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A CONVENIENT ENTRY TO THE TOXICOPHORIC FURO[2,3-b] BENZOFURAN FRAGMENT PRESENT IN AFLATOXINS

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Abstract: Analysis of the ^{1}H and ^{13}C NMR spectra of the labeled hemiacetal [3a,8a-$^{13}C_2$]1 showed that this compound exists in solution in equilibrium with the benzopyran derivative 2. This equilibrium was exploited for an alternative preparation of the furo[2,3-b]benzofuran fragment present in aflatoxins.

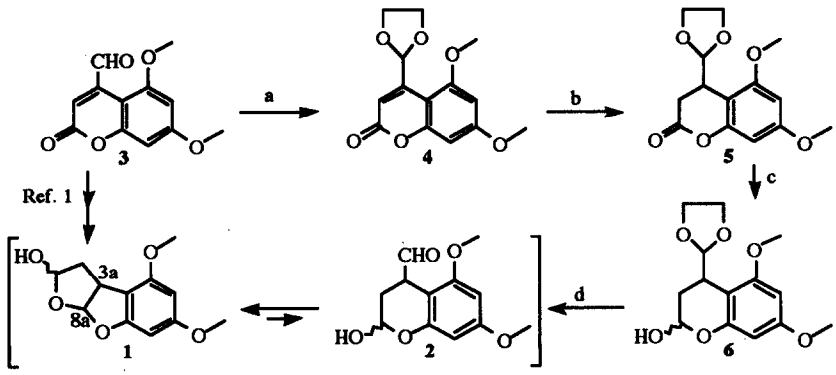
Key words : aflatoxins, furo[2,3-b]benzofuran, synthesis.

Recently we reported the synthesis of 3a,8a-dihydro-4,6-dimethoxyfuro[2,3-b]benzofuran, an aflatoxin B_1 model [1]. The synthetic pathway used involved the generation of the hemiacetal intermediate **1**. This compound, which exists as an epimeric mixture, was converted into the desired AFB_1 model by pyrolysis of the corresponding carbonates. However, the ^{1}H and ^{13}C NMR spectra of **1** revealed the presence of additional peaks to those expected for the purified epimeric mixture. In this context, although we have not found bibliographic precedents on the stability of hemiacetal structures like **1**, studies carried out on aqueous solutions of aflatoxin B_1 diol derivatives, the compounds resulting from the epoxidation and further hydration of the parent mycotoxin, suggested the formation of hydroxyaldehydes and dialdehydes resulting from the opening of the corresponding hemiacetal moieties [2]. However, this hypothesis was not confirmed by the appropriate identification of the structures involved.

Therefore, we synthesized hemiacetal **1** labeled with ^{13}C at C-3a and C-8a to study its behaviour in solution by ^{1}H and ^{13}C NMR spectroscopy. As suspected, evidence was obtained about the existence of a complex mixture of compounds in equilibrium, from which the presence of benzopyran derivative **2** was inferred. The present communication reports our preliminary results on the use of this equilibrium for the preparation of furo[2,3-b]benzofuran derivatives related to aflatoxins.

The ^{13}C NMR spectrum of the purified labeled hemiacetal **1** shows six pairs of absorptions interrelated through their $^{1}J_{C,C}$, that could be due to six different products present in the mixture. Two of the above pairs, i.e. those appearing at 112.6 and 43.0, and at 110.1 and 43.2 ppm, corresponded to the C-8a and C-3a atoms, respectively, of the epimeric forms of hemiacetal **1**, accounting for 47 and 21% of the mixture. This assignation was confirmed by the presence of the corresponding proton acetal multiplets (doublets for the case of the non labeled sample) at 6.35 and 6.32 ppm in ^{1}H NMR spectrum. More interesting were the two absorptions appearing at the carbonyl region (doublets at 204.0 and 200.9 ppm), accounting for 3 and 1.5 %, respectively, of the mixture. Evidently, these absorptions were due to the presence of labeled aldehyde moieties as it was also confirmed in the ^{1}H NMR spectrum. It is worth of noting that this spectrum showed only aldehyde hydrogens which were coupled with carbon. On the other hand, the two pair of absorptions coupled to the above ^{13}C aldehyde signals appeared at 39.0 and 41.2, respectively. All these spectroscopic features led to tentatively assign aldehyde **2** as the compound responsible for these signals. As depicted in the Scheme, the synthesis of

this aldehyde would bring up a new route for preparation of furo[2,3-b]benzofuran derivatives via this equilibrium.



a) $HOCH_2CH_2OH$/p-TsOH/C_6H_6/reflux, 90%; b) $Na(CH_3OCH_2CH_2O)_2AlH_2$/CuBr/2-BuOH/THF/-20 °C, 61%; c) DIBAH/toluene/-20 °C, 89%; d) HCl (10%)/acetone, 92%.

Protection of aldehyde **3** (obtained in two steps from 3,5-dimethoxyphenol [1]) afforded the dioxolane **4**. A stepwise reduction of **4**, first with Red-Al®/CuBr [3] to give the lactone **5** and then with DIBAH afforded the protected hemiacetal **6** as a diastereomeric mixture in 46% overall yield from **3** [4]. Final deprotection of **6** in acid medium led to the isolation of hemiacetal **1** in high yield. When the same synthetic procedure was carried out with compound **3** labeled with ^{13}C at C-4 and at the formyl carbon atom, deprotection of the corresponding dioxolane **6** afforded a crude reaction mixture solution exhibiting a ^{13}C NMR spectrum which matched that of the hemiacetal **1** obtained by using the conventional synthetic procedure [1].

In summary, the results described above have shown that hemiacetal **1**, a molecule containing the toxicophoric fragment of aflatoxin B_{2a} [5], coexists in equilibrium with structures involving benzopyran derivatives [6]. The extent at which similar equilibria could be possible for the case of aflatoxin 8,9-diol derivatives and the toxicological significance associated to these phenomena remain to be explored. In any case, an important consequence of the above equilibrium is that it offers an alternative synthetic pathway for obtaining the furo[2,3-b]benzofuran toxicophoric fragment present in the most cytotoxic aflatoxins. Therefore, this alternative procedure could be useful for the preparation of aflatoxin models that are tedious to synthesize by conventional approaches such as those reported for aflatoxin M_1 [7,8]. Work along this line is in progress in our laboratory.

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