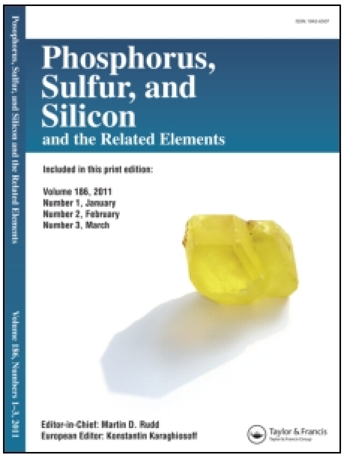

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SYNTHESIS OF 1-AMINOALKANEPHOSPHONIC ACID DERIVATIVES CONTAINING FURAN MOIETY. PART II: FIRST SYNTHESIS OF (2-FURYL)AMINOMETHANE PHOSPHONIC ACID[1]

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SYNTHESIS OF 1-AMINOALKANEPHOSPHONIC ACID DERIVATIVES CONTAINING FURAN MOIETY. PART II: FIRST SYNTHESIS OF (2-FURYL)AMINOMETHANE PHOSPHONIC ACID[1]

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The synthesis of (2-furyl)aminomethanephosphonic acid from furfural via corresponding imine, dibenzyl ester and N-benzylsubstituted acid is presented. The synthesis was performed by the hydrogenolysis of a corresponding N-benzylsubstituted dibenzyl ester.

Keywords: Furfural; furfurylimine; dibenzyl aminofurfurylphosphonates; (2-furyl)amino-methanephosphonic acid

INTRODUCTION

The first preparation of the aminoalkanephosphonic acid—glycine analogue took place in 1948[2] and till now a variety of this type of compounds was synthesized[3–5]. Recently, some similar derivatives were prepared starting from furfural[6,7] and also from thiophene and pyrrol aldehydes by sonochemical activation[8].

In the course of our studies on 2- or 2,5-substituted furan derivatives, we are dealing with aminophosphonic acids bearing the furan moiety, considering the

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*Corresponding author.

known application of such compound in the fields of medicine and agriculture[9] as well as the biological activity of furan compounds[10].

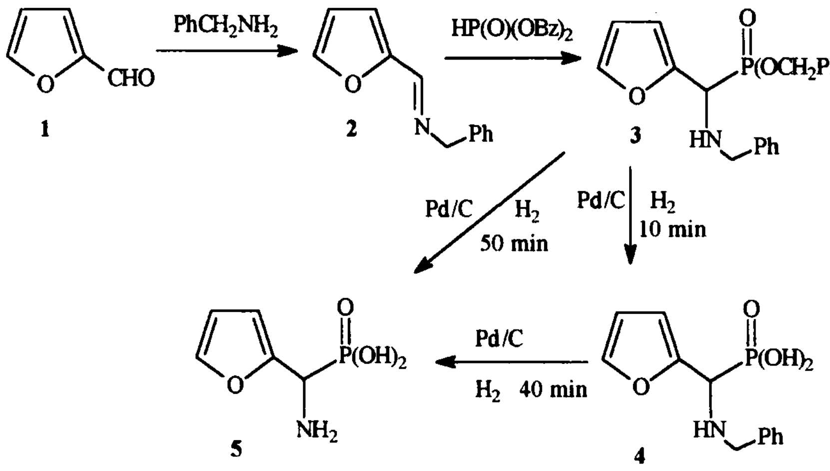
RESULTS AND DISCUSSION

We wish to report a simple and efficient method of synthesis of (2-furyl)aminomethane-phosphonic acid (**5**). To our knowledge this acid as well as some of its derivatives have never been synthesized before, except the N-substituted acid **4**, which has been prepared by Boduszek[7] in a different way.

N-Furfurylidenebenzylamine (**2**) and N-furfurylidenetritylamine (**6**) (which has never been described before) were prepared following the published[11] or modified procedure.

O,O′-Dibenzyl-N-benzylamino(2-furyl)methanephosphonate (**3**) was obtained by the addition of dibenzyl phosphite to the imino double bond of a corresponding Schiff base (**2**) in acetonitrile with a catalytic amount of trifluoroacetic acid or in toluene without a catalyst. The ester was obtained in 65% and 58% yield, respectively.

O,O′-Dibenzyl-N-benzylamino(2-furyl)methanephosphonate (**3**) has been debenzylated by the catalytic hydrogenolysis with palladium-on-charcoal. The reaction was carried out in methanol and, after 10 minutes, gave N-benzylamino(2-furyl)methanephosphonic acid (**4**) in 90% yield. If the reac-



SCHEME 1

tion was prolonged to 50 minutes, it provided (2-furyl)aminophosphonic acid (**5**) in 91% yield. Nearly the same yield was noticed after 40 minutes hydrogenolysis of acid **4**.

As it could be predicted, our kinnetic measurements have shown that hydrogenolysis of a O-benzyl group goes faster than that of a N-benzyl group. During the first 10 minutes of the reaction, the consumption of 2 molar equivalents of hydrogen has been noticed. It was consummed to remove the O-benzyl group from the ester. Another 40 minutes were necessary to deblock the amino group. The results are presented in figure 1.

In the search of different methods of the synthesis of acid **5**, we wanted to use N-tritylsubstituted aminophosphonic esters. They were synthesized by the addition of dialkyl phosphites to N-furfurylidenetritylamine (**6**). This Schiff base was obtained following the general method[12].

O,O′-Diethyl and -dibenzyl N-tritylamino(2-furyl)methanephosphonates (**7a** and **7b** respectively) were obtained by heating a mixture of the imine **6** and the phosphite without any additional solvent. Unf ortunately, the attempts to deprotect the amino group by the acidic hydrolysis caused an extensive decomposition of the furan ring as it was previously mentioned by Boduszek[7].

So, in conclusion, we want to stress that the only way to obtain aminophosphonic acids bearing the furan moiety from their esters is the catalytic hydrogenolysis. Some other conversions of these compounds are under study.

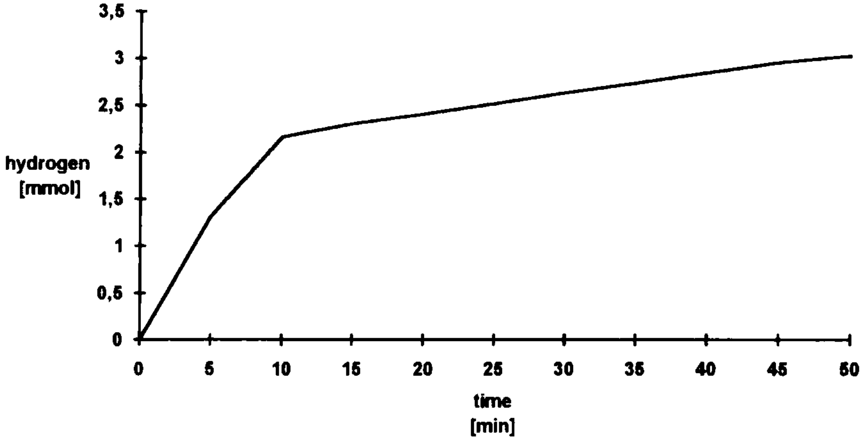
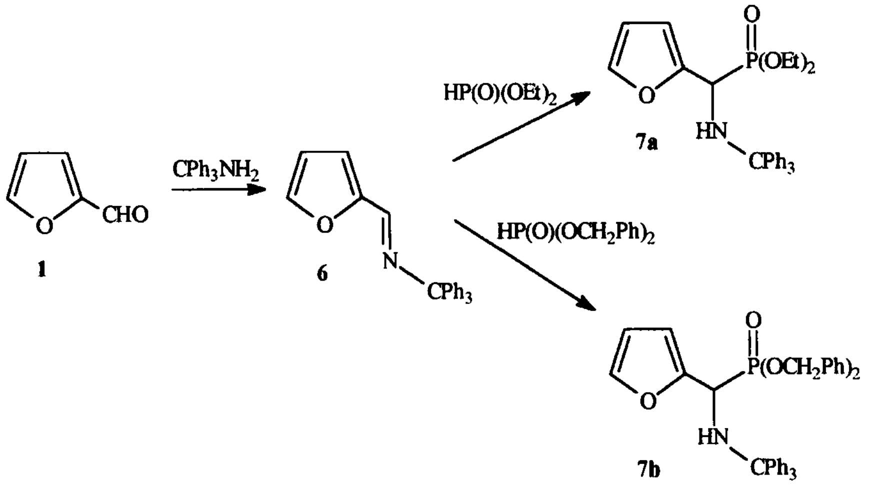


FIGURE 1 The relationship between the time of the reaction and the quantity of consummed hydrogen in the hydrogenolysis of **3**.



SCHEME 2

EXPERIMENTAL

All solvents were routinely distilled and dried prior to use. Benzylamine, diethyl and dibenzyl phosphites (Aldrich) were used as received. Furfural was distilled prior to use. Tritylamine was prepared following the published procedure[13].

Melting points were mesured on a Mel-Temp II apparatus. All spectra were recorded on a Specord 75 (IR), a Varian Gemini 200 (^1H NMR) and a Brucker 200 AC (^1H and ^{31}P NMR) spectrometers.

Elemental analyses were performed in the Laboratory of Microanalysis in the Centre of Molecular and Macromolecular Studies of Polish Academy of Science in Łódź.

N-Furfurylidenebenzylamine 2

Furfural (35 g, 0.36 mol) and benzylamine (39 g, 0.36 mol) were dissolved in toluene (73 mL). The mixture was stirred for 5 hours at room temperature. Then, the solvent was removed and the residue was distilled *in vacuo* to give 45.92 g (68%) of the imine **2**. b.p. 155–156°C/11 torr lit[14] b.p. 158–159°C/12 torr.

IR(film): 2850(CH); 1650(C=N); 1600, 1500, 1380($C=C_{arom,furan}$) cm^{-1}

^1H NMR($CDCl_3$, 200 MHz): δ 8.06(t,J=1.1 Hz, 1H,CH=N); 7.40-7.20(m,6H, CH_{arom}, H_{5fur}); 6.38(m, H_3); 6.25(dd,J=3.0 Hz and J=1.1 Hz, H_4); 4.76(d,J=1.1 Hz, CH_2Ph)

N-Furfurylidenetritylamine 6

Tritylamine (8.5 g, 33 mmol) and furfural (3.5 g, 37 mmol) were dissolved in methanol (40 mL). The mixture was refluxed for 12 hours, then evaporated and the solid residue was recrystallized from methanol to afford 7.78 g (70%) of the product **6** as white crystals. m.p. 135–137°C

IR(KBr): 1640(C=N); 1500, 1450, 1400(C-$C_{arom,furyl}$) cm^{-1}

^1H NMR($CDCl_3$,200 MHz): δ 7.67(s,CH=N); 7.56(m,H_5); 7.40-7.20(m,CH_{arom}); 6.81(m,H_3); 6.50(m,H_4)

($C_{24}H_{19}NO$) Found: C 85.58; H 6.08; N 4.25%
Calcd: C 85.18; H 5.96; N 4.14%

O,O'-Dibenzyl N-Benzylamino(2-Furyl)Methanephosphonate 3

Method A: N-Furfurylidenebenzylamine **2** (3.7 g, 20 mmol) was dissolved in toluene (50 mL) and dibenzyl phosphite (6.55 g, 25 mmol) was added. The mixture was stirred for 7 hours at 70°C, then for 12 hours at a room temperature. The solvent was removed in the vacuum and the residue dissolved in aceton (50 mL). To this solution oxalic acid (6.3 g, 50 mmol) in aceton (25 mL) was added; the formed precipitate was filtered and washed with aceton. The precipitate was then dissolved in 5% aqueous Na_2CO_3, the solution was extracted with chloroform. The organic layer was dried and evaporated. The residue was recrystallized to give 5.2 g(58%) of **3** as white crystals m.p. 71–72°C.

Method B: N-Furfurylidenebenzylamine (1.85 g, 10 mmol) was dissolved in acetonitrile (30 mL) and dibenzyl phosphite (3.93 g, 15 mmol) was added. Then, the mixture was heated to 80°C and several drops of trifluoroacetic acid were added. The mixture was stirred and refluxed for 6 hours, then it was evaporated. The residue was dissolved in 10% aqueous HCl-ethanol (4:1) and the solution was washed with ether (3 × 25 mL). The aqueous layer was then made alkaline and extracted with dichloromethane (5 × 25 mL). The organic layer was dried and evaporated. The residue was chromatographed on silica gel (AcOEt—hexane, 5:1) to give 2.9 g (65%) of **3** identical to the sample above, m.p. 71–72°C

IR(KBr): 3280(NH); 2990(CH); 1500, 1450, 1400, 1380(C-$C_{arom,fur.}$); 1250(P=O) cm^{-1}

^{31}P NMR($CDCl_3$, 81 MHz): δ 22.28

^1H NMR($CDCl_3$,200 MHz): δ 7.43(m,1H,H_{5fur}); 7.34-7.18(m, 15H, H_{arom}); 6.36(m,2H, H_3 and H_{4fur}); 5.22-5.01(part of ABX syst,$^2J_{HH}$=11.9 Hz, $^3J_{PH}$=8.1 Hz, $^3J_{PH}$=7.1 Hz, O-CH_2Ph); 5.03-4.78 (part of AMX syst, $^2J_{HH}$=11.8 Hz, $^3J_{PH}$=8.3 Hz, $^3J_{PH}$=7.3 Hz, O-CH_2Ph); 4.16(d,$^2J_{PH}$=22.4 Hz, 1H, CHP);

3.85(d,$^2J_{HH}$=13.4 Hz, 1H, N-CH$_2$); 3.60(d,$^2J_{HH}$=13.4 Hz, N-CH$_2$-, 1H); 2.20(s 1H, NH)

($C_{26}H_{26}NO_4P$) Found: C 69.50; H 5.81; N 3.36; P 7.02%
Calcd for: C 69.82; H 5.82; N 3.13; P 6.94%

O,O′-Dialkyl N-Tritylamino-(2-Furyl)Methanephosphonate 7a–b

N-Furfurylidenetritylamine (3.37 g, 10 mmol) and dialkyl phosphite (15 mmol) were mixed and placed in round-bottom flask. The mixture was stirred for 24 hours at 60°C. Then the crystaline product was isolated and recrystallized.

O,O′-Diethyl N-Tritylamino-(2-Furyl)Methanephosphonate 7a

Yield 56% (1.2 g), m.p. 139–141°C (benzene–light petroleum) IR(KBr): 3300(NH); 2940(CH); 1500, 1450, 1400, 1380(C-C$_{arom,fur}$); 1250(P-O) cm^{-1}

^{31}P NMR(CDCl$_3$, 81 MHz): δ 22.23

^{1}H NMR(CDCl$_3$, 200 MHz): δ 7.57-7.41(m, 7H, H$_{arom}$, H$_5$, H$_{3\ fur}$); 7.28-6.99(m, 11H, H$_{arom}$, H$_4$); 4.23(d, $^2J_{PH}$ = 24.8 Hz, 1H, CHP); 4.14-3.90(m, 2H, CH$_2$CH$_3$); 3.90-3.66(m, 2H, CH$_2$CH$_3$); 3.06-2.80(large s, 1H, NH); 1.36(t.J = 7.0 Hz, 3H, CH$_3$); 1.19(t.J = 7.0 Hz, 3H, CH$_3$)

($C_{28}H_{30}NO_4P$) Found: C 70.67; H 6.71; N 3.04; P 6.52%
Calcd for: C 70.73; H 6.31; N 2.95; P 6.52%

O,O′-Dibenzyl N-Tritylamino-(2-Furyl)Methanephosphonate 7b

Yield 63% (1.7 g), m.p. 108–112°C (methanol)

IR(KBr); 3280(NH); 2950(CH); 1500, 1400, 1380(C-C$_{fur,arom}$); 1250(P-O) cm^{-1}

^{31}P NMR(CDCl$_3$, 81 MHz): δ 23.08

^{1}H NMR(CDCl$_3$, 200 MHz): δ 7.46–7.02(m, 28H, H$_{arom}$, H$_{fur}$); 5.21–5.00 (Part of ABX syst, 2H, $^2J_{HH}$ = 11.7 Hz, $^2J_{PH}$ = 8.0 Hz, $^3J_{PH}$ = 7.6 Hz); 4.99–4.63(Part of AMX syst, 2H, $^2J_{HH}$ = 11.7 Hz, $^3J_{PH}$ = 8.1 Hz, $^3J_{PH}$ = 6.8 Hz); 4.30(d, $^2J_{PH}$ = 24.3 Hz, 1H, CHP).

($C_{38}H_{34}NO_4P$): Found: C 79.97; H 6.02; N 2.52; P 5.49%
Calcd for: C 80.14; H 5.98; N 2.46; P 5.45%

N-Benzylamino-(2-Furyl)Methanephosphonic Acid 4

The ester 3 (0.447 g, 1 mmol) was dissolved in methanol (20 mL) and the solution was placed in a round-bottom flask filled with hydrogen containing 10% Pd/C (1.06 g, 1 mmol). The mixture was stirred for 10 min at a room temperature. Then the mixture was filtrated, the filtrate was evaporated and the residue was recrystallized from methanol to give 0.232 g (87%) of **4** as white crystals, m.p. 239–242°C, lit[7] m.p. 235–240°C

IR(KBr): 3250(NH), 1500, 1450, 1380(C-C_{fur}); 1250(P=O) cm^{-1}

^{31}P NMR(CD_3SOCD_3, 81 MHz): δ 7.38

^1H NMR(CD_3SOCD_3, 200 MHz): δ 7.61(m, 1H, $H_{5\ fur}$); 7.42(m, 5H, H_{arom}); 6.75(m, 1H, $H_{3\ fur}$); 6.51(dd, J = 1.6 Hz i J = 2.9 Hz, 1H, $H_{4\ fur}$); 4.38(d, $^2J_{PH}$ = 17.2 Hz, 1H, CHP); 4.27(d, $^2J_{HH}$ = 19.3 Hz, 1H, CH_2 Ph); 4.03(d, $^2J_{HH}$ = 13.3 Hz, 1H, CH_2 Ph).

($C_{12}H_{14}NO_4P$): Found: C 53.66; H 5.80; N 5.16; P 10.64%
Calcd for: C 53.93; H 5.28; N 5.24; P 11.59%

(2-Furyl)Aminomethanephosphonic Acid 5

a) From ester 3: The ester **3** (0.447 g, 1 mmol) in methanol (20 mL) with 10% Pd/C (1.06, 1 mmol) stirred for 50 minutes. Work-up as above to obtain 0.160 (91%) of **5** as yellwish crystals not melting below 300°C(decomp.)

b) From acid 4: The acid **4** (0.134 g, 0.5 mmol) undergone the similar reaction but during 40 minutes followed by the same work-up to obtain 0.085 g (97%) of **5** identical to the sample above.

IR(KBr): 3200(NH_2); 1500, 1450, 1380(C=C_{fur});
1250(P=O) cm^{-1}

^{31}P NMR(CD_3OD, 81 MHz): δ 8.61

^1H NMR(CD_3OD, 200 MHz): δ 7.55(m, 1H, $H_{5\ fur}$); 6.67(m, 1H, $H_{3\ fur}$); 6.45(dd, J = 1.6 Hz and 2.8 Hz, 1H, $H_{4\ fur}$); 4.42(d, $^2J_{PH}$ = 16.7 Hz, 1H, CH)

($C_5H_8NO_4P$): Found: C 33.57; H 5.52; N 7.61; P 15.64%
Calcd for: C 33.91; H 4.54; N 7.91; P 17.49%

Acknowledgement

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