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Synthesis of 3,4-Disubstituted Phosphorus-containing Furans with Free 2 and 5 Positions

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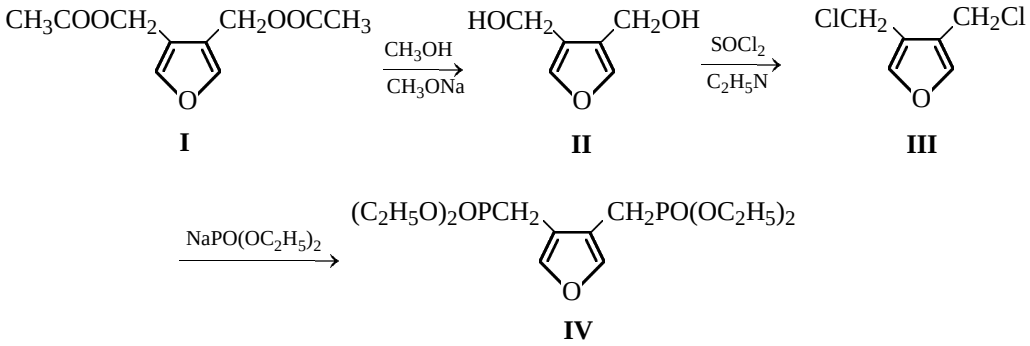
Abstract — A synthetic approach to β-(chloromethyl)furans with free 2 and 5 positions is developed. It is shown that these compounds enter the Michaelis–Becker reaction to form usual phosphorylation products. With 3,4-bis(diethoxyphosphorylmethyl)furan, two conformers with different chemical shifts of phosphorus nuclei and PCH_2 protons were detected.

3,4-Bisfunctionalized phosphorus-containing furans are rather well-documented. Among them, phosphonomethylated derivatives of alkyl carboxylates [1], ketones [2], carboxamides [3], alkoxymethyl derivatives [4], and bisphosphorylated compounds [4] are known. A specific feature of these compounds was that they contained ballast methyl groups in the 2 and 5 positions. The aim of the present work was to develop procedures for preparing analogous phosphorus-containing furans having free reactive α positions, which could be used for further functionalization of these products.

The source of furan derivatives of the abovementioned structure was diethyl furan-3,4-dicarboxylate. Its reduction with lithium aluminum hydride with subsequent acetylation gave 3,4-bis(acetoxymethyl)-furan (**I**) [5]. Methanolysis of this compound gave free diol **II** which was treated with thionyl chloride in a mixture of methylene chloride, dioxane, and pyridine to obtain dichloride **III** [6]. The latter was brought into the Michaelis-Becker reaction with sodium diethyl phosphite according to a usual procedure [1].



The reaction proceeded for 14 h, and phosphonate **IV** was isolated from the reaction mixture as a high-boiling extremely viscous liquid in 17% yield. The ^1H NMR spectrum of this compound contained a double set of signals belonging to the CH_2P group (δ 2.80 and 2.94 ppm, J_{HP} 20 Hz) and protons of the furan ring (δ 7.18 and 7.20 ppm). Therewith, an upfield methylene proton signal was related to an upfield furan proton signal. The intensity ratio for both pairs of signals was about 1:5. From the INDOR spectra of this product, existence of two phosphorus nuclei with δ_P 17.8 and 23.4 ppm was established. An upfield phosphorus signal was related to an upfield set of proton signals in the ^1H NMR spectrum. It was thus concluded that phosphonate **IV** exists as a mixture of two conformers so different in structure that even their phosphorus atoms have different shifts. At the same time, the shifts of both phosphorus atoms in each conformer are the same within the experimental accuracy, implying that both conformers are symmetrical.

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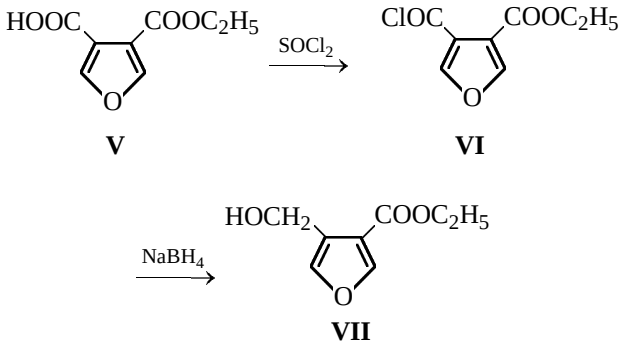
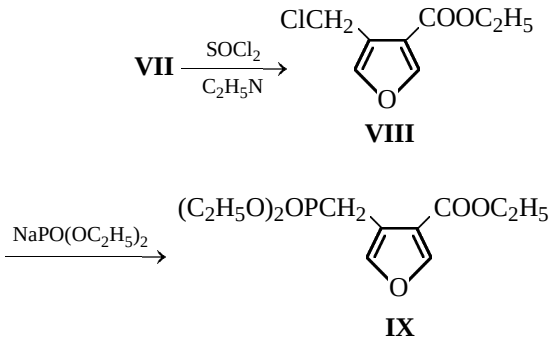
Another way of utilization of the carbon skeleton of furan-3,4-dicarboxylic acid for preparing organophosphorus compounds is selective reduction of one of the carboxy groups. Monoethyl ester **V** was prepared according to [7]. Its treatment with thionyl chloride gave acid monochloride **VI** in 53% yield. The latter was reduced with sodium borohydride in diglyme.



The reaction had quite a complicated pattern, but we could isolate from the reaction mixture a fraction whose main component was ethyl 4-(hydroxymethyl)-furan-3-carboxylate (**VII**).

This compound was converted to chloride **VIII** by a usual procedure [6] involving treatment with thionyl chloride in ether in the presence of pyridine. After removal of pyridinium chloride, distillation of the reaction mixture gave the target product **VIII** which, according to ^{1}H NMR spectral data, contained a considerable amount of admixtures.



Chloride **VIII** without further purification was brought into the Michaelis–Becker reaction with sodium diethyl phosphite. After 9-h refluxing in benzene, vacuum distillation gave pure phosphonate **IX**. Because of the strong contamination of the starting chloride **VIII**, the yield of phosphonate was not evaluated.

Hence, β-chloromethylfurans with free 2 and 5 positions react under conditions of the Michaelis–Becker reaction to give stable phosphonates, but the synthesis of the starting compounds is multistage and in some cases is complicated by side processes.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Tesla BS-487C (8O MHz) spectrometer in CCl_4 against internal HMDS.

Bis(diethoxyphosphorylmethyl)furan (IV). To a solution of sodium diethyl phosphite prepared from 0.5 g of sodium and 3.5 ml of diethyl hydrogen phosphite in 15 ml of benzene, a solution of 1.9 g of 3,4-bis(chloromethyl)furan (**III**) in 5 ml of benzene was added dropwise with stirring at 75°C. Slight heat release was observed, the reaction mixture came to boil, and sodium chloride precipitate. The reaction mixture was refluxed with stirring for 14 h and then allowed to settle for 2 h. The organic phase was then decanted, the solvent was removed at reduced pressure, and the residue was distilled in a vacuum to obtain 0.67 g (17%) of phosphonate **IV** as a viscous oil, bp 179–181°C (1 mm). ^{1}H NMR spectrum, δ, ppm: common signals: 1.16 m (ethyl CH_3), 3.92 q (CH_2OP, J_{HP} 7 Hz, J_{HH} 7 Hz); major conformer: 2.94 d (CH_2P, J_{HP} 20 Hz), 7.20 d (furan H, J_{HP} 2 Hz), δ_P 24.3 ppm; minor conformer: 2.80 d (CH_2P, J_{HP} 20 Hz), 7.18 d (furan H, J_{HP} 2 Hz), δ_P 17.8 ppm. Conformer ratio 5 : 1.

Ethyl (4-chlorocarbonyl)furan-3-carboxylate (VI). A mixture of 11.0 g of ethyl hydrogen furan-3,4-dicarboxylate, 15 ml of thionyl chloride, and 30 ml of benzene was refluxed with stirring for 5 h and then distilled in a vacuum to obtain 6.5 g (53%) of acid chloride **VI** as an oil, bp 109°C (1 mm).

Ethyl 4-(hydroxymethyl)furan-3-carboxylate (VII). To a mixture of 1.9 g of sodium borohydride and 20 ml of diglyme, a solution of acid chloride **VI** in 5 ml of diglyme was added dropwise at 15–20°C. The reaction mixture was stirred for 3 h and left overnight, after which it was decomposed with 30% sulfuric acid, treated with sodium bicarbonate solution to neutral and then with water to dissolve inorganic salts, and extracted with benzene. The extract was dried over magnesium sulfate, the solvent was removed under reduced pressure, and the residue was distilled in a vacuum to obtain 2.15 g of compound **VII**, bp 102°C (1 mm). ^{1}H NMR spectrum, δ, ppm: 1.21 t (ethyl CH_3, J_{HH} 7 Hz), 4.16 q (ethyl CH_2, J_{HH} 7 Hz), 4.46 s (hydroxymethyl CH_2), 7.86 s (furan H). The alcohol contains a considerable amount of unidentified admixtures, and, therefore, its yield was not evaluated.

Ethyl 4-(chloromethyl)furan-3-carboxylate (VIII). To a solution of 2.15 g of alcohol **VII** and

1 ml of pyridine in 15 ml of ether, a solution of 0.9 g of thionyl chloride in 3 ml of ether was added dropwise with stirring. The temperature of the reaction mixture was maintained in the range of 5–10°C. The reaction mixture was stirred for 4 h at room temperature, the pyridine hydrochloride was filtered off, the solvent was removed at reduced pressure, and the residue was distilled in a vacuum. A fraction with bp 111°C (2 mm), 0.86 g, containing chloride **VIII** and a considerable amount of admixtures from the previous stage was obtained. ^{1}H NMR spectrum, δ, ppm: 1.21 t (ethyl CH_3, J_{HH} 7 Hz), 4.16 q (ethyl CH_2, J_{HH} 7 Hz), 4.45 s (CH_2Cl), 7.42 s (furan H^5), 7.78 s (furan H^2).

Ethyl 4-(diethoxyphosphorylmethyl)furan-3-carboxylate (IX). To a solution of sodium diethyl phosphite prepared from 0.11 g of sodium and 0.8 ml of diethyl hydrogen phosphite in 5 ml of benzene, a solution of 0.86 g of the product from the previous stage in 3 ml of benzene was added in one portion at 60°C. The reaction mixture warmed up to 75°C. It was refluxed with stirring for 10 h, the precipitate of sodium chloride was removed by centrifugation, the solvent was removed at reduced pressure, and the residue was distilled in a vacuum to obtain 0.3 g of phosphonate **IX**, bp 142°C (1 mm), n_D^{20} 1.4720. ^{1}H NMR spectrum, δ, ppm: 1.18 m (ethyl CH_3), 3.14 d (CH_2P, J_{HP} 20 Hz), 3.90 m (CH_2OP), 4.16 q ($CH_2 \cdot OOC$, J_{HH} 7 Hz), 7.44 br.s (furan H^5), 7.80 s (furan H^2). The spectrum contained no foreign signals.

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