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Synthesis and Phosphorylation of 4-Functionalized 2-*tert*-Butyl-3-chloromethylfurans

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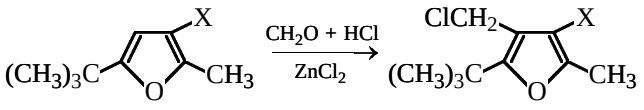
Abstract—3-Ethoxycarbonyl- and 3-acetyl-2-methyl-5-*tert*-butylfurans undergo chloromethylation under the unusually rigorous conditions (55–60°C, 3–3.5 h). The corresponding diethylamide and nitrile were prepared by standard modification of the carboxy group. In phosphorylation of the resulting chloromethylfurans under the conditions of the Michaelis–Becker reaction, in the case of the ester and diethylamide, the phosphonate yields were close to those obtained with compounds containing no *tert*-butoxy group, and in the case of acetylfuran the yield was even somewhat higher. On the contrary, the chloromethylated nitrile reacts considerably more slowly than all the other compounds under consideration and than the similar compound containing no *tert*-butyl substituent. Thus, the effect of the *tert*-butyl group in the α-position of the furan ring is clearly pronounced in the electrophilic substitutions in the neighboring position of the heteroring. When the reaction center is located in the side chain (substitution of chlorine), the effect of the bulky substituent is manifested only in special cases and can be attributed to the presence of a conformation in which the chloromethyl group is shielded.

Recently we have studied the phosphorylation and some other reactions of 2- and 3-halomethyl-5-*tert*-butylfurans [1]. We showed that the specific features of their chemical behavior are largely determined by the shielding of the oxygen atom of the heteroring, while the effect of this substituent on the remote reaction center is insignificant. In this work we attempted to reveal the effects arising when the reaction proceeds in the nearest surrounding of the *tert*-butyl group.



I, **II** **III**, **IV**

X = $COOC_2H_5$ (**I**, **III**), $COCH_3$ (**II**, **IV**).

We chose ester **I** and acetylfuran **II** as the starting compounds. These substances were chloromethylated in chloroform or carbon tetrachloride in the presence of zinc chloride as a catalyst and paraform as a source of formaldehyde. The mixture was saturated with HCl by continuous bubbling. The substrate–paraform–catalyst molar ratio was similar to that in the typical procedure [2]. Under these conditions, the reactivity of substrates can be evaluated by the reaction temperature. Chloromethylation of furan compounds containing an ester or keto group in the ring usually occurs below 30°C. At higher temperatures, polymeric products are formed, and the rate of their accumulation quickly rises with temperature. In our case, no evidence of the reaction was observed at 30°C. As the reaction temperature was increased to 55–60°C, paraform gradually dissolved, and a characteristic dark brown tarry complex was formed. After passing of HCl through the reaction mixture containing **I** for 3–3.5 h, no starting ester was recovered, and chloromethyl derivative **III** was isolated by vacuum distillation in 61% yield.

Chloromethylation of ketone **II** occurs under the same conditions but it is accompanied by considerable tarring. Therefore, the reaction was stopped at a conversion no higher than 64%. The yield of the target product under these conditions was 32% based on the converted product. It was determined by ^{1}H NMR spectroscopy, because the starting ketone **II** and chloromethyl derivative **IV** are poorly separated by vacuum distillation. Thus, *tert*-butyl derivatives **I** and **II** exhibit unusually low reactivity and high stability to the action of acidic agents.

Ester **III** was converted to chloromethyl amide **V** by a standard sequence of reactions similarly to the pathway described in [1]. Treatment of **III** with sodium acetate in acetic acid gave acetate **VI**, which was hydrolyzed with potassium hydroxide to

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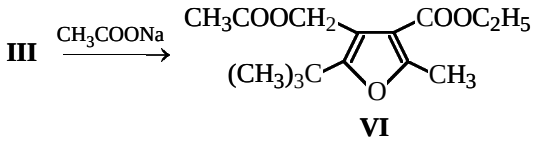
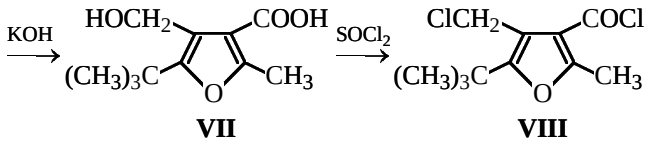
hydroxy acid **VII**. Refluxing of **VII** with thionyl chloride in benzene and subsequent distillation yielded chloromethylfurancarboxylic acid chloride **VIII**.

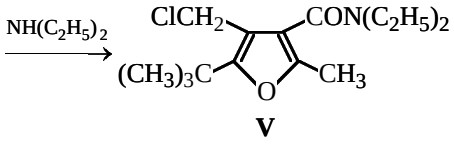
Compound **VIII** selectively reacts with dimethylamine at 20–25°C in benzene at slow addition of the amine solution. Chloromethylated diethylamide **V** was isolated by vacuum distillation in 64% yield.



III, **VI**

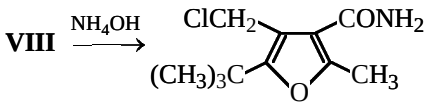


VII, **VIII**

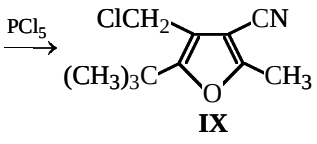


V

Acid chloride **VIII** was also used as a starting compound for preparing chloromethylated nitrile **IX**. Treatment of a dioxane solution of **VIII** with a 3–3.5-fold molar excess of aqueous ammonia at 12–14°C results in selective ammonolysis, and simple dilution of the reaction mixture with water gives chloromethyl amide **X** in 96% yield. Note that the ^{1}H NMR spectrum of this compound in $CDCl_3$ contains two signals of the chloromethyl group with the chemical shifts δ 4.78 and 4.59 ppm in 4.6 : 1 molar ratio. This means that chloromethyl amide **X** evidently exists as a mixture of two conformers.



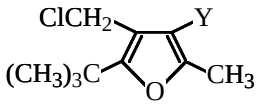
X



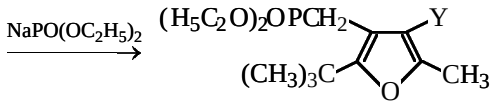
IX

Refluxing of **X** with 1 equiv of PCl_5 in benzene causes dehydration of the amide and formation of chloromethylated nitrile **IX**. Vacuum distillation of the reaction mixture gives the target compound in 76% yield. No conformational equilibrium was observed in the ^{1}H NMR spectrum of **IX**.

Phosphorylation of **III**–**V** and **IX** was performed following the usual procedure of the Michaelis–Becker reaction, described elsewhere [3]. The target product was isolated by vacuum distillation.



III–**V**, **IX**



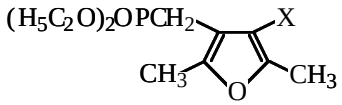
XI–**XIII**, **XV**

Y = $COOC_2H_5$ (**III**, **XI**), $COCH_3$ (**IV**, **XII**), $CON(C_2H_5)_2$ (**V**, **XIII**), CN (**IX**, **XV**).

Reaction of ester **III** with sodium diethyl phosphite was performed at 80°C for 13 h. Phosphonate **XI** was isolated in 57% yield. Phosphorylation of acetylfuran **IV** was peformed for 8 h. Keto phosphonate **XII** was isolated in 66% yield. Phosphorylation of diethylamide **V** was performed for 17 h, and the target product **XIII** was isolated in 57% yield.

The PCH_2 proton signals in the ^{1}H NMR spectrum of **XIII** are strongly broadened. At the same time, in its 2,5-dimethyl analog **XIV** no broadening was observed [3]. The line broadening in the case of *tert*-butyl derivatives may be due to the existence of conformers involved in fast exchange. Phosphonate **XIV** is not overcrowded sterically, the hindrance to the free rotation of substituents is insignificant, and no fixed conformers are detected. Nitrile **IX** appeared to be considerably less active in the Michaelis–Becker reaction than compounds **III** and **IV**. Its 10-h refluxing in benzene with sodium diethyl phosphite resulted in only 48% conversion. Phosphorylated nitrile **XV** was isolated in 39% yield based on the converted **IX**.

2,5-Dimethyl analog **XVI** of **IX** under the analogous conditions was completely converted in 6 h, but the yield of the phosphorylated product was also 39% [4].



X = $CON(C_2H_5)_2$ (**XIV**), CN (**XVI**), $COOC_2H_5$ (**XVII**), $COCH_3$ (**XVIII**).

Comparison of the yields of *tert*-butyl phosphonates **XI**–**XIII** and their 2,5-dimethyl analogs **XVII**, **XIV**, and **XVIII** showed that, with phosphorylated esters, the presence of bulky substituents does not appreciably affect the yield of the phosphonate (57% for **XI** and 58% for **XVII**) [5]. With diethylamides, the yield somewhat decreased (57 and 63% for **XIII** and **XIV**, respectively) [3]. On the contrary, with acetylfurans the yield of the phosphonate significantly increases (66% for **XII** and 43% for **XVIII**) [4].

Thus, introduction of the bulky substituent in the position neighboring to the chloromethyl group in the furan ring only slightly affects the yield of phosphonates in the case of esters, diethylamides, and nitriles. At the same time, for nitrile **IX**, as compared to the other substrates, the reaction with diethyl hydrogen phosphite is considerably slower. This may be due to the fact that the conformation in which the chlorine atom is located near the heteroring plane becomes the most thermodynamically favorable. In this case, the approach of phosphite anion from the opposite side, characteristic of S_N2 reactions, is hindered by the *tert*-butyl group. When bulkier electron-withdrawing substituents are present in the β-position of heteroring, the bulkiest chlorine atom becomes the most deflected from the ring plane. In this case, the direction of approach of nucleophile becomes approximately perpendicular to the ring plane. Hence, it is considerably less shielded by the *tert*-butyl group. As a result, the conditions of phosphorylation of these compounds, as compared to the nitriles, are more similar to those of the 2,5-dimethyl derivatives.

The increased yield of acetylphosphonate in the presence of *tert*-butyl group can also be explained in terms of this model. It is known that, in this case, the main reaction competing with the Michaelis–Becker reaction is the addition of the phosphorus-containing nucleophile to the carbonyl group. The larger the positive charge on the carbonyl carbon atom, the easier the addition. Steric overcrowding of the molecule causes the rotation of the carbonyl group about the C–C bond and hence a decrease in its conjugation with the heteroaromatic ring. Correspondingly, the effective positive charge on the carbonyl carbon atom should decrease. At the same time, the C–Cl bond should deviate from the heteroring plane to the greatest extent to decrease the steric strain. This situation facilitates the nucleophilic attack of the carbon atom of the chloromethyl group in the course of the S_N2 reaction. The whole set of these factors should facilitate the Michaelis–Becker reaction, which is actually observed as the increased yield of the phosphonate in the case of the *tert*-butyl derivative.

EXPERIMENTAL

The ^{1}H NMR spectra were measured on Tesla BS-487C (80 MHz) and Tesla BS-497C (100 MHz) spectrometers in CCl_4 and $CDCl_3$ relative to internal HMDS. The phosphorus chemical shifts were calculated from the INDOR spectra.

Ethyl 2-methyl-4-chloromethyl-5-*tert*-butylfuran-3-carboxylate III. Hydrogen chloride was passed at a high rate for 3 h at 55–60°C through a stirred mixture of 39.5 g of ethyl 2-methyl-5-*tert*-butyl-3-carboxylate **I**, 8.5 g of paraform, 6.1 g of freshly pulverized zinc chloride, and 150 ml of chloroform. After cooling, the reaction mixture was treated with 120 ml of water, the organic layer was separated, the aqueous layer was extracted with chloroform, and the combined organic phases were washed with two portions of water and dried over calcium chloride. The solvent was removed at reduced pressure, and the residue was distilled in a vacuum. Chloromethyl derivative **III**, 29.9 g (61%), was obtained, bp 118–120°C/1 mm Hg. ^{1}H NMR spectrum, δ, ppm: 1.36 m [$(CH_3)_3C$ + CH_3-ethyl], 2.47 s (CH_3-furan), 4.24 q (CH_2O-ethyl), 4.80 s (CH_2Cl).

2-Methyl-3-acetyl-4-chloromethyl-5-*tert*-butylfuran IV. Hydrogen chloride was passed at a high rate for 1 h at 60°C through a vigorously stirred mixture of 8.2 g of ketone **II**, 2 g of paraform, 1.5 g of zinc chloride, and 70 ml of chloroform. The reaction mixture turned dark brown, and a large amount of tarry particles formed. The resulting mixture was treated with 100 ml of water, the liquid phase was decanted, and the tarry fraction was stirred with 100 ml of chloroform for 30 min at room temperature. The organic solutions were combined and filtered. The chloroform layer of the filtrate was separated using a separatory funnel, and the aqueous layer was extracted with 20 ml of chloroform. The combined extracts were washed with water and dried over calcium chloride. Then the solvent was removed, and the residue was vacuum-distilled. The starting ketone **II** (2.0 g) and 2.6 g of a mixture of the starting ketone and chloromethyl derivative **IV** (bp 118°C/1 mm Hg) were obtained. According to the ^{1}H NMR spectrum, the mixture contained 65% of the target product. The conversion of the starting ketone was 64%, yield of chloromethyl derivative 32% based on consumed **II**. ^{1}H NMR spectrum, δ, ppm: 1.35 s [$(CH_3)_3C$], 2.38 s (CH_3CO), 2.50 q (CH_3-furan), 4.47 s (CH_2Cl).

Ethyl 2-methyl-4-acetoxymethyl-5-*tert*-butylfuran-3-carboxylate VI. A mixture of 13.6 g of chloride **III**, 8 g of sodium acetate, and 50 ml of glacial acetic acid was refluxed with stirring for 13 h. The sodium chloride precipitate was filtered off, and the solvent was removed at reduced pressure until sodium acetate started to crystallize. The mixture was treated with water, the resulting emulsion of the target product was extracted with chloroform, and the extract was dried over calcium chloride. The solvent was removed at reduced pressure, and the residue was vacuum-distilled to give 12.5 g of **VI**, bp 129°C, 1 mm Hg. ^{1}H NMR spectrum, δ, ppm: 1.29 m

[$(CH_3)_3C$ + CH_3-ethyl], 1.89 s (CH_3CO), 2.44 s (CH_3-furan), 4.14 q (CH_2O-ethyl), 5.05 s (OCH_2-furan).

2-Methyl-4-hydroxymethyl-5-*tert*-butylfuran-3-carboxylic acid VII. Ester **VI** (5.6 g), 10 ml of ethanol, and a solution of 5 g of KOH in 15 ml of water were mixed and refluxed with vigorous stirring for 4 h. The resulting homogeneous clear solution was acidified to pH 2. The precipitate was filtered off, washed with water, and dried. Yield of hydroxymethylated acid **VII** 3.4 g, mp 93–94°C.

2-Methyl-4-chloromethyl-5-*tert*-butylfuran-3-carboxylic acid chloride VIII. A mixture of 2.5 g of acid **VII**, 3.4 g of thionyl chloride, 0.2 ml of dimethylformamide, and 20 ml of benzene was refluxed for 7 h. The solvent and excess thionyl chloride were removed at reduced pressure, and the residue was vacuum-distilled to give 2.2 g of chloride **VIII**, bp 117–118°C/1 mm Hg.

***N,N*-Diethyl-2-methyl-4-chloromethyl-5-*tert*-butylfuran-3-carboxamide V.** A solution of 1.9 g of diethylamine in 5 ml of benzene was added at 20–25°C with vigorous stirring to a solution of 2.2 g of chloride **VIII** in 10 ml of benzene. The reaction mixture was left overnight, diethylamine hydrochloride was filtered off, the solvent was removed at reduced pressure, and the residue was vacuum-distilled to give 16 g (64%) of chloromethyl amide **V**, bp 146–148°C/1 mm Hg. ^{1}H NMR spectrum, δ, ppm: 0.73 t (CH_3-ethyl, J_{HH} 7 Hz), 1.31 s [$(CH_3)_3C$], 2.11 s (CH_3-furan), 3.34 q (CH_2N, J_{HH} 7 Hz), 4.64 s (CH_2Cl).

2-Methyl-4-chloromethyl-5-*tert*-butylfuran-3-carboxamide X. To a solution of 6 g of **VIII** in 30 ml of dioxane, 10 ml of 25% aqueous ammonia was added dropwise with stirring at 12–14°C. The resulting mixture was kept at this temperature for 30 min and diluted with ice-cold water. An abundant precipitate formed, which was filtered off, washed with a small amount of water, and dried. Carboxamide **X**, 5.3 g (96%), was obtained, mp 159–160°C. ^{1}H NMR spectrum, δ, ppm: 1.30 s [$(CH_3)_3C$], 2.41 s (CH_3-furan), 4.59 s, 4.78 s (both $ClCH_2$-furan, intensity ratio 1 : 4.6), 6.05 br.s (NH_2).

2-Methyl-4-chloromethyl-5-*tert*-butylfuran-3-carbonitrile IX. To a suspension of 4.4 g of **X** in 20 ml of benzene, 4 g of phosphorus pentachloride was added in three or four portions. The amide quickly dissolved with heat evolution. The resulting solution was refluxed for 4 h and vacuum-distilled. Nitrile **IX**, 3.1 g (76%), was obtained, bp 104°C/1 mm Hg. ^{1}H NMR spectrum, δ, ppm: 1.31 s [$(CH_3)_3C$], 2.31 s (CH_3-furan), 4.39 s (CH_2Cl).

Ethyl 2-methyl-4-(diethoxyphosphorylmethyl)-5-*tert*-butylfuran-3-carboxylate XI. A solution of 4.0 g of **III** in 5 ml of benzene was added at 75°C to a solution of sodium diethyl phosphite obtained from 0.4 g of sodium and 2.5 ml of diethyl hydrogen phosphite in 20 ml of benzene. The reaction mixture was refluxed with stirring for 13 h, the sodium chloride precipitate was separated by centrifugation, the solvent was distilled off at reduced pressure, and the residue was vacuum-distilled. Phosphonate **XI**, 3.2 g (57%), was obtained, bp 159–160°C/1 mm Hg. ^{1}H NMR spectrum, δ, ppm: 1.22 t (CH_3-ethyl, J_{HH} 7 Hz), 1.32 s [$(CH_3)_3C$], 2.42 s (CH_3-furan), 3.30 d (CH_2P, J_{HP} 20 Hz), 3.77–4.20 m (CH_2OP + CH_2OOC).

2-Methyl-3-acetyl-4-(diethoxyphosphorylmethyl)-5-*tert*-butylfuran XII. A mixture of 2.6 g of **II** and its chloromethyl derivative **IV** was added with stirring at 80°C to a solution of sodium diethyl phosphite prepared from 0.26 g of sodium and 2 ml of diethyl hydrogen phosphite in 20 ml of benzene. The resulting mixture was stirred for 8 h, the sodium chloride was separated by centrifugation, the solvent was distilled off at reduced pressure, and the residue was vacuum-distilled. Phosphonate **XII**, 1.6 g (66%), was obtained, bp 168–171°C/1 mm Hg. ^{1}H NMR spectrum, δ, ppm: 1.23 m [$(CH_3)_3C$ + CH_3-ethyl], 2.28 s (CH_3CO), 2.44 s (CH_3-furan), 3.28 d (CH_2P, J_{HP} 20 Hz), 3.86 m (CH_2OP, J_{HH} 7 Hz, J_{HP} 11 Hz).

2-Methyl-4-(diethoxyphosphorylmethyl)-5-*tert*-butylfuran-3-diethylcarboxamide XIII. To a solution of sodium diethyl phosphite prepared from 0.13 g of sodium and 1.2 ml of diethyl hydrogen phosphite in 8 ml of benzene, a solution of 1.6 g of chloromethylamide **V** in 4 ml of benzene was added at 80°C. The resulting mixture was refluxed with stirring for 17 h, the sodium chloride precipitate was separated by centrifugation, the solvent was distilled off at reduced pressure, and the residue was vacuum-distilled. Phosphonate **XIII**, 1.2 g (57%), was obtained, bp 181°C/1 mm Hg. ^{1}H NMR spectrum, δ, ppm: 1.19 m (CH_3-ethyl), 1.31 s [$(CH_3)_3C$], 2.13 s (CH_3-furan), 3.04 br.d (CH_2P, J_{HP} 20 Hz), 3.34 m (NCH_2, J_{HH} 7 Hz), 3.88 m (CH_2OP. J_{HH} 7 Hz, J_{HP} 10 Hz).

2-Methyl-4-(diethoxyphosphorylmethyl)-5-*tert*-butylfuran-3-carbonitrile XV. A solution of 3.1 g of nitrile in 4 ml of benzene was added at 80°C to a solution of sodium diethyl phosphite prepared from 0.34 g of sodium and 2.2 ml of diethyl hydrogen

phosphite in 20 ml of benzene. The resulting mixture was refluxed with stirring for 10 h, the sodium chloride precipitate was separated by centrifugation, the solvent was distilled off at reduced pressure, and the residue was vacuum-distilled to give 1.6 g of starting nitrile **IX** and 0.88 g of phosphonate **XV** (bp 150–151°C/1 mm Hg). Conversion of the starting product 48%, yield of the target product 39%. ^{1}H NMR spectrum, δ, ppm: 1.16–1.18 m [$(CH_3)_3C$ and CH_3-ethyl], 2.34 s (CH_3-furan), 2.90 d (CH_2P, J_{HP} 21 Hz), 3.96 m (CH_2OP, J_{HH} 7 Hz, J_{HP} 11 Hz).

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