Russian Journal of General Chemistry, Vol. 74, No. 5, 2004, pp. 706–707. Translated from Zhurnal Obshchei Khimii, Vol. 74, No. 5, 2004, pp. 770–772.

Aminomethylation of 2- and 3-(Diethoxyphosphorylmethyl)furans

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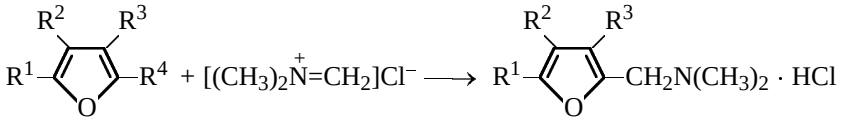
Received May 20, 2003

Abstract — Dimethyl(methylene)ammonium chloride reacts with 2- and 3-(diethoxyphosphorylmethyl)furans by the free α position of the furan ring to give the corresponding aminomethyl derivatives. 2,5-Disubstituted furans do not enter this reaction.

Aminophosphonic acids and their derivatives hold great promise in terms of biological activity. At the same time, derivatives of furylmethanephosphonic acids containing an amino group have scarcely been explored.

It is known that the dialkylaminomethyl group can be introduced into the furan ring by means of the Mannich reaction with simultaneous treatment with formaldehyde and a secondary amine hydrochloride [1–3]. But it occured that under these conditions dialkoxyphosphorylmethylfurans form polymeric products of unknown structure. We suggested that this result is explained by a reaction like aldol condensation between the methylene group on phosphorus with formaldehyde. To avoid the side reaction, we decided to use dimethyl(methylene)ammonium chloride which was recently successfully used for α-aminomethylation of furan-containing terpenes [4].

We took as substrates three types of compounds differing in the mutual location of substituents in the ring. The reaction was carried out at 1:1.1 substrate–reagent molar ratio in anhydrous acetonitrile at 80°C. The process can be described by the following equation.



I–**VI** **VII**–**XI**

$R^1 = CH_2PO(OC_2H_5)_2$, $R^2 = R^3 = R^4 = H$ (**I**); $R^1 = CH_2PO(OC_2H_5)_2$, $R^2 = R^3 = H$, $R^4 = CH_3$ (**II**); $R^1 = CH_3$, $R^2 = R^4 = H$, $R^3 = CH_2PO(OC_2H_5)_2$ (**III**); $R^1 = (CH_3)_3C$, $R^2 = R^4 = H$, $R^3 = CH_2PO(OC_2H_5)_2$ (**IV**); $R^1 = CH_3$, $R^2 = CH_2PO(OC_2H_5)_2$, $R^3 = R^4 = H$ (**V**); $R^1 = (CH_3)_3C$, $R^2 = CH_2PO(OC_2H_5)_2$, $R^3 = R^4 = H$ (**VI**); $R^1 = CH_2PO(OC_2H_5)_2$, $R^2 = R^3 = H$ (**VII**); $R^1 = CH_3$, $R^2 = CH_2PO(OC_2H_5)_2$, $R^3 = H$ (**VIII**); $R^1 = (CH_3)_3C$, $R^2 = CH_2PO(OC_2H_5)_2$, $R^3 = H$ (**IX**); $R^1 = CH3$, $R^2 = H$, $R^3 = CH_2PO(OC_2H_5)_2$ (**X**); $R^1 = (CH_3)_3C$, $R^2 = H$, $R^3 = CH_2PO(OC_2H_5)_2$ (**XI**).

The resulting tertiary amine hydrochlorides **VII**–**XI** give well-formed crystals neither in acetonitrile nor in less polar solvents. Therefore, the target aminophosphonates were converted to free bases by treatment with a stoichiometric amount of ethanolic sodium ethoxide and then distilled in a vacuum. Aminophosphonates are viscous liquids stable at room temperature but noticeably evolving dimethylamine at elevated temperatures. The same effect was observed in the course of vacuum distillation of aminophosphonates.

It was found that aminomethylation of phosphorylated furans proceeds only when the substrate molecule has a free α position. 2,5-Disubstituted furan **II** does not enter the reaction even under prolonged (several days) heating in acetonitrile. Separation of the reaction mixture resulted in an almost complete recovery of the starting furan.

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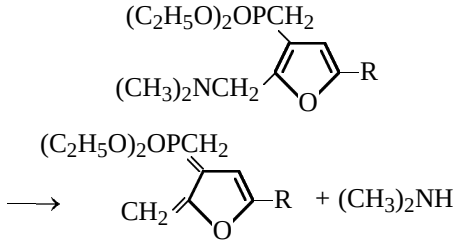
Substrates **I, III**–**VI** behave similarly under the reaction conditions. The yields of aminophosphonates vary within 55–44%, the lowest observed with 2,4-disubstituted furans **III, IV**. This fact is most likely explained by more favorable conditions for the elimination of dimethylamine rather than by the reactivity of the furan ring.



We tried to extend the reaction to methyleneammonium salts **XII, XIII**. However, the reaction in the cold failed, whereas at elevated temperatures polymeric products formed.

$[(CH_3)_2\overset{+}{N}{=}CHCl]Cl^-$

XII

$[(CH_3)_2\overset{+}{N}{=}CHOCH_3]SO_3OCH_3$

XIII

Hence, (dialkoxyphosphorylmethyl)furans react with dimethyl(methylene)ammonium chloride by a way similar to electrophilic heteroaromatic substitution. The methylene group on phosphorus does not take part in the process. At the same time, furans containing no phosphorylmethyl group, even such acidophobic as 2-furylmethanol, are aminomethylated under the classical conditions of the Mannich reaction. Consequently, the reason for the polymerization of phosphorylmethylfurans under these conditions lies in the reaction of the methylene group on phosphorus with free formaldehyde. The latter reaction is evidently faster than the electrophilic substitution in the furan ring.

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Tesla BS-497C (100 MHz) spectrometer. The chemical shifts were calculated from INDOR spectra.

Aminomethylation of (dialkoxyphosphorylmethyl)furans I–**VI** *(general procedure).* Dimethyl(methylene)ammonium chloride, 0.011 mol, was added to a solution of 0.01 mol of compound **I**–**IV** in 30 ml of acetonitrile. The mixture was stirred at 80°C for 3–4 h in air-proof conditions, cooled to room temperature, and a solution of 0.011 mol of sodium ethoxide in 5 ml of absolute ethanol was added dropwise with stirring. The sodium chloride precipitate was removed by centrifugation, the solvent was evaporated at reduced pressure, and the residue was distilled in a vacuum.

2-(Diethoxyphosphorylmethyl)-5-(dimethylaminomethyl)furan (VII). Yield 55%, bp 142°C (1 mm). ^{1}H NMR spectrum (CCl_4, HMDS), δ, ppm: 1.10 t (ethyl CH_3, J_{HH} 7 Hz); 2.17 s (CH_3–N); 3.15 d (CH_2P, J_{HP} 20 Hz); 3.33 s (CH_2N); 4.00 m (CH_2OP, J_{HP} 11 Hz, J_{HH} 7 Hz); 6.08 s (furan H^4); 6.11 d (furan H^3, J_{HP} 2 Hz); δ_P 20.3 ppm.

3-(Diethoxyphosphorylmethyl)-2-(dimethylaminomethyl)-5-methylfuran (VIII). Yield 44%, bp 142–150°C (2 mm) (decomp.) ^{1}H NMR spectrum (CCl_4, HMDS), δ, ppm: 1.18 t (ethyl CH_3, J_{HH} 7 Hz); 2.07 s (CH_3–N); 2.15 s (CH_3–furan); 2.71 d (CH_2P, J_{HP} 21 Hz); 3.24 s (CH_2N); 3.89 m (CH_2OP, J_{HP} 11 Hz, J_{HH} 7 Hz); 5.87 s (furan CH); δ_P 23.6 ppm.

5-*tert*-Butyl-3-(diethoxyphosphorylmethyl)-2-(dimethylaminomethyl)furan (IX). Yield 44%, bp 146°C (1 mm). ^{1}H NMR spectrum (CCl_4, HMDS), δ, ppm: 1.20 m [ethyl CH_3 + $(CH_3)_3$C, overlap]; 2.07 s (CH_3–N); 2.69 d (CH_2P, J_{HP} 20 Hz); 3.27 d (CH_2N, J_{HP} 2 Hz); 3.89 m (CH_2OP, J_{HP} 11 Hz, J_{HH} 7 Hz); 5.85 s (furan CH); δ_P 23.6 ppm.

4-(Diethoxyphosphorylmethyl)-2-(dimethylaminomethyl)-5-methylfuran (X). Yield 50%, bp 143–154°C (2 mm) (decomp.). ^{1}H NMR spectrum (CCl_4, HMDS), δ, ppm: 1.11 t (ethyl CH_3, J_{HH} 7 Hz); 2.02 br. s (CH_3–furan + CH_3N); 2.61 d (CH_2P, J_{HP} 21 Hz); 3.20 s (CH_2N); 3.75 m (CH_2OP, J_{HP} 11 Hz, J_{HH} 7 Hz); 5.15 s (furan CH); δ_P 23.5 ppm.

5-*tert*-Butyl-4-(diethoxyphosphorylmethyl)-2-(dimethylaminomethyl)furan (XI). Yield 52%, bp 158°C (1mm). ^{1}H NMR spectrum (CCl_4, HMDS), δ, ppm: 1.20–1.32 m [ethyl CH_3 + $(CH_3)_3$C]; 2.10 s (CH_3N); 2.82 d (CH_2P, J_{HP} 20 Hz); 3.27 m (CH_2N); 3.90 m (CH_2OP, J_{HP} 11 Hz, J_{HH} 7 Hz); 5.97 s (CH_3–furan); δ_P 23.6 ppm.

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