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# Synthesis of Alkyl 2-Bromomethyl-4-(diethoxyphosphorylmethyl)-5-*tert*-butylfuran-3-carboxylates and Their Reactions with Nucleophilic Agents

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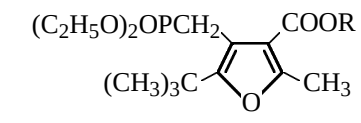
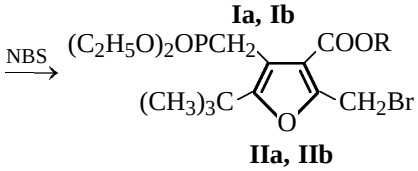
**Abstract** — Alkyl 2-methyl-4-(diethoxyphosphorylmethyl)-5-*tert*-butylfuran-3-carboxylates are selectively brominated with *N*-bromosuccinimide at the methyl group in position 2 of the ring. The resulting bromomethyl derivatives react with secondary amines to form tertiary amines and with sodium butylthiolate in methanol to form the corresponding sulfide. The reaction with potassium thiocyanate in DMF at 80°C gives a mixture of thiocyanate and isothiocyanate. When treated with phenolate or alcoholate ions, the bromomethylfurans decompose.

We have studied previously [1] the ways of functionalization of 2-phosphonomethylated derivatives of 5-*tert*-butylfuran-3-carboxylic acid at position 4 of the furan ring. In this work we examined the isomers with the reversed location of substituents, i.e., the derivatives of 2-methyl-4-(diethoxyphosphorylmethyl)-5-*tert*-butylfuran-3-carboxylic acid. The aim of this work was to determine the pathway of radical bromination of the above compounds and study the reactivity of the bromination products toward N-, S-, and O-nucleophiles.

Esters **Ia** and **Ib** were brominated with *N*-bromosuccinimide (NBS) in the presence of azobis(isobutyronitrile) in carbon tetrachloride similarly to [1]. To shorten the reaction time, the amount of the initiator was increased to 10 wt % relative to *N*-bromosuccinimide. Under these conditions, the bromination is complete in 1 h at 80°C instead of 3 h as in [1], and no impurities arising during prolonged heating of the reaction mixture were accumulated. Bromination proceeded selectively at the methyl group in position 2 of the furan ring.



**Ia, Ib**

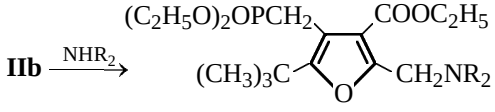


**IIa, IIb**

R = $CH_3$ (**a**), $C_2H_5$ (**b**).

The $^1H$ NMR spectra contained no signals assignable to the starting products or to the products of decomposition of bromophosphonates **IIa** and **IIb**. This fact allowed the products obtained after removal of succinimide, distillation of carbon tetrachloride, and keeping in a vacuum (1 mm) for 1 h to be regarded as pure compounds. Bromides **IIa** and **IIb** are viscous slightly colored oils stable at room temperature but decomposing during attempted vacuum distillation.

Reaction of phosphonates **IIa** and **IIb** with secondary amines was studied with morpholine and piperidine as examples. Alkylation was performed in benzene at 60°C in the presence of excess amine. The reaction products were isolated similarly to [1].



**III, IV**

$R_2$ = $(CH_2)_5$ (**III**), $(CH_2)_2O(CH_2)_2$ (**IV**).

Bromophosphonate **IIb** gives amino esters **III** and **IV** in the yields of 70% and 49%, respectively. We believe that the low yield of **IV** is largely due to the improper isolation procedure, as this compound forms very stable emulsions with water.

Reaction of phosphonate **II** with S-nucleophiles was studied with sodium butylthiolate in ethanol as example, similarly to [1]. Contrary to the previously studied compounds **V** and **VI** [2], the reaction with

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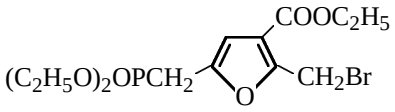
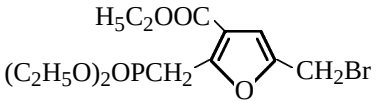
the charged nucleophile in a protic solvent did not lead to decomposition of the molecule.

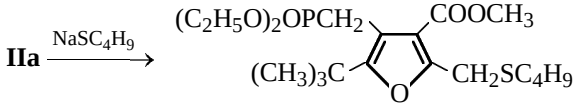


**V**



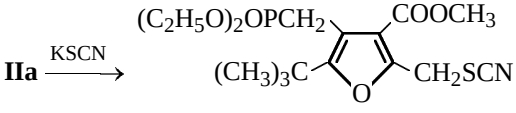
**VI**

On the contrary, the desired phosphonate **VII** was isolated in 82% yield as a light yellow oil stable at room temperature but decomposing below its boiling point upon attempted vacuum distillation.

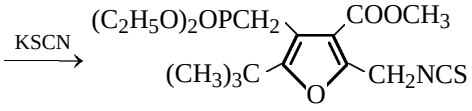


**VII**

In view of success in S- and N-alkylation with bromides **IIa** and **IIb**, we performed the reaction with an ambident S,N-nucleophile, thiocyanate ion. The reaction was carried out with potassium thiocyanate in DMF at 70–80°C and 1.6 : 1 thiocyanate/phosphonate **IIa** molar ratio for 4 h. A mixture of substitution products was isolated in 50% total yield. The $^1$H NMR spectrum of this product contained two signals with chemical shifts δ 4.44 and 4.88 ppm in 1.8 : 1 molar ratio. Based on the data [3] for furfuryl thiocyanate and isothiocyanate ($CH_2SCN$ δ 4.22 ppm, $CH_2NCS$ δ 4.67 ppm), we assigned the upfield signal to the thiocyanate, and the downfield signal, to the isothiocyanate. The presence of thiocyanate and isothiocyanate in the product was confirmed by IR spectroscopy. Its spectrum in chloroform contained characteristic absorption bands at 2160 (–SCN) and 2040 $cm^{-1}$ (–NCS). Thus, the reaction of bromide **IIa** with potassium thiocyanate in DMF at 80°C gives products **IX** and **X**. In spite of relatively rigorous conditions and significant excess of potassium thiocyanate, compound **IX** remains the major product, whereas furfuryl thiocyanate isomerizes to isothiocyanate under these conditions to 80% [3].



**IX**



**X**

Bromide **IIb** was also involved in the reaction with sodium phenolate in ethanol, but, similarly to the previous cases [1, 2], the furan compound decomposed.

Thus, bromination of the methyl group in phosphonate **I** yields compounds acting as alkylating agents for secondary amines and mercaptans and readily reacting with potassium thiocyanate. At the same time, isomerization of thiocyanate **IX** to isothiocyanate **X** under the examined conditions proceeds inefficiently, which prevents the use of this compound in further transformations, e.g., into substituted ureas and amines with phosphorylated furan ring.

## EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer in chloroform. The $^1$H NMR spectra were obtained on a Tesla BS-497C spectrometer (100 MHz) in $CCl_4$ against internal HMDS. The chemical shifts of phosphorus were calculated from INDOR spectra.

**Bromination of alkyl 2-methyl-4-(diethoxyphosphorylmethyl)-5-*tert*-butylfuran-3-carboxylates with *N*-bromosuccinimide** *(general procedure).* A mixture of 0.1 mol of appropriate ester, 0.105 mol of *N*-bromosuccinimide, and azobis(isobutyronitrile) in an amount of 10 wt % relative to *N*-bromosuccinimide was heated with vigorous stirring in 100 ml of carbon tetrachloride until an exothermic reaction started. After the completion of heat evolution, the mixture was refluxed at 80°C for 1 h. The reaction completion was judged from the absence of crystals of *N*-bromosuccinimide which precipitate on the bottom of the flask after stopping the stirrer. The reaction mixture was left overnight for the complete crystallization of succinimide. The crystals were filtered off, and the filtrate was evaporated at room temperature and the residual pressure of 10–15 mm. The bromomethyl derivative obtained was kept in a vacuum (1 mm) at room temperature for 2 h.

**Methyl 2-bromomethyl-4-(diethoxyphosphorylmethyl)-5-*tert*-butylfuran-3-carboxylate IIa.** Light brown oil, yield 99%. $^1$H NMR spectrum, δ, ppm: 1.21 t ($CH_3$-ethyl, $J_{HH}$ 7 Hz), 1.40 s [$(CH_3)_3C$], 3.38 d ($CH_2P$, $J_{HP}$ 21 Hz), 3.84 s ($CH_3OOC$), 3.94 m ($CH_2OP$, $J_{HH}$ 7 Hz, $J_{HP}$ 11 Hz), 4.66 s ($CH_2Br$), $\delta_P$ 23.0 ppm.

**Ethyl 2-bromomethyl-4-(diethoxyphosphorylmethyl)-5-*tert*-butylfuran-3-carboxylate IIb.** Dark yellow oil. Yield 90%. $^1$H NMR spectrum, δ, ppm: 1.18 t ($CH_3$-ethyl of phosphonate, $J_{HH}$ 7 Hz), 1.40 m [$(CH_3)_3C$ + $CH_3$ of ester ethyl], 3.31 d ($CH_2P$, $J_{HH}$

22 Hz), 3.87 m ($CH_2OP$, $J_{HH}$ 7 Hz, $J_{HP}$ 11 Hz), 4.28 q ($CH_2OOC$, $J_{HH}$ 7 Hz), 4.64 s ($CH_2Br$).

**Ethyl 2-(piperidinomethyl)-4-(diethoxyphosphorylmethyl)-5-*tert*-butylfuran-3-carboxylate III.** To a solution of 1.7 g of phosphonate **IIb** in 15 ml of benzene, 3 ml of piperidine was added with stirring, and the resulting mixture was heated for 11 h at 50–60°C. The next day, the reaction mixture was extracted with dilute hydrochloric acid (1:2), the aqueous extract was saturated with sodium chloride, and sodium carbonate was added in small portions with vigorous stirring to pH 9. Then the reaction mixture was alkalized to pH 10.5 with a small amount of 50% aqueous solution of KOH, and the resulting mixture was immediately extracted with ether (4 times). The extract was settled for 30 min, and the organic layer was decanted and dried over calcium chloride. The ether was distilled off, and the residue was kept in a vacuum (1 mm) at room temperature for 2 h. Phosphonate **III**, 1.2 g (70%), was obtained. $^1$H NMR spectrum, δ, ppm: 1.20–1.37 m [$CH_3$-ethyl + $CH_2$ of piperidine ring + $(CH_3)_3C$], 2.20–2.30 m ($CH_2N$-piperidine), 3.50 d ($CH_2P$, $J_{HP}$ 21 Hz), 3.93 s ($CH_2N$-furan), 4.03 m ($CH_2OP$, $J_{HP}$ 10 Hz, $J_{HH}$ 7 Hz), 4.29 q ($CH_2OOC$, $J_{HH}$ 7 Hz). $\delta_P$ 23.9 ppm.

**Ethyl 2-(morpholinomethyl)-4-(diethoxyphosphorylmethyl)-5-*tert*-butylfuran-3-carboxylate IV.** To a solution of 1.6 g of phosphonate **II** in 15 ml of benzene, 3 ml of morpholine was added with stirring, and the resulting mixture was heated for 10 h at 60°C. The next day, the mixture was extracted with dilute (1:3) hydrochloric acid, the aqueous extract was saturated with sodium chloride, and sodium carbonate was added in small portions with vigorous stirring to pH 9. The resulting mixture was immediately extracted with ether (4 times), the ether extract was settled for 1 h, and the organic layer was decanted and dried over calcium chloride. The ether was distilled off, and the residue was kept in a vacuum (1 mm) for 2 h at room temperature. Phosphonate **IV**, 0.8 g (49%), was obtained as a brown oil. $^1$H NMR spectrum, δ, ppm: 1.10–1.30 m ($CH_3$-ethyl), 1.38 s [$(CH_3)_3C$], 2.48 m ($CH_2N$-morpholine), 3.53 d ($CH_2P$, $J_{HP}$ 22 Hz), 3.71 m ($CH_2O$-morpholine), 3.92 s ($CH_2N$-furan), 4.06 m ($CH_2P$, $J_{HP}$ 11 Hz, $J_{HH}$ 7 Hz), 4.32 q ($CH_2OOC$, $J_{HH}$ 7 Hz). $\delta_P$ 24.1 ppm.

**Methyl 2-(butylthiomethyl)-4-(diethoxyphosphorylmethyl)-5-*tert*-butylfuran-3-carboxylate VII.** To a solution of sodium ethylate prepared from 0.07 g of sodium and 15 ml of ethanol, 0.4 ml of butyl mercaptan was added. The mixture was stirred for 5 min, and then a solution of bromide **IIa** in 5 ml of ethanol was added in one portion. The resulting mixture was stirred at 70–80°C for 5 h, the major fraction of ethanol was removed at reduced pressure, and the residue was poured into 20 ml of water. The mixture was extracted three times with ether, the extract was dried over calcium chloride, the solvent was removed, and the residue was kept in a vacuum (1 mm) at room temperature for 2 h. Sulfide **VII**, 1.1 g (82%), was obtained as a light yellow oil. $^1$H NMR spectrum, δ, ppm: 0.90 m ($CH_3$-butyl), 1.25 m ($CH_3$-ethyl + $CH_3$-butyl), 1.42 s [$(CH_3)_3C$], 2.44 t ($CH_2S$-butyl, $J_{HH}$ 7 Hz), 3.41 d ($CH_2P$, $J_{HP}$ 22 Hz), 3.78 s ($CH_2S$-furan), 3.88 s ($CH_3OOC$), 3.94 m ($CH_2OP$, $J_{HP}$ 11 Hz, $J_{HH}$ 7 Hz). $\delta_P$ 23.9 ppm.

**Reaction of methyl 2-bromomethyl-4-(diethoxyphosphorylmethyl)-5-*tert*-butylfuran-3-carboxylate IIa with potassium thiocyanate.** A mixture of 1.4 g of bromide **IIa**, 0.5 g of potassium thiocyanate, and 15 ml of DMF was stirred at 70–80°C for 4 h. After that, the solvent was distilled off at residual pressure of 1 mm, and the residue was treated with 20 ml of water. The oil that separated out was extracted with ether, washed with water, and dried over calcium chloride. The solvent was distilled off, and the residue was kept in a vacuum (1 mm) at room temperature for 2 h. IR spectrum, ν, $cm^{-1}$: 2150 (SCN), 2040 (NCS) [published data [3]: ν(SCN) 2160, ν(NCS) 2070–2150 $cm^{-1}$]. $^1$H NMR spectrum, δ, ppm: 1.26 t ($CH_3$-ethyl, $J_{HH}$ 7 Hz), 1.43 s [$(CH_3)_3C$], 3.40 d ($CH_2P$, $J_{HP}$ 22 Hz), 3.84 s ($CH_3OOC$), 4.02 m ($CH_2OP$, $J_{HP}$ 11 Hz, $J_{HH}$ 7 Hz), 4.44 s ($CH_2SCN$), 4.88 s ($CH_2NCS$). The ratio of the thiocyanate and isothiocyanate, according to the spectral data, is 1.8:1.

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3. Shurlock, L.A. and Fayter, A.M., *J. Org. Chem.*, 1969, vol. 34, no. 12, p. 4035.