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Synthesis and Selected Reactions of Ethyl 5-(1-Chloroethyl)-2-methylfuran-3-carboxylate

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Abstract—Ethyl 2-methylfuran-3-carboxylate is smoothly chloroethylated at 0°C in the 5 position of the ring. The resulting halide alkylates secondary amines but eliminates HCl with sodium diethyl phosphite under the Michaelis–Becker reaction conditions and with trimethyl phosphite under the Arbuzov reaction conditions. In the reaction with sodium diethyl phosphite, small amounts of 5-[1-(diethoxyphosphoryl)ethyl]furan-3-carboxylate and 5-ethylfuran-3-carboxylate are formed. In the Arbuzov reaction at a 1 : 1.22 furan : trimethyl phosphite molar ratio, methyl 2,4-dimethyl-1-methoxy-1-oxo-1λ^5-1,2-dihydrophospheto[3,2-*b*]furan-5-carboxylate was isolated.

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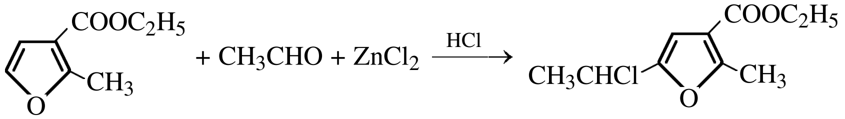
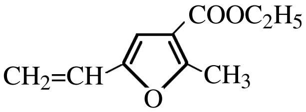
Chloroethylation of furan derivatives with the acetaldehyde–hydrogen chloride–zinc chloride system was studied formerly by Midzhoyan and co-workers [1, 2] on an example of alkyl furan-2-carboxylates. This research was not continued, probably, because of the limited choice of furan derivatives available at that time. At the same time, this is one of the simple, convenient, and cheap methods for forming an asymmetric center in the α position of the side chain of furan derivatives. Therefore, chemical properties of the 1-chloroethyl fragment seem actual to study.

Since the chemical properties of α-(1-chloroethyl)-furan with the stabilizing α'-alkoxycarbonyl group are fairly well studied [1, 3], we turned to the case when the electronacceptor substituent occupies the β position of the ring. Ethyl 2-methylfuran-3-carboxylate (**I**) was chosen as substrate. The furan **I** : acetaldehyde : zinc chloride molar ratio, like in [1], was 1 : 2 : 0.1.

The reaction was carried out in chloroform, and saturation of the system with hydrogen chloride was maintained by its bubbling through the reaction mixture.



I **II**

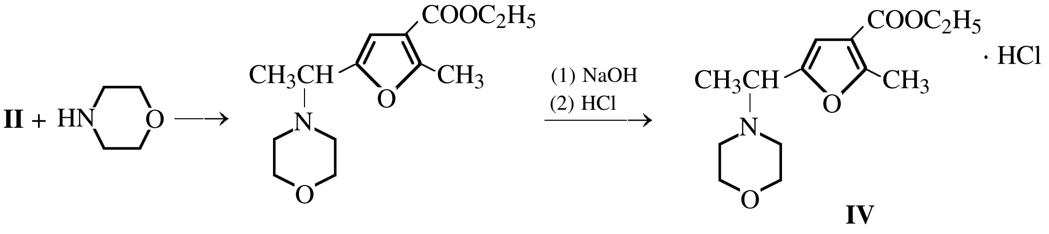


III

It was found that controlled chloroethylation proceeds at –2 to 2°C, and at 15–20°C the amount of polymeric products sharply increases. The yield of chloroethyl derivative **II** was 66%, when the reaction was carried out in the optimal temperature range. The product contained a small admixture of compound **III**.

Chloride **II** alkylates morpholine (80°C, 5 h, benzene), and subsequent hydrolysis of crude amino ester leads to amino acid **IV** identified as hydrochloride.

Attempted dehydrochlorination under the action of



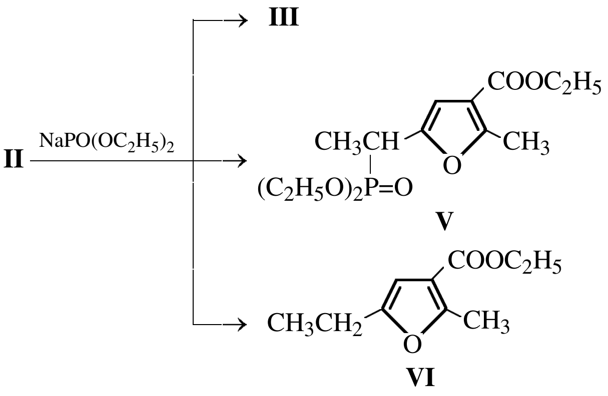
diazabicyclooctane in pyridine [4] and lithium carbonate in DMF [5] led to decomposition of chloride **II**.

Further we turned to reactions of compound **II** with phosphorus nucleophiles, such as sodium diethyl phosphite and trimethyl phosphite.

The reaction with sodium diethyl phosphite was carried out in benzene at 80°C for 12 h at a 1 : 1 molar ratio and a small excess of diethyl hydrogen phosphite. Distillation of the reaction mixture in a vacuum (1 mm Hg) gave two fractions boiling at 85–88 and 156°C. The first fraction comprised alkene **III** and a small admixture of diethyl hydrogen phosphate. The ^{1}H NMR spectrum of the second fraction contained two sets of signals. The first included the following signals (here and hereinafter, δ, δ_P, and δ_C are in ppm and *J* are in Hz): a singlet at δ 2.454 (CH_3–furan), a doublet of doublets at δ 1.454 ppm (J_{HH} 7.4, J_{HP} 17.6), a doublet of quartets at δ 3.187 (J_{HH} 7.4, J_{HP} 22.8), and a singlet at δ 6.425. The phosphorus signal of this compound is at δ_P 26.5.

The second set of signals included a singlet at δ 2.498 (CH_3–furan), a quartet at δ 2.941 (J_{HH} 7.2), and a singlet at δ 6.388 (furan H).

Hence, chloride **II** reacts with sodium diethyl phosphite to give three products, alkene **III**, phosphonate **V**, and ethylfuran **VI**. The yields of these products were evaluated as 53, 8, and 6 %, respectively, and their molar ratio was 9.2 : 1.4 : 1.



The reaction of chloride **II** with trimethyl phosphite was carried out under reflux at a 5.09–1.15 phosphite : furan molar ratio for 1.5–4 h, depending on the temperature of the reaction mixture. The reaction was considered complete, when a constant boiling point of the reaction mixture was achieved. Alkene **III** and dimethyl hydrogen phosphite were isolated and identified as reaction products. The yield of alkene **III** increased from 31 to 40% as the phosphite : chloride **II** molar ratio was decreased from 5.09 to 3.39 and sharply decreased (to 18%) at a 1.15 reactant molar ratio. The final boiling point of the reaction mixture increased from 132–135 to 160°C. In all the cases, vigorous polymer formation was observed.

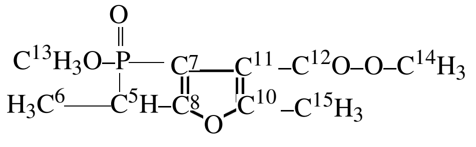
The resulting data are listed in the table.

When the reaction of chloride **II** with trimethyl phosphite was carried out at a 1 : 1.22 molar ratio under milder conditions (1.5 h, final temperature 135°C), one more product was isolated by vacuum distillation of the reaction mixture [bp 125–128°C (1 mm Hg)]. Its ^{1}H NMR spectrum contained two doublets of doublets at δ 1.169 (J_{HH} 6.8, J_{HP} 18.4) and 1.214 (J_{HH} 7.4, J_{HO} 19.4), a singlet at δ 2.111 (CH_3–furan), a singlet at δ 3.590 (CH_3OOC), two

Yields of alkene **III** in the reaction of chloride **II** with trimethyl phosphite in at varied reactant molar ratio and temperature

Exp. no.	Phosphite : chloride molar ratio	Reaction time	Final boiling point of the reaction mixture	Yield of alkene **III**, %
1	5.05	3 h 45 min	132	31
2	4.77	3 h 45 min	132	37
3	3.39	1 h 25 min	135	40
4	1.15	3 h	160	18

doublets at δ 3.685 (J_{HP} 10.4) and 3.759 (J_{HP} 10.8) with the intensity ratio 2.6 : 1, two multiplets at δ 2.740 and 4.090, and a multiplet of low intensity at δ 2.885, evidently belonging to the minor product. Under conditions of phosphorus decoupling, these multiplets transformed to strongly distorted quartets with broadened lines. The ^{31}P NMR spectrum of the isolated substance displayed two strong signals at δ_P 49.14 and 46.64 and two signals of low intensity at δ_P 48.09 and 45.50. The spectral data suggest that the major product contains a methoxycarbonyl group and a phosphinate phosphorus atom bound to aliphatic and aromatic carbon atoms. The product was assigned structure **VII**.



VII

This substance should be a mixture of *cis* and *trans* isomers differing in mutual location of the methyl and methoxy groups in the four-membered ring. It was confirmed by means of ^{13}C NMR spectroscopy. The ^{13}C NMR spectrum of compound **VII** contained by two signals of C^5 (δ_C 28.086, J_{PC} 120.9; δ_C 29.071, J_{PC} 19.1), C^{13} (δ_P 52.124, J_{PC} 8.5; δ_C 53.219, J_{PC} 5.9), C^{11} (δ_C 119.239, J_{PC} 9.6; δ_C 110.342, J_{PC} 9.3), and C^8 (δ_C 162.266, J_{PC} 7.4; δ_C 162.986, J_{PC} 9.2), which provides evidence for the existence of two compounds having the four-membered phosphorus-containing heterocycle.

Product **VII** contained some amount of admixtures, and, therefore, its yield was estimated approximately (20%). Such an unusual cyclization was not previously observed in the furan series. Most surprising is the formation of a stable four-membered heteroring, because even a five-membered fused carbocycle cannot be formed in the furan series [6].

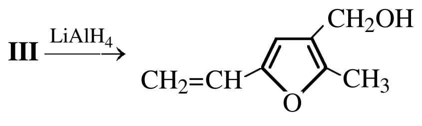
Hence, it was shown that alkene **III** is a fairly available product. Therefore, we tried to involve it in reactions leading to substrates suitable for phosphorylation.

The presence of the methyl group in the furan ring of alkene **III** induced us to brominate it with *N*-bromosuccinimide. The reaction was carried out in carbon tetrachloride at 80°C and initiated with azobis(isobutyronitrile).

It occurred that in the course of the reaction *N*-bromosuccinimide is consumed very slowly. Its complete convertion was achieved only in 10 h, provided the initiator was continuously added every 2 h. In the ^1H NMR spectrum of the reaction mixture, the signal of the methyl group in the furan ring (δ 2.557) does not alter, and the signal of the furan ring proton shifts downfield [δ 6.457 in starting alkene **III** and δ 6.679 in the bromination product]. The signal of the H_{trans} proton (δ 5.618, J_{HH} 17.6) disappears, and the signal at δ 6.384 (=CH–furan) shifts downfield (δ 6.416, d.d). Vacuum distillation of the reaction mixture after removal of *N*-bromosuccinimide leads to decomposition of the products.

Thus, even though we failed to isolate individual products, it is safe to state that the radical reaction with *N*-bromosuccinimide involves, instead of allylic bromination, the double bond of alkene **III**.

Alkene **III** was also reduced with lithium alumohydride in ether. The reaction mixture was decomposed with saturated ammonium chloride and dried over sodium sulfate. The product obtained is relatively stable in solution but readily polymerizes in the course of vacuum distillation. Nevertheless, we managed to isolate alcohol **VIII** in 31% yield and to take its ^1H NMR spectrum before it had polymerized completely.



VIII

The spectral data showed that the reaction involves exclusively the reduction of the carboxy group, leading to compound **VIII**, but the resulting unsaturated alcohol, being highly labile, could not be brought in further transformations.

Hence, 2-(1-chloroethyl)furan **II** alkylates secondary amines, but with phosphorus nucleophiles it gives mainly dehydrochlorination product **III**. The reaction of compound **II** with a slight excess of trimethyl phosphite also involves an unusual cyclization to form a four-membered phosphorus-containing heteroring fused with the furan ring.

EXPERIMENTAL

The ^1H NMR spectra were taken on a Bruker DPX-400 (400.13 MHz) spectrometer. The ^{13}C and ^{31}P NMR spectra were measured on a Bruker AC-200 spectrometer (50.328 MHz for ^{13}C; 81.014 MHz for ^{31}P) in $CDCl_3$. The INDOR spectrum was obtained on a Tesla BS-497C (100 MHz) spectrometer.

Ethyl 5-(1-chloroethyl)-2-methylfuran-3-carboxylate (II). Acetaldehyde, 13 ml, was added dropwise at 0°C to a vigorously stirred mixture of 16.6 g of ethyl 2-methylfuran-3-carboxylate, 1.5 g of a finely pulverized zinc chloride, and 150 ml of chloroform, after which a strong stream of hydrogen chloride was passed through the reaction mixture until saturation. The resulting mixture was kept for 2 h at 0–2°C, the conditions of saturation with hydrogen chloride being maintained. After that it was decomposed with water, the organic layer was separated, and the aqueous layer was extracted with chloroform. The combined solutions were washed with water, dried over $CaCl_2$, the solvent was removed at reduced pressure, and the residue was distilled in a vacuum to give 15.5 g (66%) of chloride **II**, bp 99–102°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 1.255 t (ethyl CH_3, J_{HH} 7 Hz), 1.766 d (chloroethyl CH_3, J_{HH} 7 Hz), 2.514 s (CH_3–furan), 4.219 q (CH_2OOC, J_{HH} 7 Hz), 5.002 q (chloroethyl CH, J_{HH} 7 Hz), 6.504 s (furan H).

2-Methylfuran-5-[1-(*N*-morpholyl)ethyl]-3-carboxylate hydrochloride (IV). Morpholine, 3 ml, was added in one portion to a vigorously stirred solution of 3 g of chloride **II** in 40 ml of benzene, and the resulting mixture was refluxed for 5 h. After that the reaction mixture was washed with two 20-ml portions of of 10% HCl. The combined extracts were cooled to 0°C, saturated with sodium chloride, and treated with 40% aqueous NaOH to pH 9. The mixture was immediately extracted with ether, the ethereal extracts were dried over sodium sulfate, and the solvent was distilled off. The residue was dissolved in 3 ml of ethanol, and a solution of 1.7 g of sodium hydroxide in 17 ml of water was added. The solution was boiled with stirring and distillation of a water–ethanol mixture until the distillate temperature of 100°C was achieved. The hydrolyzate was cooled, acidified with 36% HCl to pH 2, saturated with sodium chloride, and extracted with several portions of butanol. The combined extracts were evaporated at reduced pressure until a tarry residue formed. It was triturated with ethyl acetate, the crystals obtained were filtered off, washed with acetone, and dried. Amino acid hydrochloride **IV**, 1.5 g, was obtained, decomp. point 195°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.662 d (aminoethyl CH_3, J_{HH} 7 Hz), 2.500 s (CH_3–furan), 2.758–2.914 br.s (CH_2N), 3.884 m (CH_2O), 4.628 br.s (N–CH–furan), 6.899 s (furan H^4), 12.103 br.s (HOOC + HCl).

Reaction of chloride II with sodium diethyl phosphite. A solution of 3.4 g of chloride **II** in 4 ml of benzene was added in one portion at 80°C to a solution of sodium diethyl phosphite, prepared from 0.4 g of sodium and 3 ml of diethyl hydrogen phosphite in 40 ml of benzene. The resulting mixture was refluxed with stirring for 12 h, sodium chloride was removed on a centrifuge, the solvent was removed at reduced pressure, and the residue was distilled in a vacuum to give 1.5 g of alkene **III**, bp 85–88°C (1 mm Hg) and 0.6 g of a fraction, bp 156°C (1 mm Hg), consisting of phosphonate **V** and ethylfuran **VI**. According to the ^{1}H NMR spectrum, the phosphonate : ethylfuran ratio was 1.4 : 1.

Ethyl 2-methyl-5-vinylfuran-3-carboxylate (III). Yield 53%, bp 80°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 1.314 t (ethyl CH_3, J_{HH} 6.8 Hz), 2.561 s (furan H^3), 4.245 q (CH_2OOC, J_{HH} 6.8 Hz), 5.140 d (H_{cis}, J_{HH} 11.2 Hz), 5.618 d (H_{trans}, J_{HH} 17.6 Hz), 6.384 d.d (=CH–furan, J_{cis} 11.2 Hz, J_{trans} 17.6 Hz), 6.457 s (furan H^4). Furan **III** slowly polymerizes on handling.

Ethyl 5-[1-(diethoxyphosphoryl)ethyl]-2-methylfuran-3-carboxylate (V). Yield 8%. ^{1}H NMR spectrum, δ, ppm: 1.259 m (ethyl CH_3), 1.454 d.d (ethoxyphosphoryl CH_3, J_{HH} 7.4 Hz, J_{HP} 17.6 Hz), 3.187 d.q (CHP, J_{HH} 7.4 Hz, J_{HP} 22.8 Hz), 4.040 m (CH_2OP), 4.204 m (CH_2OOC), 6.425 s (furan H^4). δ_P 26.5 ppm.

Ethyl 5-ethyl-2-methylfuran-3-carboxylate (VI). Yield 6%. ^{1}H NMR spectrum, δ, ppm: 1.259 m (ethyl CH_3), 2.498 s (CH_3–furan), 2.941 q (CH_2–furan, J_{HH} 7.2 Hz), 6.388 s (furan H^4).

Reaction of chloride II with trimethyl phosphite. A mixture of chloride **II** and trimethyl phosphite was refluxed with stirring until a constant boiling point was achieved. After that the reaction mixture was distilled in a vacuum. The fraction boiling in the range 78–90°C (1 mm Hg) was collected and distilled in a vacuum once more to give product **III**, bp 80°C (1 mm Hg). The conditions and results of exp. nos. 1–4 are listed in the table.

Experiment no. 5. A mixture of 12.0 g of chloride **II** and 8 ml of trimethyl phosphite was heated for 1.5 h to 135°C and then distilled in a vacuum to give 1 g (10%) of alkene **III** and 2.7 of a fraction, bp 125–128°C (1 mm Hg), consisting mainly of product **VII**, yield ~20%, n_D^{20} 1.4700.

Methyl 2,4-dimethyl-1-methoxy-1-oxo-1λ^5-1,2-dihydrophospheto[3,2-*b*]furan-5-carboxylate (VII). bp 121–122°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 1.169 d.d (CH_3–phosphetane, J_{HH} 6.8 Hz, J_{HP} 18.4 Hz), 1.214 d.d (CH_3–phosphete, J_{HH} 7.4 Hz, J_{HP} 19.4 Hz), 2.111 s (CH_3–furan), 3.590 s (CH_3OOC), 3.685 d (CH_3OP, J_{HP} 10.4 Hz), 3.759 d (CH_3OP, J_{HP} 10.8 Hz), 2.740 br.m, 4.090 br.m (phosphate CH). ^{13}C NMR spectrum, δ_C, ppm: 12.726 s, 13.488 s (C^{15}), 15.402 d (C^6, J_{CP} 7.7 Hz), 28.086 d (C^5, J_{CP} 120.9 Hz), 29.971 d (C^5, J_{CP} 119.1 Hz), 58.530 s

(C^{14}), 52.124 d (C^{13}, J_{CP} 8.5 Hz), 53.219 d (C^{13}, J_{CP} 5.9 Hz), 109.853 d (C^{7}, J_{CP} 198.5 Hz), 110.342 d (C^{11}, J_{CP} 9.3 Hz), 111.239 d (C^{11}, J_{CP} 9.6 Hz), 162.266 d (C^{8}, J_{CP} 7.4 Hz), 162.986 d (C^{8}, J_{CP} 9.2 Hz), 163.572 s (C^{10}), 163.950 s (C^{12}). ^{31}P NMR spectrum, δ_P, ppm: 49.140 s, 46.642 s.

3-(Hydroxymethyl)-2-methyl-5-vinylfuran (VIII). To a suspension of 0.9 g of lithium aluminum hydride in 40 ml of ether, a solution of 4.2 g of ester **III** in 5 ml of ether was added dropwise with stirring at a rate providing slight boiling of the reaction mixture. After the addition was complete, the mixture was stirred for 1 h and left overnight. On the next day it was treated with stirring with 10 ml of ethyl acetate and decomposed with saturated ammonium chloride until phase separation. The organic phase was decanted, and the water–salt gel was stirred with 30 ml of ether. The combined organic layers were dried for 1 h over sodium sulfate, the solvent was evaporated in a waterjet-pump vacuum, and the residue was distilled in a vacuum. The solution darkened just during its concentration, and vacuum distillation is accompanied by polymerization. Compound **VIII**, 1.0 g (31%), was obtained, bp 91–93°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 2.260 s (CH_3–furan), 4.377 s (CH_2OH), 5.055 d (H_{cis}, J_{HH} 12 Hz), 5.555 d (H_{trans}, J_{HH} 16.8 Hz), 6.387 d.d (=CH–furan, J_{cis} 12 Hz, J_{trans} 16.8 Hz), 6.192 s (furan H^4). In a refrigerator (ca. –4°C), the product polymerizes within several hours.

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