Synthesis of 2-Substituted 3,4-Bis(diethoxyphosphorylmethyl)furans

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Received November 27, 2014

Abstract—Bromination of ethyl 4-(diethoxyphosphorylmethyl)-5-methylfuran-2-carboxylate and 4-(diethoxyphosphorylmethyl)-5-methylfuran-2-carbonitrile with N-bromosuccinimide followed by phosphorylation via the Arbuzov reaction have yielded the corresponding 2-substituted 4,5-bis(diethoxyphosphorylmethyl)furans. Synthesis and transformations of bisphosphorylated 2-furoic acid and its derivatives are described.

Keywords: diphosphonate, synthesis, 2,4,5-substituted furan, furancarboxylic acid derivative

DOI: 10.1134/S1070363215020139

Aromatic and heteroaromatic compounds containing two fragments of phosphonic acid have been widely studied as inhibitors of various enzymes; affecting the exchange processes during osteoporosis treatment is among the major fields of interest [1]. Diphosphonates are known to inhibit pyrophosphatase-induced ion transfer as well [2]. Diphosphonates bearing imidazole, pyridine, or benzofuran rings or diphenyl moieties bound to these nitrogen-containing heterocycles inhibit enzymes involved in isoprenoids synthesis [3]. In view of the above, bisphosphonic acid derivatives of furans are promising as inhibitors and ion carriers. These with adjacent methanephosphonic substituents in the furan ring are of special interest due to the possible chelating effect.

In this work we present and discuss methods of synthesis and chemical transformations of 2-substituted 4,5-bis(diethoxyphosphorylmethyl)furans. Preparation of non-substituted tetraalkyl bisphosphonate was reported earlier [4], but its chemical properties were not studied.

Dialkyl (2-methyl-5-ethoxycarbonylfur-3-yl) and (2-methyl-5-cyanofur-3-yl)methanephosphonates I and Ia were used as starting compounds. Their bromination with N-bromosuccinimide led to 2-bromomethyl derivatives II and IIa; the products were phosphorylated with triethyl phosphite under the conditions of Arbuzov reaction to give diphosphonates III and IIIa in the 94% and 92% yield, respectively. The prepared diphosphonates were viscous syrup-like liquids not crystallizing within several months and decomposing upon heating in vacuum below their boiling points (≈200°C) (Scheme 1).

31P NMR spectra of compounds III and IIIa each contained a pair of signals of interacting phosphorus...
atoms [III]: \( \delta_p \), ppm: 21.74 (P\(^4\)), 25.78 (P\(^5\)), \( J_{PP} \) 13.9 Hz; 
III\(a\): \( \delta_p \), ppm: 21.06 (P\(^4\)), 25.04 (P\(^5\)), \( J_{PP} \) 13.4 Hz.

Signals of carbon atoms in positions 4 and 5 of the furan ring were also split due to the interactions with the both phosphorus atoms. In both cases \( 2J_{PC} = 3J_{PC} \) but the splitting constants were different for the carbon atoms [III]: \( \delta_C \), ppm: 114.90 (C\(^4\), \( 2J_{PC} = 3J_{PC} = 8.7 \) Hz), 147.93 (C\(^5\), \( 2J_{PC} = 3J_{PC} = 11.0 \) Hz); III\(a\): \( \delta_C \), ppm: 111.76 (C\(^4\), \( 2J_{PC} = 3J_{PC} = 8.6 \) Hz), 149.51 (C\(^5\), \( 2J_{PC} = 3J_{PC} = 11.2 \) Hz).

The reaction of compound III with the ethanol solution of potassium hydroxide proceeded as saponification of the ester group while the phosphonate groups remained intact. The reaction was complete at the KOH : the ester molar ratio of no less than 1.5 yielding 98% of the acid IV. Coupling constant between the phosphorus atoms \( J_{PP} \) of 13.8 Hz was observed in \(^{31}\)P NMR spectra of the product. Similarly to compound III, the coupling constants for C\(^4\) and C\(^5\) carbon atoms in \(^{13}\)C NMR spectra of the acid IV were different (C\(^4\), \( 2J_{PC} = 3J_{PC} = 8.6 \) Hz; C\(^5\), \( 2J_{PC} = 3J_{PC} = 11.1 \) Hz) (Scheme 2).

Acid IV was converted to acid chloride V in 86% yield via refluxing with thionyl chloride in benzene in the presence of DMF during 7 h. Compound V was a syrup-like liquid not crystallizing on storage. The reaction proceeded selectively involving the carboxyl group whereas the phosphonate fragments were stable under the reaction conditions. Coupling between the phosphorus atoms with \( J_{PP} \) 13.2 Hz was observed in \(^{31}\)P NMR spectra of the product. Similarly to compound III, the coupling constants for C\(^4\) and C\(^5\) carbon atoms in \(^{13}\)C NMR spectra of the acid chloride V were different (C\(^4\), \( 2J_{PC} = 3J_{PC} = 8.6 \) Hz; C\(^5\), \( 2J_{PC} = 3J_{PC} = 11.8 \) Hz) (Scheme 2).

The acid IV was converted to acyl azide VI as described elsewhere [5]. Treating of acetone solution of compound IV with ethyl chloroformate in the presence of triethylamine upon ice bath cooling led to mixed anhydride of monocarbonate and furcic acid which was further involved in the reaction with saturated aqueous solution of sodium azide without isolation. After decomposition of the reaction mixture with ice water a yellow syrup-like liquid was isolated via extraction with ethyl acetate. IR spectrum of the product contained a band at 2147 cm\(^{-1}\) characteristic of azide group was observed. The product structure was further confirmed with the \(^1\)H, \(^{13}\)C, and \(^{31}\)P NMR data.

Azide VI was stable within several days at room temperature, but decomposed upon heating to give a complex mixture of products. IR spectrum of the mixture showed an absorption band at 2226 cm\(^{-1}\) assigned to isocyanate, but its concentration was too low to detect a signal of H\(^3\) proton of the isocyanate furan ring (about 6.0 ppm [5]). \(^{13}\)C NMR spectrum of the major decomposition products contained several signals of the carbonyl carbon bound to the furan ring at 159–163 ppm. Hence, the Curtius rearrangement was not the major pathway of the acyl azide VI transformation.

Reduction of acid chloride V with sodium borohydride gives corresponding alcohol VII in 58% yield. The reaction was carried out according to the description in [6] in DMF–dioxane mixture. Similarly to the case of monophosphonates, diethoxyphosphorylmethyl group was not involved in the reaction.

The prepared alcohol VII was light-yellow syrup-like liquid not crystallizing upon storage and decomposing below its boiling point in the course of vacuum distillation. \(^1\)H NMR spectrum of compound VII contained a signal of hydroxymethyl group at 4.45 ppm. Signal of the corresponding carbon atom was registered in the \(^{13}\)C NMR spectrum at 56.97 ppm. Coupling constant between the phosphorus atoms \( J_{PP} \) was up to 15.5 Hz. The \( 2J_{PC} \) and \( 3J_{PC} \) coupling