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Reaction of 2,4-Difunctional Esters of 5-*tert*-Butylfuran-3-carboxylic Acid with Nucleophilic Reagents

L. M. Pevzner

St. Petersburg State Institute of Technology, St. Petersburg, Russia

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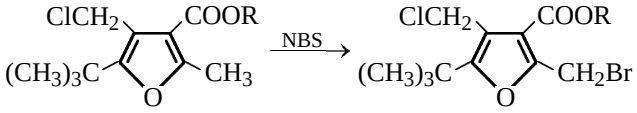
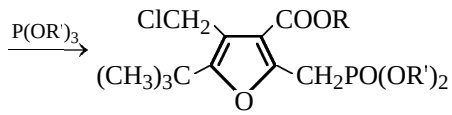
Abstract — Ethyl 5-*tert*-butyl-4-(chloromethyl)-2-methylfuran-3-carboxylate was brominated with *N*-bromosuccinimide to obtain the corresponding 2-bromomethyl derivative. The latter is selectively phosphorylated with trimethyl and triethyl phosphites by the bromomethyl group. The resulting [4-(chloromethyl)furyl]methylphosphonates in the presence of secondary amines and sodium butanethiolate behave as alkylating agents, while sodium phenolate causes their decomposition. 4-Acetoxymethyl- and 4-phenoxymethyl derivatives of the starting product are also selectively brominated with *N*-bromosuccinimide by the 2-methyl group. The first of the 2-(bromomethyl)furans formed is smoothly phosphorylated with trimethyl phosphite, while the second one under the action of triethyl phosphite gives a mixture of phosphorylation and debromination products. In all the cases, an additional electron-acceptor group in position 4 of alkyl 2-(bromomethyl)-5-*tert*-butylfuran-3-carboxylate considerably accelerates the Arbuzov reaction.

Recently [1] we established that the 4-chloromethyl substituent in ethyl 5-*tert*-butyl-4-(chloromethyl)-2-methylfuran-3-carboxylate (**Ia**) is rather inert in phosphorylation reactions. Basing on this fact we suggested that by bromination of the 2-methyl group we could prepare a compound with the halomethyl groups differing considerably in their activity and thus capable of selective phosphorylation. Therewith, the chloromethyl group in the products could be used for their further functionalization.

Ester **Ia** was brominated with *N*-bromosuccinimide (NBS) in CCl_4 in the presence of 2,2'-azobisisobutyronitrile (AIBN) for 3 h to obtain dihalide **IIa** as a stable crystalline substance melting at 59–60°C. Dihalide **IIb** was obtained in a similar way.



I **II**

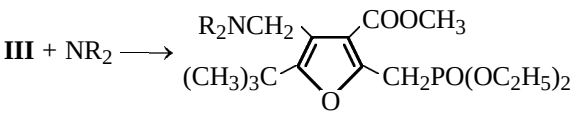


III

I, II, R = CH_3 (**a**), C_2H_5 (**b**); **III**, R = CH_3, R' = C_2H_5; **IV**, R = C_2H_5, R' = CH_3.

Dihalides **IIa, IIb** were phosphorylated with excess trimethyl or triethyl phosphite under Arbuzov reaction conditions. The reaction with trimethyl phosphite was considered complete when the boiling point of the reaction mixture achieved 135–140°C. With triethyl phosphite, after the reaction mixture was heated to 80°C, an exothermic reaction commenced. Therewith, the temperature of the reaction mixture spontaneously rose to 125°C. After heat release was complete, the temperature fell fast to 90–95°C, which was accompanied by distillation of ethyl bromide. After that the reaction mixture was heated to 135°C for 2–3 min. In both cases, phosphorylation was complete within 15 min. Volatile by-product phosphonates were removed to isolate target products **III** and **IV** as viscous syrups. These compounds are stable at room temperature but decompose in a vacuum (1 mm) below the boiling point. Hence, the 4-chloromethyl group fails to enter the Arbuzov reaction under the conditions studied, even though an excess of the phosphorylating agent is present.

Investigation of reactions of compounds **III** and **IV** with nucleophilic agents we began with the reaction with secondary amines. Diethylamine and morpholine were chosen as typical representatives. The alkylation was carried out in the presence of excess amine in benzene or toluene at 70–80°C.



V, VI

R = C_2H_5 (**V**), R_2 = $CH_2CH_2OCH_2CH_2$ (**VI**).

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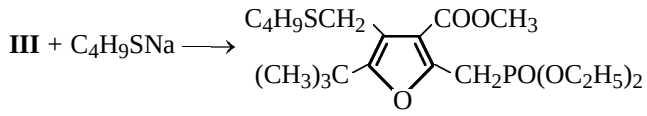
With compound **IV**, decomposition of the phosphorus-containing fragment is observed, while phosphonate **III** gives tertiary amines **V** and **VI**.

Treatment of phosphonate **III** with equimolar amount of sodium butanethiolate in a methanol–benzene mixture for 5 h affords sulfide **VII**.

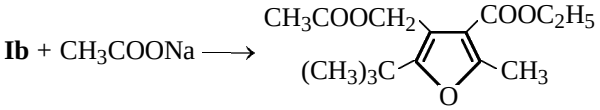


VII

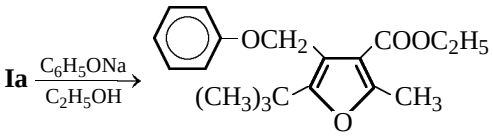
Treatment of phosphonate **IV** with sodium phenolate in the methanol–benzene medium leads to decomposition of the latter.

Hence, the presence of a phosphorus-containing fragment in the starting halide allows nucleophilic substitution reactions with nitrogen- and sulfur-containing nucleophiles only. The same situation we earlier observed with 5-phosphonomethylated 2-bromomethyl derivatives of 3- and 4-furancarboxylic acids [2].

Having established the scope of application of halogen substitution in phosphonate **IV**, we tried to prepare compounds having an oxygen-containing fragment in position *4*, by altering the order of introduction of substituents.



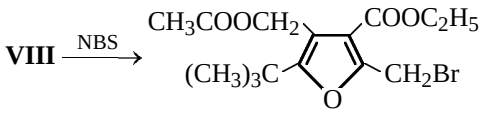
VIII



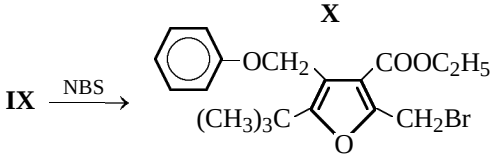
IX

Treatment of halide **Ib** with sodium acetate in acetic acid at 120°C gives acetate **VIII**. Phenyl ether **IX** was obtained by reaction of compound **Ia** with sodium phenolate in ethanol. Both products are readily and selectively brominated with *N*-bromosuccinimide in carbon tetrachloride by the 2-methyl group.

Acetate **X** was phosphosphorylated with trimethyl phoshite under Arbuzov reaction conditions. Similarly to the above-mentioned case, the reaction was considered complete when the boiling point of the reaction mixture reached 130–140°C. After methyl bromide began to evolve at 100°C, the temperature of the reaction mixture virtually continuously rose to

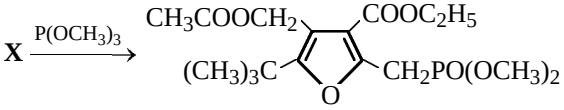


X

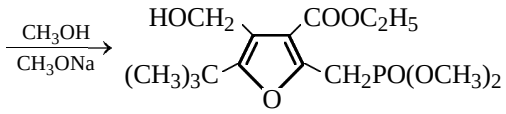


XI

reach 140°C within 12 min. Volatile products were removed in a vacuum, and acetate **XIII** was obtained as a light brown syrup. The acetyl protection was removed by treating the product with methanol in the presence of a catalytic amount of sodium methylate. Boiling for 6 h gave phosphorus-containing alcohol **XIV**.

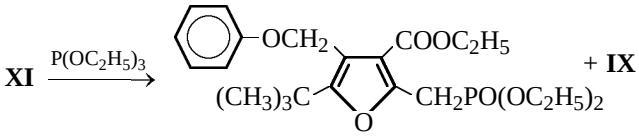


XII



XIV

One of the unsolved problems of furan chemistry is preparation of phosphorus-containing aldehydes. Therefore, an attempt was made to find some suitable oxidant for alcohol **XIV**. Active manganese dioxide prepared according to Attenburrow, and a solution of chromic acid in pyridine, we successfully used previously for oxidation of hydroxymethylfurancarboxylates [3, 4], were tested. The first oxidant did not react with the substrate even on prolonged boiling in benzene or carbon tetrachloride. Contrary to that, the second oxidant caused profound destruction of the starting compound.



XV

Phenyl ether **XI** was phosphorylated with triethyl phosphite under Arbuzov reaction conditions. The reaction mixture began to change its color at 80°C. At 100–110°C, ethyl bromide evolution was observed, and then the temperature of the reaction mixture rose to 130°C. The total reaction time was 5–7 min. The reaction mixture was additionally kept at 130–140°C

for 10 min, and volatile products were removed in a vacuum. Triethyl phosphite and diethyl ethylphosphonate were found among them. The residue was a dark yellow syrup. The ^{1}H NMR spectrum permitted us to characterize it as a mixture of phosphonate **XV** and phenyl ether **IX**. Hence, with bromide **XI**, an additional reaction pathway appears, beginning with halogenophilic attack of the phosphite on the substrate. Though this pathway is minor (the **XV**:**IX** ratio is 6:1), its appearance provides evidence suggesting that the remote and shielded phenoxymethyl substituent exerts a significant effect on the reaction center.

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on Tesla BS-487C and Tesla BS-497C (100 MHz) spectrometers in CCl_4 against internal HMDS. The phosphorus chemical shifts were calculated from INDOR spectra.

Methyl 2-(bromomethyl)-5-*tert*-butyl-4-(chloromethyl)furan-3-carboxylate (IIa). To a solution of 15.7 g of chloromethyl derivative **Ia** in 100 ml of CCl_4, 12.5 g of *N*-bromosuccinimide and 0.5 g of AIBN were added in one portion with stirring. The resulting suspension was heated to 80°C and, after the exothermic reaction was complete, stirred under refux for 3 h. After cooling to room temperature, the succinimide precipitate was filtered off, the solvent was removed at reduced pressure, and the residue was kept in a vacuum (1 mm) for 1 h to obtain 20.1 g (97%) of compound **II**, mp 59–60°C. ^{1}H NMR spectrum, δ, ppm: 1.37 s [$(CH_3)_3C$], 3.79 s (CH_3OOC), 4.59 s (CH_2Br), 4.71 s (CH_2Cl). Ethyl ester **IIb** was obtained analogously, mp 45–46°C. ^{1}H NMR spectrum, δ, ppm: 1.35 m [$(CH_3)_3C$ + ethyl CH_3], 4.22 q (CH_2OOC, J_{HH} 7 Hz), 4.60 s (CH_2Br), 4.68 s (CH_2Cl).

Methyl 5-*tert*-butyl-4-(chloromethyl)-2-(diethoxyphosphorylmethyl)-furan-3-carboxylate (III). A mixture of 10 g of dihalide **IIa** and 7 ml of triethyl phosphite was heated at vigorous stirring. At 80°C, the reaction mixture changed color, boiled up vigorously, and the temperature rose to 125°C. Ethyl bromide began to evolve, and the temperature of the reaction mixture quickly came down to 95–90°C. The mixture was heated to 135°C for 2–3 min to remove residual ethyl bromide. The total reaction time was 15–16 min. The reaction mixture was kept in a vacuum (1 mm). Therewith, diethyl ethylphosphonate distilled bp 49°C (1 mm). Phosphonate **III** was obtained as a a light brown very viscous syrup. The yield of the crude product was quantitative. The product was identified as a mixture of two conformers. ^{1}H NMR spectrum, δ, ppm: 1.24 t (ethyl CH_3, J_{HH} 7 Hz), 1.37 s [$(CH_3)_3C$], 3.76 s (CH_3OOC), 3.91 m (CH_2OP, J_{HH} 7 Hz, J_{HP} 11 Hz), 4.81 s (CH_2Cl); major conformer: 3.51 d (CH_2P, J_{HP} 21 Hz), δ_P 18.1 ppm; minor conformer: 3.39 d (CH_2P, J_{HP} 20 Hz). δ_P 23.5 ppm. Conformer ratio 10:3.

Ethyl 5-*tert*-butyl-4-(chloromethyl)-2-(dimethoxyphosphorylmethyl)furan-3-carboxylate (IV). A solution of 4.9 g of dihalide **IIb** in 4 ml of trimethyl phosphite was heated with stirring. At 40°C the mixture became turbid, at 105°C it boiled up, and methyl bromide evolution began. The temperature of the reaction mixture gradually rose to 135°C within 15 min. Then gas evolution ceased, and the mixture became clear. The product was kept in a vacuum at 1 mm. Therewith, the by-product dimethyl methylphosphonate distilled (bp 30°C, 1 mm). The target phosphonate **IV** was obtained as a yellow viscous syrup. The yield of the target product was quantitative. ^{1}H NMR spectrum, δ, ppm: 1.36 m [$(CH_3)_3C$ + ethyl–CH_3], 4.21 q (CH_2OOC, J_{HH} 7 Hz), 4.74 s (CH_2Cl); major conformer: 3.52 d (CH_2P, J_{HP} 20 Hz), 3.67 d (CH_2OP, J_{HP} 10 Hz), δ_P 21.0 ppm; minor conformer: 3.34 d (CH_2P, J_{HP} 20 Hz), 3.58 d (CH_2OP, J_{HP} 10 Hz). δ_P 25.4 ppm. Conformer ratio 11:5.

Methyl 5-*tert*-butyl-2-(diethoxyphosphorylmethyl)-4-(diethylaminomethyl)furan-3-carboxylate (V). A mixture of 2.1 g of phosphonate **IV**, 3 ml of diethylamine, and 10 ml of benzene was heated with stirring at 70–80°C for 10 h. An abundant precipitate formed. The reaction mixture was washed with dilute hydrochloric acid (1:1, 2 × 15 ml). The aqueous extract was treated with sodium carbonate to pH 10, saturated with sodium chloride, and extracted with ether (3 × 30 ml). The ethereal extract was dried over calcium chloride, filtered, and the ether was distilled off. The residue was kept in a vacuum for 2 h to give 1.1 g (48%) of aminophosphonate **V** as a brown oil. ^{1}H NMR spectrum, δ, ppm: 0.94 t (N–ethyl CH_3, J_{HH} 7 Hz), 1.26 t (O–ethyl CH_3, J_{HH} 7 Hz), 1.40 s [$(CH_3)_3C$], 2.45 q (N–ethyl CH_2, J_{HH} 7 Hz), 3.59 d (furan–CH_2P, J_{HP} 20 Hz), 3.68 s (furan–CH_2N), 3.82 s (CH_3OOC), 4.06 m (CH_2OP, J_{HP} 11 Hz, J_{HH} 7 Hz). δ_P 19.7 ppm.

Methyl 5-*tert*-butyl-2-(diethoxyphosphorylmethyl)-4-(morpholinomethyl)furan-3-carboxylate (VI). A mixture of 2.0 g of phosphonate **IV**, 3 ml of morpholine, and 15 ml of benzene was heated at 70–80°C for 12 h. An abundant precipitate formed. The mixture was washed with dilute hydrochloric acid (1:1, 2 × 15 ml), the aqueous extract was treated with sodium carbonate to pH 9, saturated with sodium chloride, and extracted with ether (3 × 30 ml). The ethereal extract was dried over calcium chloride, filtered, the ether was distilled off, and the residue was kept in a vacuum for 1 h to obtain 1.1 g (49%) of

aminophosphonate **VI** as a light yellow oil. ^{1}H NMR spectrum, δ, ppm: 1.28 t (ethyl CH_3, J_{HH} 7 Hz), 1.40 br.s [$(CH_3)_3C$], 2.40 m (morpholine CH_2N), 3.55 d (CH_2P, J_{HP} 20 Hz), 3.62 br.s (morpholine CH_2O + furan–CH_2N), 3.84 s (CH_3OOC), 4.06 m (CH_2OP, J_{HH} 7 Hz, J_{HP} 11 Hz). δ_P 19.7 ppm.

Methyl 5-*tert*-butyl-4-(butylthiomethyl)-2-(diethoxyphosphoryl)furan-3-carboxylate (VII). To a solution of sodium methylate prepared from 0.17 g of sodium and a mixture of 4 ml of methanol and 6 ml of benzene, 0.8 ml of butylmercaptan was added. The reaction mixture was stirred for 5 min, and then a solution of 2.8 g of phosphonate **IV** in 5 ml of benzene was added. The resulting solution was refluxed for 5 h, poured into 25 ml of water, the benzene layer was removed, and the aqueous layer was extracted with benzene (2 × 10 ml). The combined extracts were dried over calcium chloride. The solvent was removed at reduced pressure, and the residue was kept for 1 h in a vacuum (1 mm) to obtain 2.3 g (72%) of phosphonate **VII** as a light yellow oil. ^{1}H NMR spectrum, δ, ppm: 0.86 t (butyl CH_3, J_{HH} 7 Hz), 1.14–1.40 m [$(CH_3)_3C$ + ethyl CH_3 + butyl CH_2], 2.44 (butyl CH_2–S, J_{HH} 7 Hz), 3.60 d (CH_2P, J_{HP} 20 Hz), 3.77 s (CH_3OOC), 3.84 s (furan–CH_2S), 4.02 m (CH_2OP, J_{HH} 7 Hz, J_{HP} 11 Hz).

Ethyl 4-(acetoxymethyl)-2-(bromomethyl)-5-*tert*-butylfuran-3-carboxylate (X). To a solution of 3.1 g of acetate **VIII** in 30 ml of CCl_4, 2.1 g of *N*-bromosuccinimide and 0.2 g of AIBN were added in one portion. The resulting mixture was refluxed for 3 h with stirring, cooled to room temperature, the succinimide precipitate was filtered off, the solvent was removed at reduced pressure, and the residue was kept in a vacuum (1 mm) for 2 h to obtain 3.1 g of bromide **X** as a yellow viscous oil. ^{1}H NMR spectrum, δ, ppm: 1.36 m [$(CH_3)_3C$ + ethyl CH_3], 1.92 s (CH_3COO), 4.20 q (ethyl CH_2, J_{HH} 7 Hz), 4.62 s (CH_2Br), 5.07 s (furan–CH_2O).

Ethyl 5-*tert*-butyl-2-methyl-4-(phenoxymethyl)-furan-3-carboxylate (IX). To a solution of sodium ethylate obtained by dissolution of 0.3 g of sodium in 15 ml of ethanol, 1.2 g of phenol was added. The reaction mixture was stirred for 5 min, and, after addition of 3.1 g of chloride **Ia**, refluxed for 13 h. The sodium chloride precipitate was filtered off, the ethanol was removed at reduced pressure, and the residue was distilled in a vacuum to obtain 2.6 g (68%) of phenyl ether **IX**, bp 168–170°C (1 mm), mp 56–58°C.

Ethyl 2-(bromomethyl)-5-*tert*-butyl-4-(phenoxymethyl)furan-3-carboxylate (XI). To a solution of 1.6 g of phenyl ether **IX** in 15 ml of CCl_4, 1 g of *N*-bromosuccinimide and 0.1 g of AIBN were added in one portion. The resulting mixture was refluxed with stirring for 1 h, cooled to room temperature, the succinimide precipitate was filtered off, the solvent was removed at reduced pressure, and the residue was kept for 2 h in a vacuum (1 mm) at room temperature to obtain 1.7 g (84%) of bromide **XI** as a yellow syrup. ^{1}H NMR spectrum, δ, ppm: 1.25–1.40 m [$(CH_2)_3C$ + ethyl CH_3], 3.72 q (ethyl CH_2, J_{HH} 7 Hz), 4.75 s (CH_2Br), 5.05 (CH_2O–phenyl), 6.55–7.25 m (phenyl).

Ethyl 4-(acetoxymethyl)-5-*tert*-butyl-2-(dimethoxyphosphorylmethyl)furan-3-carboxylate (XIII). A mixture of 3.3 g of bromide **X** and 5.5 ml of trimethyl phosphite was heated with stirring. At 100°C, the mixture boiled up, and its temperature began to increase, reaching 140°C within 12 min. The mixture was cooled to room temperature, and dimethyl methylphosphonate was distilled off at 1 mm. The residue was kept in a vacuum at 40 °C for 2 h to obtain 3.2 g (90%) of phosphonate **XIII** as a brown syrup. ^{1}H NMR spectrum, δ, ppm: 1.36 m [$(CH_3)_3C$ + ethyl CH_3], 2.00 s (CH_3COO), 3.58 d (CH_2P, J_{HP} 20 Hz), 3.66 d (CH_3OP, J_{HP} 11 Hz), 4.25 q (CH_2OOC, J_{HH} 7 Hz), 5.16 s (furan–CH_2O). δ_P 21.0 ppm.

Methyl 5-*tert*-butyl-2-(dimethoxyphosphorylmethyl)-4-(hydroxymethyl)furan-3-carboxylate (XIV). To a solution of sodium methylate prepared from 0.2 g of sodium and 15 ml of methanol, 3.2 g of phosphonate **XIII** was added with stirring. The resulting mixture was refluxed for 6 h with stirring, 1 ml of acetic acid was added, the methanol was distilled off at reduced pressure, and the residue was dissolved in 80 ml of chloroform and washed with 10 ml of water. The chloroform layer was dried over calcium chloride and then stirred for 3 h with 1 g of charcoal. The clarified solution was filtered, the solvent was distilled off at reduced pressure, and the residue was kept in a vacuum (1 mm) for 2 h to give 2.1 g (77%) of hydroxymethyl derivative **XIV.** ^{1}H NMR spectrum, δ, ppm: 1.40 s [$(CH_3)_3C$], 3.63 d (CH_2P, J_{HP} 22 Hz), 3.72 d (CH_3OP, J_{HP} 11 Hz), 3.88 s (CH_3OOC), 4.65 s (furan–CH_2O).

Reaction of bromomethylfuran XI with triethyl phosphite. A mixture of 1.7 g of bromomethylfuran **XI** and 4.5 ml of triethyl phosphite was heated with stirring. At 80°C the mixture began to darken, at 100–110°C ethyl bromide began to evolve, and then the temperature spontaneously rose to 130°C and maintained for 5 min. After that the reaction mixture was kept at 130–140°C for 10 min, volatile products (triethyl phosphite and diethyl ethylphosphonate) were removed in a vacuum. The residue was kept in a

vacuum (1 mm) at 50°C for 2 h to give 1.3 g of a brown syrup. ^{1}H NMR spectrum, δ, ppm: 1.00–1.50 m [$(CH_3)_3C$ + ethyl CH_3], 2.41 s (CH_3–furan), 3.53 d (CH_2P, J_{HP} 22 Hz), 4.00 m (CH_2OP + CH_2OOC), 5.07 (CH_2O–phenyl), 6.70–7.27 m (phenyl), δ_P 18.1 ppm. From the spectral data it follows that we deal with a mixture of phosphonate **XV** and phenyl ether **IX.** From the intensity ratio of the signals at 2.41 and 3.53 ppm their ratio was estimated at 6 : 1.

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