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Reactions of 5-Functionalyzed 2-(1-Haloethyl)furans with Sodium Diethylphosphite and Trialkyl Phosphites

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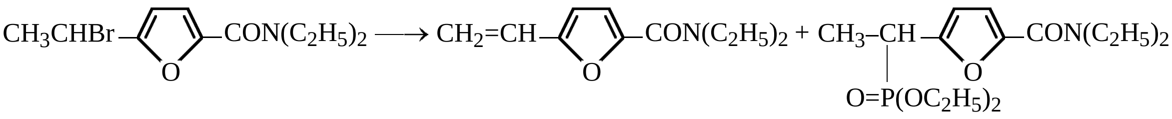
Abstract—5-(1-Haloethyl)furan-2-carboxylic acid derivatives react with sodium dialkyl phosphite and trialkyl phosphite in two directions to form phosphonates and alkenes. The alkene fraction in the reaction products diminishes as the electron-acceptor power of the 2-substituent in the ring increases in going from dialkylamide to ether and then to nitrile. 5-Bromoethyl-2-cyanofuran reacts with sodium diethyl phosphite to give no other products than those formed by halogenophilic attack, implying a significant withdrawal of the electron density from the bromine atom in this compound.

Reactions of halomethylfurans with phosphites and their salts have been thoroughly studied. At the same time, α-haloethyl derivatives have never been investigated in these processes. It may be expected that α-haloethylfurans, along with phosphorylation and halogenophilic attack, will undergo dehydrohalogenation to form furylalkenes. The influence of the structure of the substrate, the nature of the reagent, and the reaction conditions on the relative contributions of these processes in reactions of phosphorus nucleophiles has been unexplored at all.

The aim of this work was to study the behavior of a small series of 2-(1-chloroethyl)- and 2-(1-bromoethyl)furans containing substituents with varied electron-acceptor properties in the 5 position of the ring in reactions with trimethyl phosphite, triethyl phosphite, and sodium diethyl phosphite.

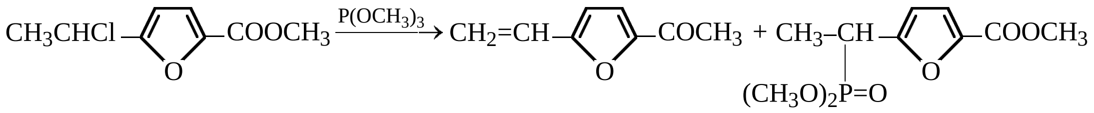
It is known [1] that bromomethyl derivatives of dialkyl furancarboxamides are almost inactive in the Arbuzov reaction. Therefore, we involved bromoethylamide **I** only in the Michaelis–Becker reaction with sodium diethyl phosphite. The process was carried out under usual conditions [2] in benzene at a 1 : 1 molar ratio for 8.5 h at 80°C. After separation of inorganic products and distillation of the reaction mixture in a vacuum, a fraction boiling in the range 136–178°C (1 mm) was obtained. The ^{1}H NMR spectrum of this material showed that it consists of two compounds, alkene **II** and phosphonate **III**.



I **II** **III**

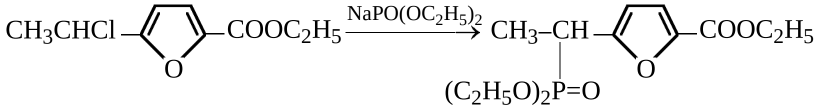
From spectral data the yield of alkene **II** was estimated at 31% and the yield of phosphonate **III**, at 27%. The starting product was found neither in the reaction mixture obtained after removal of the solvent nor in the distillate.

Methyl 5-(1-chloroethyl)furan-2-carboxylate **IV** was involved in the Arbuzov reaction with trimethyl phosphite, and its ethyl analog **IVa**, in the Michaelis–Becker reaction with sodium diethyl phosphite. The Arbuzov reaction was carried out with excess trimethyl phosphite under reflux. The reaction completion was detected, when the boiling point of the reaction mixture had risen to 135°C. The reaction time was 5 h. Distillation of the reaction mixture in a vacuum (1 mm) gave two fractions boiling at 90–105 and 149–153°C. Inspite of the addition of oleic acid as foam quencher, strong foaming took place, resulting in heavy mechanic losses. For this reason, the yield of the final products was not estimated.



IV **V** **VI**

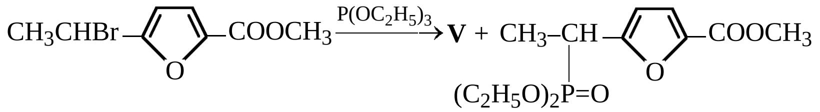
The ^1H NMR spectra showed that the low-boiling fraction consisted almost exclusively of pure alkene **V**, and the major component of the high-boiling fraction was phosphonate **VI**.



IVa **VIa**

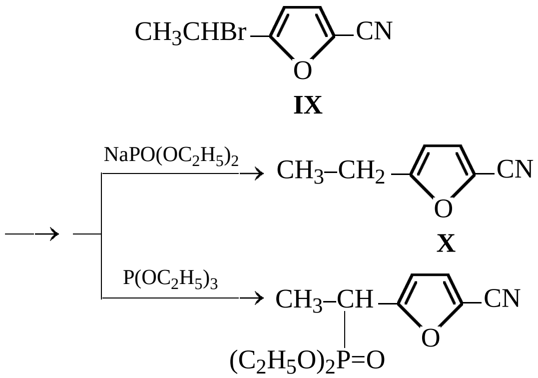
The Michaelis–Becker reaction with compound **IVa** was carried out at 80°C for 15 h. The reaction mixture was separated to find that the conversion of chloride **IVa** within this period was 52%, and the yield of phosphonate **VIa** was 48%. Formation of an alkene analogous to product **V** was not observed.

The Arbuzov reaction was studied on an example of bromoethyl derivative **VII**. This compound reacts with excess triethyl phosphite for 2 h at 122–140°C, providing alkene **VIII** and phosphonate **IX** in 15% and 34% yields, respectively (by ^1H NMR). We failed to isolate individual products from the reaction mixture by means of vacuum distilation.



VII **VIII**

Bromomethylnitrile **X** was involved in the Arbuzov reaction with triethyl phosphite and in the Michaelis–Becker reaction with sodium diethyl phosphite.



IX

X

XI

The Arbuzov reaction was carried out with excess triethyl phosphite for 1 h at 135–145°C. Vacuum distillation of the reaction mixture gave phosphonate **XII**, but no alkene formation was observed. The yield of phosphonate **XII** was 44%.

Bromide **X** was reacted with sodium diethyl phosphite at a 1 : 1 molar ratio for 6 h in benzene at 80°C. The reaction pathway proved complicated. From the reaction mixture we isolated and identified ethylfuran **XI**. By means of NMR spectroscopy, the presence of phosphate (δ_P –3 ppm) was established. No phosphonate phosphorus was found in the reaction mixture. Because of the heavy mechanic losses in the course of several vacuum distillations of the reaction mixture, the yield of nitrile **XI** was not estimated.

EXPERIMENTAL

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

Reaction of *N*,*N*-diethyl-5-(1-bromoethyl)-furan-2-carboxamide (I) with sodium diethyl phosphite. To a solution of sodium diethyl phosphite prepared from 2.8 ml of diethyl hydrogen phosphite and 0.4 g of sodium in 30 ml of benzene, a solution of 4.2 g of bromide **I** in 5 ml of benzene was added in one portion. The resulting mixture was refluxed for 8.5 h, the precipitate of sodium bromide was removed by centrifugation, and the residue was distilled in a vacuum to give 2.3 g of a material boiling in the range 136–178°C (1 mm Hg). All attempts to separate it into fractions boiling in a narrow range did not lead to the isolation of pure products. ^{1}H NMR spectrum, δ, ppm: alkene **II**: 1.15 m (ethyl-CH_3, J_{HH} 7 Hz), 3.40 m (CH_2N, J_{HH} 7 Hz), 5.12 d (H_A, J_{AC} 11 Hz), 5.60 d (H_B, J_{BC} 17 Hz), 5.93 d (furan-H^4, J_{HH} 2 Hz), 6.40 d.d (H_C, J_{AC} 11 Hz, J_{BC} 17 Hz), 6.72 d (furan-H^3, J_{HH} 2 Hz); phosphonate **III**: 1.15 m (ethyl-CH_3, J_{HH} 7 Hz), 2.44 d.d (CH_3–CHP; J_{HH} 7 Hz, J_{HP} 11 Hz), 3.19 d.q (CHP, J_{HH} 7 Hz, J_{HP} 21 Hz), 3.40 m (CH_2–N, J_{HH} 7 Hz), 3.99 m (CH_2OP, J_{HH} 7 Hz, J_{HP} 11 Hz), 6.17 d (furan-H^4, J_{HH} 2 Hz), 6.82 d.d (furan-H^3, J_{HH} 2 Hz, J_{HP} 4 Hz); δ_P 22.6 ppm.

Basing on the spectral data, the yield of alkene was estimated at 31% and the yield of phosphonate, at 27%.

Reaction of methyl 5-(1-chloroethyl)furan-2-carboxylate (IV) with trimethyl phosphite. A mixture of 2.3 g of chloride **IV** and 6 ml of trimethyl phosphite was heated with stirring. At 112°C, the reaction mixture came to boil. The boiling point of the reaction mixture gradually rose and reached 135°C within 5 h. Repeated distillation of the reaction mixture gave two fractions boiling at 90–105°C (1 mm Hg) and 149–153°C (1 mm Hg) and consisting mainly of alkene **V** and phosphonate **VI**, respectively. ^{1}H NMR spectrum, δ, ppm: alkene **V**: 3.90 s (CH_3OOC), 5.38 d (H_A, J_{AC} 11 Hz), 5.92 d (H_B, J_{AB} 18 Hz), 6.48 d (furan H^4, J_{HH} 2 Hz), 6.57 d.d (H_C, J_{AC} 11 Hz, J_{AB} 18 Hz), 7.17 d (furan H^3, J_{HH} 2 Hz); phosphonate **VI**: 1.54 d.d (ethyl CH_3, J_{HH} 7 Hz, J_{HP} 8 Hz), 3.25 d.q (CHP, J_{HH} 7 Hz, J_{HP} 21 Hz), 3.63 d (CH_3OP, J_{HP} 12 Hz), 3.90 s (CH_3OOC), 6.40 d (furan H^4, J_{HH} 2 Hz), 7.10 d (furan H^3, J_{HH} 2 Hz); δ_P 22.2 ppm.

Ethyl 5-(1-diethoxyphosphorylethyl)furan-2-carboxylate (VIa). To a solution of sodium diethyl phosphite prepared from 0.23 g of sodium and 2 ml of diethyl hydrogen phosphite in 15 ml of benzene, 2.1 g of chloride **IVa** was added in one portion with stirring at 80°C. The reaction mixture was refluxed for 15 h, sodium chloride was removed by centrifugation, the solvent was removed at reduced pressure, and the residue was distilled in a vacuum. To quench strong forming, 1 drop of oleic acid was added. Fractions boiling at 98–105°C (1 mm Hg), 1.0 g, and 168–170°C (1 mm Hg), 0.8 g, were obtained. The first fraction contained mainly starting chloride **IVa**, and the second fraction, phosphonate **VIa**. The conversion of the starting product was 52%, and the yield of phosphonate was 48%. ^{1}H NMR spectrum, δ, ppm: 1.20 m (ethyl CH_3), 1.41 d.d (CH_3–CH, J_{HH} 7 Hz, J_{HP} 12 Hz), 3.18 d.q (CHP, J_{HH} 7 Hz, J_{HP} 21 Hz), 3.93 m (CH_2OP, J_{HH} 7 Hz, J_{HP} 11 Hz), 4.15 d (CH_2OOC, J_{HH} 7 Hz), 6.23 m (furan H^4, J_{HH} 3 Hz, J_{HP} 3 Hz), 6.93 d (furan H^3, J_{HH} 3 Hz); δ_P 21.1 ppm.

Reaction of methyl 5-(1-bromoethyl)furan-2-carboxylate (VII) with triethyl phosphite. A mixture of 4.9 g of bromide and 5 ml of triethyl phosphite was heated with stirring. At 123°C, bubble formation was observed, and at 140°C, the reaction mixture came to boil. Vigorous evolution of ethyl bromide took place, and after 5 min the temperature falled to 122°C. The reaction mixture was heated with stirring for 2 h. During this period, the temperature of the reaction mixture gradually rose to 140°C, after which boiling ceased. The resulting mixture was distilled in a vacuum to give 2.5 g of a material with bp 156°C (1 mm Hg). According to the ^{1}H NMR spectra, it consisted of alkene **V** and phosphonate **VIII**. The yield of alkene **V** was 15% and the yield of phosphonate **VIII** was 34% at complete conversion of the starting product. ^{1}H NMR spectrum, δ, ppm: alkene **VIII**: 3.72 s (CH_3OOC), 5.20 d (H_A, J_{AC} 12 Hz), 5.83 d (H_B, J_{BC} 18 Hz), 6.26 d (furan H^4, J_{HH} 3 Hz), 6.34 d.d (H_C, J_{AC} 12 Hz, J_{BC} 18 Hz), 6.96 d (furan H^3, J_{HH} 3 Hz); phosphonate **IX**: 1.20 q (ethyl CH_3, J_{HH} 7 Hz), 1.42 d.d (CH_3–CHP, J_{HH} 7 Hz, J_{HP} 10 Hz), 3.20 d.q (CHP, J_{HH} 7 Hz, J_{HP} 20 Hz), 3.72 s (CH_3OOC), 3.93 m (CH_2OP, J_{HH} 7 Hz, J_{HP} 11 Hz), 6.26 d.d (furan H^4, J_{HH} 3 Hz, J_{HP} 3 Hz), 6.95 d (furan H^3, J_{HH} 3 Hz); δ_P 20.3 ppm.

Reaction of 5-(1-bromoethyl)-2-cyanofuran (IX) with sodium diethyl phosphite. To a solution of sodium diethyl phosphite prepared from 0.33 g of sodium and 2.5 ml of diethyl hydrogen phosphite in 15 ml of benzene, 2.8 g of nitrile **IX** was added in one portion with stirring at 70°C. Strong heat release was observed, and a precipitate formed 4–5 min after the reagents had been mixed. The reaction mixture was stirred for 6 h at 80°C, sodium bromide was removed by centrifugation, and the organic phase was distilled in a vacuum. After three distillations, a narrow fraction with bp 59–60°C (1 mm Hg) was obtained. It was identified as 2-cyano-5-ethylfuran (**X**). Because of the heavy mechanic losses, the yield of the product was not estimated. ^{1}H NMR spectrum, δ, ppm: 1.22 t (ethyl CH_3, J_{HH} 7 Hz), 2.45 q (furan CH_2, J_{HH} 7 Hz), 6.02 d (furan H^4, J_{HH} 2 Hz), 6.82 d (furan H^3, J_{HH} 2 Hz).

In the course of the first vacuum distillation, a fraction with bp 94–99°C (1 mm Hg) was also obtained. We failed to establish its composition by means of ^{1}H NMR spectroscopy but showed that it contains a phosphorus atom with δ_P –3 ppm characteristic of phosphites.

2-Cyano-5-(1-diethoxyphosphorylethyl)furan (XI). A mixture of 2.1 g of 5-(1-bromoethyl)-2-cyanofuran (**IX**) and 3 ml of triethyl phosphite was heated with stirring. At 140°C, ethyl bromide began to evolve, and the temperature of the reaction mixture falled to 130°C. After further 45-min heating, the temperature of the reaction mixture reached 140°C, and evolution of volatile products ceased. The total reaction time was 1 h. Vacuum distillation of the reaction mixture gave 1.2 g (44%) of phosphonate **XI**, bp 143°C (1 mm Hg). The conversion of the starting product was complete. Alkene formation was not observed. ^{1}H NMR spectrum of phosphonate **XI**, δ, ppm: 1.22 m (ethyl CH_3, J_{HH} 7 Hz), 1.43 d.d (CH_3–CH, J_{HH} 7 Hz, J_{HP} 9 Hz), 3.22 d.q (CHO, J_{HH} 7 Hz, J_{HP} 22 Hz), 3.95 m (CH_2OP, J_{HH} 7 Hz, J_{HH} 11 Hz), 6.31 d.d (furan H^4, J_{HH} 3 Hz, J_{HP} 2 Hz), 6.99 d (furan H^3, J_{HH} 3 Hz); δ_P 21.5 ppm.

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