hydroxycoumarin or its derivatives[7–19] as in general the halogenation of bioactive molecules is of interest as halogen atoms could impact their bioavailability.[20]

Thus 4-hydroxycoumarin or its derivatives were brominated using molecular bromine,[7–8] N-bromosuccinimide,[9–11] or by other methods.[12] The chlorination reaction of these compounds was also performed.[13] The iodination of the 4-hydroxycoumarin and its methyl ether was accomplished using molecular iodine,[14a,b] *N*-iodosuccinimide (NIS)[15,16] or by other methods.[17, 18]

Recent reports in the synthesis of linear[15] or angular[11,16,17] furocoumarins, interesting bioactive scaffolds, highlighted the synthetic utility of 3-bromo or 3-iodo-4-hydroxycoumarin or its corresponding O-methyl and O-acetyl derivatives in Sonogashira type reactions leading to compounds from the class of coumestans (Scheme 1) [21]

The halogenation of coumarins with iodine or bromine monochloride seems to be under investigated. Iodine monochloride however proved to be a very efficient iodination and iodocyclization reagent and its chemistry was reviewed.[22]

Herein we report the halogenation reaction of 4-hydroxy, 4-methoxy, and 4-acetoxycoumarin using iodine monochloride or iodine monobromide.

RESULTS AND DISCUSSION

Iodine monochloride is known from the literature as a versatile iodination reagent.[22–24] Thus starting from the 4-hydroxycoumarin **1** we obtained in good yield the 3-iodo-4-hydroxycoumarin **2** by reaction with ICl in acetic acid at room temperature (Scheme 2). When trying to obtain the iodinated *O*-acetyl derivative **4** we observed that the reaction with ICl did not occur when the 4-acetoxycoumarin **3**, obtained in a previous step was employed as starting material. Thus the obtaining of **4** can be done performing the acetylation reaction after the iodination step (Scheme 2). Compounds **2** and **4** were obtained in 82 % and 72 % yields respectively. Thus 3-iodo-4-acetoxycoumarins could be also easly accesed for coupling reactions such as Sonogashira.[11]

The reaction of 4-hydroxycoumarin with iodine monobromide in acetic acid resulted in a mixture containing 4:1 of 3-iodinated and 3-brominated 4-hydroxycoumarins **2** and **5**. In order to confirm the structure of the brominated compound we performed the reaction of 4-hydroxycoumarin with molecular bromine in AcOH as solvent (Scheme 3).

The ratio of the two halogenated coumarins could not be established by ^{1}H-NMR as the proton signals shifts are almost identical for the two compounds thus the signals are superimposed. However the ^{13}C-NMR spectrum showed two signals in the aliphatic area

corresponding to C-Br at 91.1 ppm and C-I at 68.2 ppm (Figure 1). The integral of the signals was calculated for the signals at 133 ppm corresponding to a 4:1 ratio.

The 3-iodo-4-methoxycoumarin is an important synthetic tool for Sonogashira coupling reactions[15,16] which give access to more complex coumarin derivatives.[11,15-17] However the 4-methoxycoumarin was available commercially and the iodination was made using a literature method by employing NIS as iodination reagent.[13, 14] We envisioned the obtaining of 3-iodo-4-methoxycoumarin by using ICl as iodination reagent, starting from 4-hydroxycoumarin **1**, knowing the need of synthetic methods for this type of halogenated derivatives.

Thus the compound **6** was first obtained by treating 4-hydroxycoumarin with a methanol-hydrochloric acid solution according to Scheme 4. The compound **6** was then reacted with ICl but the reaction seemed to give a complex mixture with no traces of the iodinated compound **7**. We tried also to perform the *O*-methylation reaction starting with the iodinated compound **2**, but the reaction lead after a careful examination of the NMR spectra, to the formation of dehydroiodinated products **1** and **6** (Scheme 4).

In pursuing our goal to obtain the 3-iodo-4-methoxycoumarin **7** we employed a synthetic protocol consisting in reacting of **2** with diazomethane. The methylation of 4-hydroxycoumarin with diazomethane is known in the literature.[25, 26] In our case starting from the iodinated compound **2** we obtained after the methylation reaction a mixture of

two compounds which were structurally assigned to be 3-iodo-4-methoxycoumarin **7** and 3-iodo-2-methoxychromone **8** (Scheme 5).

In the literature the reaction of the analogous 3-bromo-4-hydroxycoumarin with diazomethane led also to two types of crystals with different melting points but the authors recovered and characterized only the 3-bromo-4-methoxycoumarin, the lower melting point compound.[6]

In our attempts to obtain suitable crystals for X-ray analysis from iodinated compounds by slow evaporation from different solvents (i.e. 3-iodo-4-hydroxycoumarin) we observed the liberation of iodine in some cases and crystals transform in an amorphous mass. Thus we studied the behavior of 3-iodo-4-hydroxycoumarin in presence of UV radiation by exposing a solution of **2** in acetone for two hours to the sunlight (Scheme 6). The reaction products were examined by NMR spectroscopy. The careful investigation of the NMR spectra led to the conclusion that the reaction proceeded to the complete conversion of the 3-iodo-4-hydroxycoumarin **2**. Examining the NMR spectra we observed the formation of 4-hydroxycoumarin as major product, thus confirming that a deiodination reaction occurred by the disappearance of the peak at 67 ppm corresponding to the C-I and appearance of a peak at 91 ppm assigned to the C-3 in the ^{13}C-NMR and appearance of a signal at 5.60 ppm corresponding also to a H-3 in the ^{1}H-NMR spectrum. The signals in the aliphatic region confirmed the presence of iodoacetone with ^{13}C-NMR signals at 6.72 ppm for the CH_2-I (lit.[27] 6.11 ppm) and 26.6 for the CH_3 (lit. [27] 25.7 ppm. A signal at 1.50 ppm corresponding to CH_2 group was also present and this suggest

the presence of the iodoacetone photochemical disproportionation product, namely diiodoacetone (lit.[27] 1.68 ppm).

In the case of 4-methoxy-3-iodocoumarin and 4-acetoxy-3-iodocoumarin the photochemical deiodination seems that didn't occur. Moreover in the case of 4-acetoxy-3-iodocoumarin crystals suitable for X-ray analysis (the X-ray results will be discussed elsewhere) were obtained and no iodine liberation was observed.

The reaction should be explained by the activation of the C-I bond by the two neighboring keto groups as in **II** (Scheme 7). In the case of 4-methoxy-3-iodocoumarin and 4-acetoxy-3-iodocoumarin this type of tautomerism is not possible and hence the C-I bond is stronger.

The disproportionation of iodoacetone in UV light was studied by Shagun et al.[26] with the obtaining of 1,3-diiodoacetone and acetone. Most probably the formation of 1,3-diiodoacetone in our case follows a similar mechanism.

CONCLUSIONS

The iodination of 4-hydroxycouamarin with iodine monochloride gives exclusively 3-iododerivative meanwhile iodine monobromide led to a mixture of 3-iodo and 3-bromocoumarin. The halogenation with ICl and IBr at the three position of coumarin is possible only in the presence of the OH at position 4 which activates the C-H bond.

The action of visible light on three 3-iodocoumarins in acetone led to the conclusion that the rate of deiodination is dependent on the nature of 4-substituents. Thus the rate of deiodination for 3-iodo-4-hydroxycoumarin is very fast and gives 4-hydroxycoumarin. For the first time the halogenation of 4-hydroxycoumarin and its *O*-derivatives with ICl and IBr was accomplished.

EXPERIMENTAL SECTION

3-Iodo-4-Hydroxycoumarin (2)

In a round bottomed flask are added 1.8 g 4-hydroxycoumarin in 10 mL AcOH. Over this solution are added dropwise 2 g ICl dissolved in 10 mL glacial AcOH. The reaction mixture is stirred for 15 min and then is poured over 30 mL water. The yellow-orange precipitate is filtered under vacuum and then dried to give **2**. M.p 155-157 ^{o}C. Yield 82 %; Anal. Calcd. for $C_9H_5IO_3$: C, 37.53; H, 1.75. Found: C, 37.89; H, 2.09. ^{1}H-RMN (300 MHz, $CDCl_3$) δ: 6.40-7.10 (bs, 1H, OH); 7.31-7.39 (m, 2H, H-6, H-8); 7.60-7.66 (m, 1H, H-7); 7.92 (dd, 1H, *J* = 2.0, 1.7 Hz, H-5); ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 68.0 (C-3); 113.6 (C-4a); 116.6 (C-8); 123.6, 124.6 (C-6, C-7); 133.5 (C-5); 152.9 (C-8a); 159.2 (C-4); 164.7 (CO).

3-Iodo-4-Acetoxycoumarin (4)

To a solution of 3-iodo-4-hydroxycoumarin **2** in 5 mL Ac_2O is added 0.1 mL pyridine. A white precipitate is formed after 1-2 minutes. The reaction mass is heated 30 min on water bath and the precipitate is dissolved upon heating. After this, the reaction is let to cool to the room temperature and crystals were formed and were removed by vacuum

filtration and washed with isopropanol. M.p 159-161 ^{o}C. Yield 76 %; Anal. Calcd. for $C_9H_5IO_3$: C, 37.53; H, 1.75. Found: C, 37.89; H, 2.09. ^{1}H-RMN (300 MHz, $CDCl_3$) δ: 2.62, 7.42-7.44, 7.49-7.52, 7.57-7.59, 7.70-7.75 (4m, 4H, H, H-5, H-6, H-7, H-8); ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 21.3 (Me); 82.7 (C-3); 116.0 (C-4a); 117.0 (C-8); 122.8, 125.0 (C-6, C-7); 133.5 (C-5); 153.0 (C-8a); 159.0 (C-4); 162.6 (CO); 165.7 (CO).

3-Iodo-4-Hydroxycoumarin (2) And 3-Bromo-4-Hydroxycoumarin (5)

To a suspension of 4-hydroxycoumarin (1.6 g, 10 mmol) in 10 mL AcOH is added dropwise a solution of IBr (2.1 g in 5 mL AcOH) under continuous stirring and heating at 40-50 ^{o}C for an hour. The reaction mass is then poured over 30 mL water and the formed precipitate is removed by filtration and dried. The NMR spectrum concluded that it was obtained a mixture 4:1 of the iodinated versus brominated compound with a global yield of 66 %.

3-Iodo-4-Methoxycoumarin (7) And 3-Iodo-2-Methoxychromone (8)

To an ethereal solution of CH_2N_2 (obtained in a previous step by literature methods[25,26]) is added 3-iodo-4-hydroxycoumarin (**2**, 2.7 g). The evolution of N_2 is immediately observed with the formation of a white precipitate. The excess of CH_2N_2 was destroyed with AcOH and the precipitate was removed and dried (**8**). The filtrate was evaporated with formation of colorless crystals (**7**). **3-Iodo-4-methoxycoumarin (7)**[18]: M.p 81-84 ^{o}C. Yield 71%; ^{1}H-RMN (300 MHz, $CDCl_3$) δ: 4.15 (OMe) 7.30-7.39 (m, 2H, H-6, H-8); 7.58-7.64 (m, 1H, H, H-6); 7.76 (dd, 1H, *J* = 7.8, 1.4 Hz, H-5); ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 61.8 (OMe); 76.8 (C-3); 116.9 (C-4a); 117.0 (C-8); 123.4, 124.7 (C-6, C-7);

133.1 (C-5); 153.4 (C-8a); 160.1 (C-4); 170.7 (CO). **3-Iodo-2-methoxychromone** (**8**): M.p 153-155 ^{o}C. Yield 19%; Anal. Calcd. for $C_{11}H_7IO_4$: C, 40.03; H, 2.14. Found: C, 40.31; H, 2.45. ^{1}H-RMN (300 MHz, $CDCl_3$) δ: 4.23 (OMe) 7.40-7.45 (m, 2H, H-6, H-8); 7.63-7.69 (m, 1H, H-6); 7.93 (dd, 1H, *J* = 6.9, 1.4 Hz, H-5); ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 57.0 (OMe); 90.0 (C-3); 116.6 (C-8); 116.8 (C-4a); 126.1, 126.6 (C-6, C-7); 133.3 (C-5); 152.4 (C-8a); 163.1 (C-2); 174.8 (CO).

SUPPORTING INFORMATION

Full experimental detail, ^{1}H and ^{13}C NMR spectra of all the new compounds **2**, **4** and **8** and known compounds **3**, **5**, **6**, **7**. This material can be found via the "Supplementary Content" section of this article's webpage

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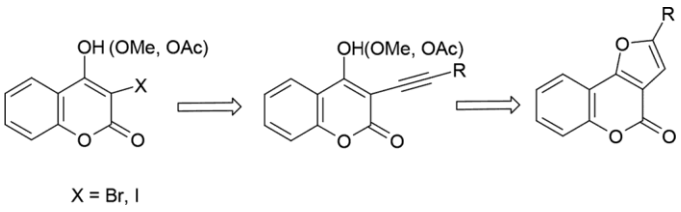
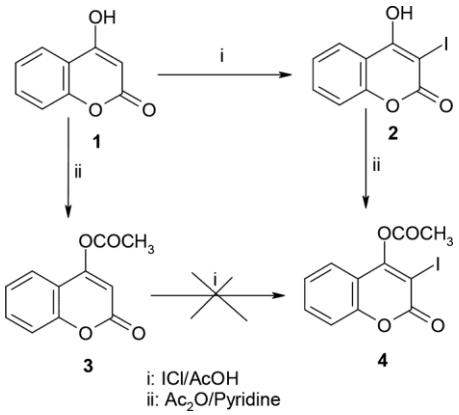
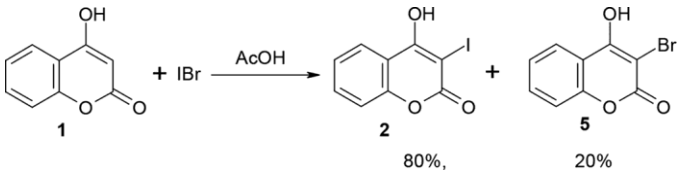
Scheme 1. The synthetic utility of halogenated 4-hydroxycoumarin in the synthesis of bioactive compounds.



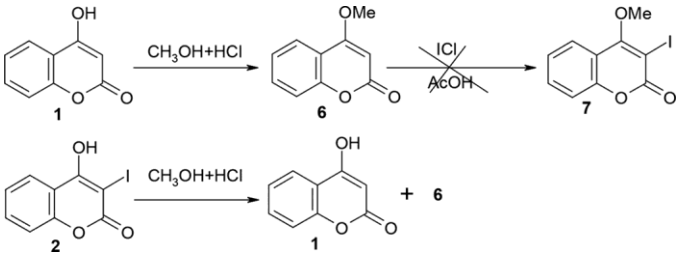
Scheme 2. The obtaining of the 3-iodo derivative of 4-hydroxycoumarin and 4-acetoxycoumarin using iodine monochloride.



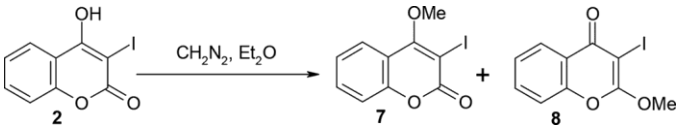
Scheme 3. Obtaining of the 3-iodo and 3-bromo derivatives of 4-hydroxycoumarin using IBr



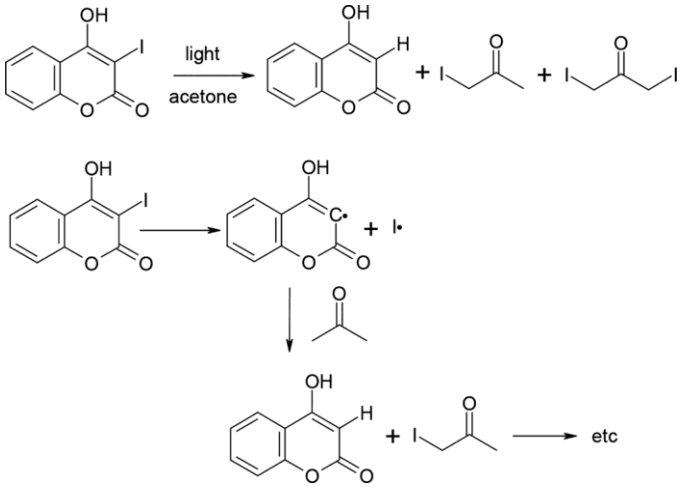
Scheme 4. Attempts to obtain 3-iodo-4-methoxycoumarin **7**.



Scheme 5. Synthesis of 3-iodo-4-methoxycoumarin and 3-iodo-2-methoxychromone.



Scheme 6. The products of the photochemical reactions of 4-hydroxy-3-iodocoumarin **1** in acetone.



Scheme 7. Tautomerism of the 3-iodo-4-hydroxicoumarin.

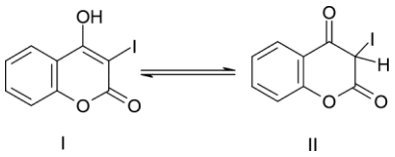


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Figure 1. The NMR spectrum of the 3-iodo-4-hydroxycoumarin and 3-bromo-4-hydroxycoumarin mixture resulted by reaction of **1** with IBr.