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Synthesis of Chlorinated 5-Hydroxy 4-Methyl-2(5*H*)-Furanones and Mucochloric Acid.

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Abstract : An improved procedure for the synthesis of chlorinated 5-hydroxy-4-methyl-2(5*H*)-furanones is described. By this method also carbon-labelled (^{13}C and ^{14}C at C-3) hydroxyfuranones, including mucochloric acid, can be prepared. Each step of the method was examined in an effort to optimize both the yield and the purity of the compounds.

Several chlorinated 5-hydroxy-4-methyl-2(5*H*)-furanones (**HMFs**) and mucochloric acid (3,4-dichloro-5-hydroxy-2(5*H*)-furanone, **MCA**) have been identified as by-products of the chlorine disinfection of drinking water and of the chlorine bleaching of pulp.[1] These compounds have been shown to generate mutagenicity in the *Salmonella typhimurium* assay (the Ames test) and the compound 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone (**MX**), especially, is an extremely potent bacterial mutagen.[2,3] Synthetically pure **HMFs** and the ^{13}C-, and ^{14}C-labeled analogues (including **MCA**), are needed in studies concerning their interactions with base moieties of DNA, with cellular DNA and in whole animal studies.[4,5]

A method for the total synthesis of **MX** has been described by Padmapriya *et al.*[6] but in our hands and in other laboratories the method does not work satisfactorily.[3,7] Furthermore, the starting material, 1,1,3,3-tetrachloroacetone, is no longer commercially available from the main chemical suppliers. The objective of this work was to modify and improve the original method for the synthesis of **MX** and to apply this method to the synthesis of other chlorinated **HMFs**. The procedure allows for the synthesis of ^{13}C- and ^{14}C-labelled **HMFs** and **MCA**.

RESULTS and DISCUSSION

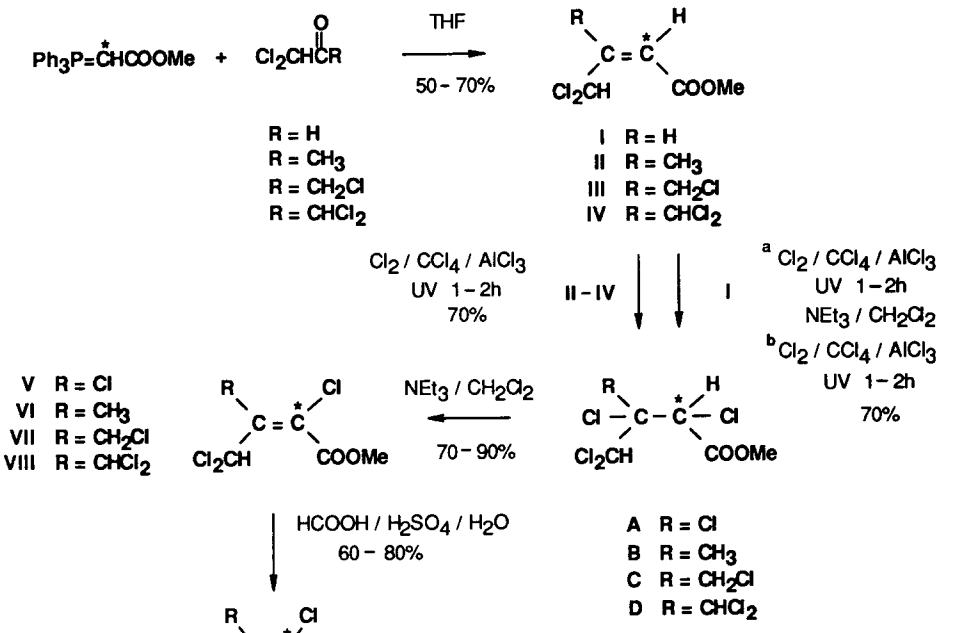
The ylides required were prepared from bromoacetic acid, bromoacetic-2-^{13}C acid and bromoacetic-2-^{14}C acid according to Fieser and Fieser.[8] The Wittig condensation of the chlorinated aldehyde and the propanones gave the olefinic esters (**I-IV**) in 50 - 70% yields (Scheme 1). We noticed that chlorination of the olefinic esters to **A, B, C** and **D** proceeded extremely slowly (*viz.* for 1-4 weeks). Purification of the olefinic esters by flash chromatography, replacement of the ferric chloride catalyst with aluminium chloride and chlorination under UV irradiation accelerated the reaction drastically (1-2 h). The chlorinated olefins (**V-VIII**) were quantitatively obtained upon triethylamine treatment of **A - D** in CH_2Cl_2. In the original method of **MX** synthesis the chlorinated olefin (**VIII**) was hydrolyzed to the corresponding carboxylic acid and then the hydroxyfuranone was afforded by treatment of the acid with aqueous potassium carbonate. The main drawback of this method is that **MX** and the other **HMF**s are slowly degraded at neutral and basic conditions. We found that when the chlorinated olefins (**V-VIII**) were hydrolyzed with formic acid / H_2SO_4 / H_2O the corresponding hydroxyfuranones could be obtained in one step in 60 - 80% yield.

In attempts to prepare a 5-hydroxy-2(5*H*)-furanone, with a trichloromethyl group at C-4, by Wittig condensation of phosporane with pentachloroacetone (**PCA**) we observed that instead of the desired pentachlorobutenoate the tetrachlorobutenoate (**IV**) was obtained in 47% yield. When the Wittig reaction was carried out with hexachloroacetone (**HCA**) the butenoate (**IV**) was formed in 22% yield. The yield of **IV** could be increased when the condensation was carried out with two equivalents of **PCA** (yield 60%) or four equivalents of **HCA** (yield 42%). GC analyses of the reaction mixtures showed that under these conditions tetrachloroacetone was formed. A likely explanation for these observations is that the phosphorane has abstracted chlorine from the Cl_3C-group in the acetones, and in turn the resulting Cl_2C^- - group has removed a proton from the chlorophosphonium salt to give tetrachloroacetone and chlorinated phosphorane (Scheme 2). Padmapriya *et al.*[6] observed that the reverse reaction also takes place: when tetrachloroacetone was reacted with the chlorinated phosphorane, pentachloroacetone was obtained together with about 50% of the tetrachloro olefin (**IV**).

EXPERIMENTAL

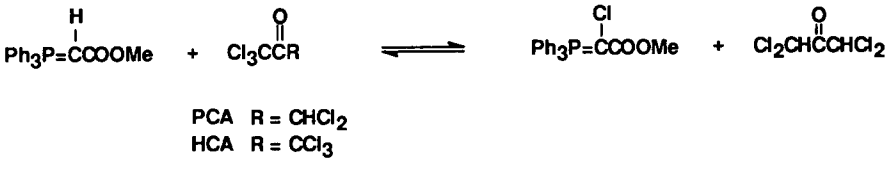
***Caution** : Several hydroxyfuranones have tested positive in the Ames mutagenicity assay with S. Typhimurium (TA100) without metabolic activation. Therefore, caution should be excercised in their handling and disposal.*

Synthesis of HMFs and MCA : One equivalent of (carbomethoxymethyl) triphenylphoshonium bromide and 1.2 equivalents of triethylamine in dry THF were stirred at room temperature. After 24 h the chlorinated propanones, or the chlorinated aldehyde (**MCA** synthesis), were added and the resulting mixture was stirred for another 24 h. The resulting precipitate was removed by filtration and the filtrate was evaporated to give a residue which, upon purification on SiO_2 with n-hexane - diethylether (9:1) as eluent,



Scheme 1

(* indicating the labelled carbon)



Scheme 2

yielded the pure butenoates (**I - IV**) as white crystals. A suspension of **I - IV** and aluminium chloride in CCl_4 saturated with chlorine was UV-irradiated for 1 - 2 hours. After removal of the solvent the compounds **A - C** were obtained as yellow oils. Compound **D** was prepared similarly by an additional chlorination step. Triethylamine was added to a solution of **A - D** in CH_2Cl_2 at room temperature. After stirring for 4 h the solvent was removed. Purification on SiO_2 with n-hexane - diethylether (9:1) as eluent yielded the pure butenoates (**V - VIII**). The butenoates were dissolved in HCOOH - H_2SO_4 - H_2O (3.5 - 1.0 - 0.5). The solutions were heated to 120°C and maintaned at this temperature for 13 - 18 h. The reaction mixture was then cooled in a ice-bath and water was added to the solution. The crude hydroxyfuranones were obtained following extraction of the aqueous solution with ethyl acetate and the evaporation of the solvent. Subsequent purification on SiO_2 using ethyl acetate - n-hexane - acetic acid (50:50:0.1) gave pure **MX, CMCF, MCF,** and **MCA** as pale-yellow oils in 25, 22, 17 and 15% overall yields. The spectral properties (^{1}H NMR, ^{13}C NMR, MS) of **MX, CMCF** and **MCF** were in accordance with those previously published. [6, 9, 10] The spectral data of **MCA** agreed with those of commercial **MCA.**

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