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The Acylphosphonate Function as an Activating and Masking Moiety for the α -Chlorination of Fatty Acids.

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Abstract

α -Chloroacylphosphonates were prepared in situ by chlorination of acylphosphonates using sulfuryl chloride and were subsequently cleaved to the corresponding α -chlorinated fatty acids with hydrogen peroxide - sodium bicarbonate. © 1998 Elsevier Science Ltd. All rights reserved.

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The preparation of α -chloro fatty acids has been the subject of numerous industrial studies because of their importance in several domains, e.g. agrochemistry [1,2] and flotation chemistry [3]. Several methods have been described for their synthesis including: chlorination with sulfuryl chloride mediated by ultraviolet light in the presence of benzoyl peroxide and pyridine [4]; chlorination of the neat fatty acid with gaseous chlorine at 140 °C and chlorosulfonic acid as catalyst in the presence of a free radical inhibitor e.g. oxygen [5,6]; chlorination of fatty acids with chlorine gas in the presence of 7,7,8,8-tetracyanoquinodimethane as radical inhibitor with different catalysts [7,8,9]; treatment of carboxylic acids with chlorine gas in the presence of phosphorus [10].

Most of these methods, however, face the problem of free-radical chlorination in the alkyl chain, especially when higher temperatures are required. Therefore, radical scavengers are used extensively to suppress the radical chlorination.

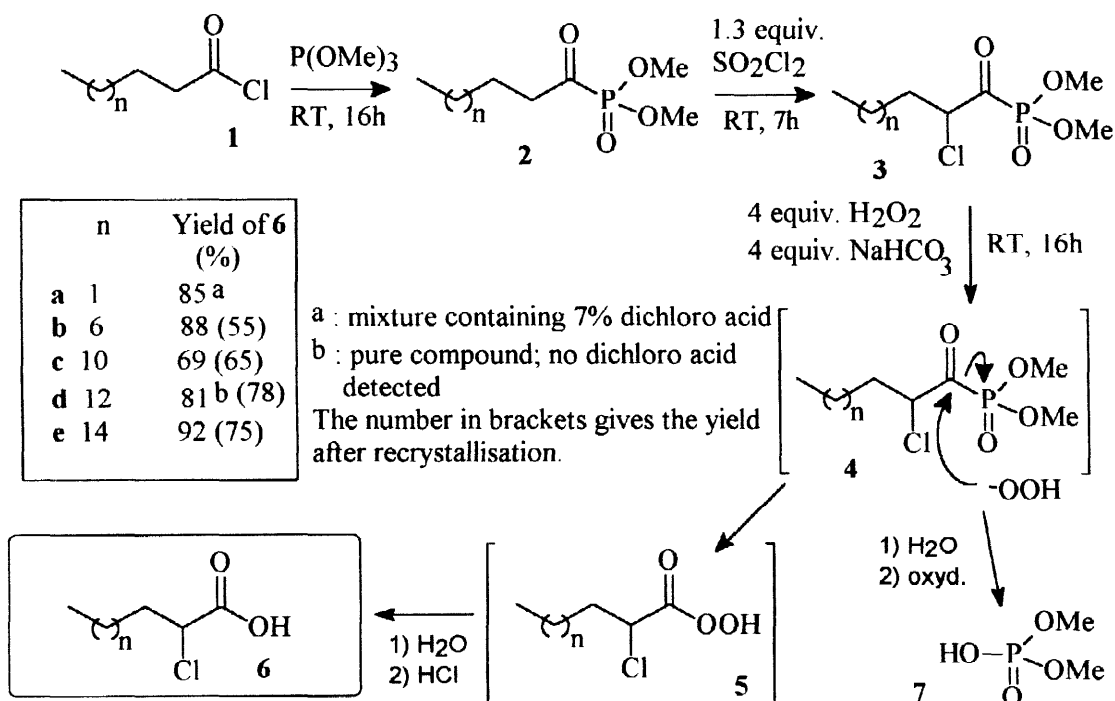
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Acylphosphonates, prepared by an Arbuzov reaction, are very sensitive to hydrolysis under neutral and alkaline conditions but are easily enolized in an acidic medium [11]. The reaction of acylphosphonates with a multitude of nucleophiles such as amines, thiols and alcohols leads to the cleavage of the phosphorus - carbon (P-C) bond with expulsion of phosphite [12].

In this paper, the use of acylphosphonates in the α -chlorination of fatty acids is described. The phosphonate function serves as a strong activating group for the enolization of the carbonyl function facilitating α -monochlorination by sulfuryl chloride at room temperature. The extreme lability of the α -chlorinated acylphosphonate function is then exploited to deprotect the acid function in a very mild way.

In the first step of the reaction sequence, the fatty acid chlorides **1** were reacted neat with trimethyl phosphite with the formation of the corresponding acylphosphonate **2** in quantitative yields and high purity. The acylphosphonates were easily characterized by ^{31}P -NMR. For the synthesis of the α -chlorinated acylphosphonates **4**, several reaction conditions were evaluated. At first, the chlorination conditions were evaluated using sulfuryl chloride as the chlorinating agent in very low concentrations at 60 - 100 °C in the presence of dimethyl formamide, N,N-dimethyl octylamine or 2-methylpyridine [13]. It is known that at these temperatures sulfuryl chloride decomposes into sulfur dioxide and chlorine, which can act as the chlorinating agent. Under these conditions, the monochlorinated acylphosphonates were not stable and suffered P-C bond cleavage, resulting in complicated reaction mixtures. The preferential conditions consist of the dropwise addition of 1.3 equivalents of sulfuryl chloride (without catalyst) to the acylphosphonate **2** at room temperature and stirring the reaction mixture for seven hours in the dark. When the reaction slows down during this time, the reaction vessel was warmed gently to 37 °C for one minute, so that the generation of hydrochloric acid and sulfur dioxide was stimulated. These conditions are in sharp contrast with the high temperatures required in the methods described in the literature for the production of the α -chloro carboxylic acids, which therefore suffer from non-regiospecific free radical chlorination, i.e. side chain chlorination. The acidic medium together with the electron withdrawing phosphonate moiety strongly facilitates the enolization of the keto function so that the chlorination can occur at room temperature, and hence

without the competing radical chlorination. Attempts to perform the chlorination with N-chlorosuccinimide or chlorine gas did not lead to the desired α -chlorinated compounds.



It was, however, impossible to suppress completely the dichlorination of the acylphosphonates. In all reaction mixtures, at least 5 % of α,α -dichlorinated carboxylic acids (after hydrolysis of the acylphosphonates) were detected. On the other hand, attempts to prepare the α,α -dichloro fatty acids did not succeed upon addition of more equivalents of sulfuryl chloride. Therefore, this methodology is preferably applied for the chlorination of fatty acids because the mono- and dichlorinated products were easily separated using crystallization (after the regeneration of the acid function; *vide infra*), although the reaction sequence can also be used for lower acids, e.g. 2-chlorovaleric acid **6a**.

The α -chlorinated acylphosphonates **4** are very labile compounds, so that it was not possible either to purify the compounds, or to get all the spectral data of the chlorinated phosphonates. Only for the dimethyl 2-chloro-1-tetradecanoyl phosphonate, the ^{31}P -NMR resonance could be determined as -1.69 ppm (85% phosphoric acid as reference). Therefore, attempts to synthesize more stable derivatives are currently under investigation in order to characterize the chlorinated acylphosphonates completely.

The regeneration of the acid function from the α -chlorinated acylphosphonates **4** was performed by treating the acylphosphonates with 4 equivalents of hydrogen peroxide in the presence of 4 equivalents of sodium bicarbonate. Hydrogen peroxide cleaves the P-C bond with formation of dimethyl phosphite, which is further oxidized to dimethyl phosphate **7** that remains almost completely in the aqueous phase during work-up. The monochloro peracids **5** are transformed to the monochloro acids **6** upon stirring in the aqueous medium overnight. The carboxylic acid is isolated in good yield after acidification of the reaction mixture with concentrated hydrogen chloride. The pure α -monochloro carboxylic acids **6** were isolated after crystallization from the reaction mixture.

The hydrolysis of the acylphosphonate can also be performed using only sodium bicarbonate, but the isolation of the end product is more difficult and the reaction mixture contains large amounts of the dimethyl phosphite.

In conclusion, a new method for the monochlorination of fatty acids under very mild conditions is described using the phosphonate function as an activating and protecting functionality. This activating property of the phosphonate group will be further investigated.

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