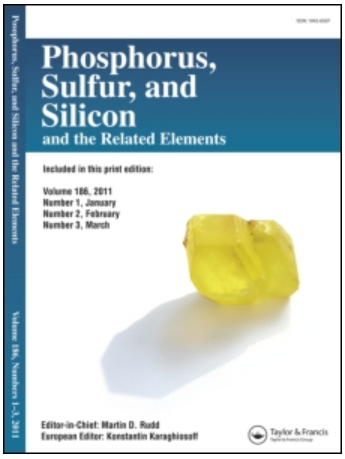

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SYNTHESIS AND ITS STEREOCHEMISTRY OF AMINOPHOSPHONIC ACIDS DERIVED FROM 5-HYDROXYMETHYLFURFURAL

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Some dialkyl N-substituted-α-amino-α-furylmethanephosphonates were synthesized via the addition of dialkyl phosphites to corresponding imines in mild conditions in a short time. When an imine is chirally N-substituted the reaction is stereoselective. Stereochemical aspects of the reaction in the light of Cram rules is discussed in this paper.

Keywords: 5-Hydroxymethylfurfural; imine; stereoselective addition; aminofurfurylphosphonates

After the first preparation of aminoalkanephosphonic acids and their esters[1–4], some similar derivatives were prepared starting from furfural[5,6] and also from thiophene and pyrrol aldehydes by sonochemical activation[7].

Considering the known application of such compound in the fields of medicine and agriculture[8] as well as the biological activity of 2,5-disubstituted furan compounds[9], we tried to develop a general synthesis of 2,5-disubstituted furanic derivatives of α-aminophosphonic acid from 5-hydroxymethylfurfural (HMF) as a commercial starting material **1**.

After the conversion of HMF into N-substituted imines **2** following a modified Garrigues' method[10], the conversion of **2** into α-aminophosphonic esters **4** was performed by the addition reaction of phosphite **3** to an azomethine bond. The conversion rate did not exceed 75% after 72 hours of a reaction at 60°C

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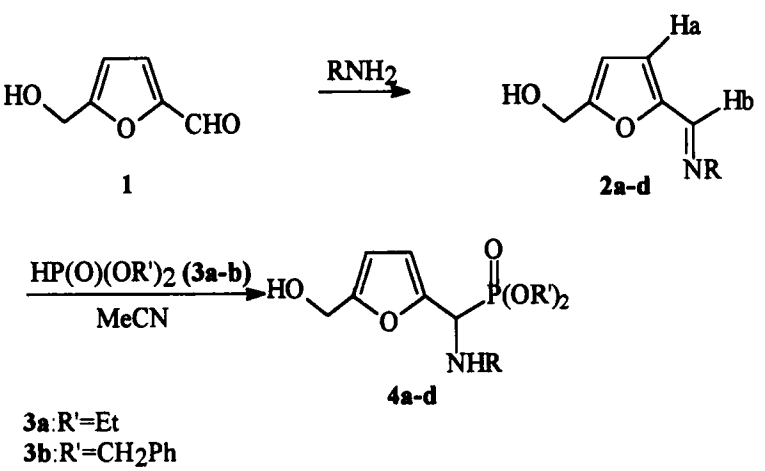
TABLE I Synthesis of Dialkyl amino-2-(5-hydroxymethyl)furylmethylphosphonates

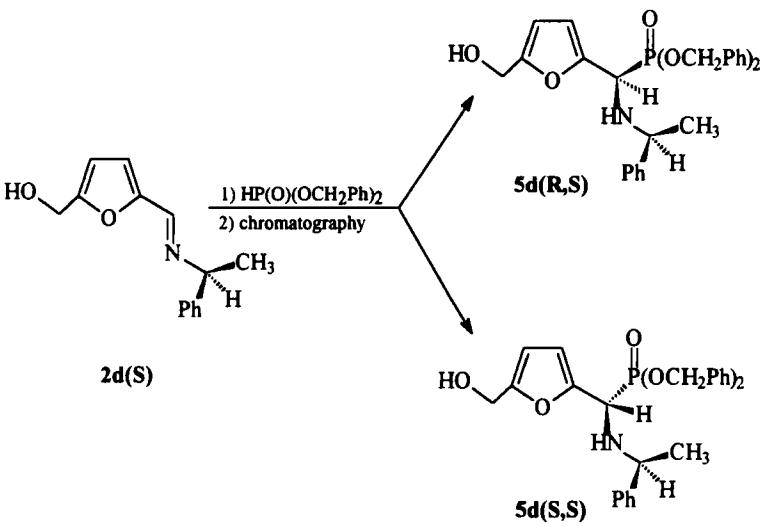
Entry	*Symbol of imine*	*R*	*R'*	*Molar ratio 2:*	*time [hrs]*	*Conditions T[°C]*	*Catalyst*	*Conversion rate [%]*	*Yield of 4 [%]*
1	2a	CH_2Ph	CH_2CH_3	1:1	72	60	None	75	42
2	2a	CH_2Ph	CH_2CH_3	1:1.5	48	60	None	100	65
3	2a	CH_2Ph	CH_2CH_3	1:1.5	12	60	CF_3COOH	100	66
4	2a	CH_2Ph	CH_2CH_3	1:1.5	6	80	CF_3COOH	100	71
5	2b	CH_2Fur	CH_2CH_3	1:1.5	6	80	CF_3COOH	100	67
6	2c	$C(CH_3)_3$	CH_2CH_3	1:1.5	6	80	CF_3COOH	100	90
7	2d	$CH(CH_3)Ph$	CH_2CH_3	1:1.5	6	80	CF_3COOH	100	69
8	2d(R)	(R)-$CH(CH_3)Ph$	CH_2CH_3	1:1.5	48	60	None	100	58
9	2d(S)	(S)-$CH(CH_3)Ph$	CH_2CH_3	1:1.5	48	60	None	100	55
10	2d(R)	(R)-$CH(CH_3)Ph$	CH_2CH_3	1:1.5	6	80	CF_3COOH	100	70
11	2d(S)	(S)-$CH(CH_3)Ph$	CH_2CH_3	1:1.5	6	80	CF_3COOH	100	69
12	2d(S)	(S)-$CH(CH_3)Ph$	CH_2Ph	1:1.5	6	80	CF_3COOH	100	70

with an equimolar ratio of reagents, even with an excess of imine **2**. An excess of phosphite **3** led to 100% conversion rate in 48 hours at 60°C. The presence of a catalytic amount of trifluoroacetic acid at 80°C permitted to obtain **4** in fair yields after 6 hours of heating (Table I) (Scheme I).

The results obtained for **2d** showing a diastereoisomeric mixture of 2:1 ratio, encouraged us to test the steroselectivity of a phosphite addition to chiral imines derived from HMF, with or without an acidic catalyst, using **2d(R)** or **2d(S)** enantiomer. Till now, several papers concerning the stereoselective synthesis of aminophosphonic acids were published[11–18] and they present some very interesting results but none of them concerns furan derivatives.



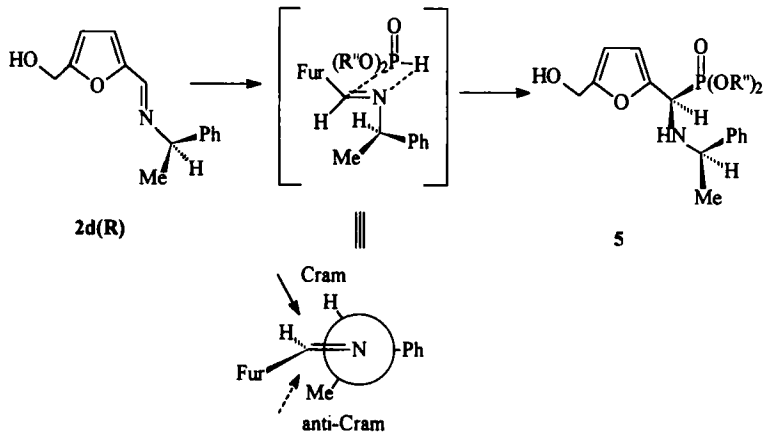
SCHEME I



SCHEME II

In our case, the addition of diethyl phosphite **3a** led to a diastereoisomeric mixture of **4d** in 2:1 ratio, according to NMR data (peaks at 4.50 and 4.55 in ^{1}H NMR). After unproductive attempts of separation of diethyl derivative diastereoisomers, we performed the addition of dibenzyl phosphite **3b** to chiral imines **2d(R)** and **2d(S)**; this reaction gave products in 68% yield and diastereoisomers were successfully separated by column chromatography. The weight ratio was determined as 2:1 of separated isomers from both **2d(R)** and **2d(S)** imines confirming the previous stereoselectivity estimations by NMR calculations (Scheme II).

The absolute configuration of such isolated non crystalline diastereoisomers was not determined. But as imines present for its imino double bond an anti configuration determined by NOE measurements for **2a** (Ha = 5.5%, Hb = 5%) and for **2d** (Ha = 5.4%, Hb = 5.8%), we can expect the major formation of compound **5**, if the reaction of dialkyl phosphonate follows the Cram addition to the imino double bond of **2d(R)** according to preceding observations[19] (Scheme III). Our method, although its stereoselectivity is not very high, seems to us to be of interest, because of an easy work-up and inexpensive starting materials. As the stereoselectivity depends on the chiral substitutent, perspectively it is to search for an appropriate N-substituent to increase the selectivity. This problem is still under study.



SCHEME III

EXPERIMENTAL

All solvents (Prolabo) were routinely distilled and dried. All amines and phosphites (Aldrich) were used as received. All spectra were recorded on a Brucker 200 (^{1}H and ^{31}P NMR) and an Elmer Perkin (IR) spectrometers.

N-(5-hydroxymethyl)furfurylideneamines **2a–d**

5-Hydroxymethylfurfural (1.26 g, 10 mmol) and amine (10 mmol) were mixed together and left for several hours to react. Then the mixture was dissolved in ethanol and evaporated azeotropically to remove water. The residue was recrystallized from ether—hexane (5:1) or chromatographed on alumina (AcOEt).

N-(5-hydroxymethyl)furfurylidenebenzylamine **(2a)**

Y = 86%, mp = 56–57°C

Elem.anal: found: C-72.61; H-6,19; N-6.55% Calc: C-72.54; H-6.09; N-6.51%

IR (KBr): 3400 (OH); 1640 (CH=N); 1600, 1580, 1490 (C-Carom) cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.08 (t, J = 1.1 Hz, CH=N); 7.21–7.39 (m, 5H, Charom), 6.70(d, J = 3.3 Hz, =CHCH=), 6.33(d, J = 3.3 Hz, =CHCH=), 4.77 (d, J = 1.1 Hz, CH_2Ph), 4.60 (s, CH_2OH), 2.90 (s, OH).

N-(5-hydroxymethyl)furfurylidenefurfurylamine **(2b)**

Y = 68%, mp = 68–69°C

Elem.anal: found: C-64.44; H-5.63; N-6.83% Calc: C-64.38; H-5.40; N-6.83%

IR (KBr): 3400 (OH); 1630 (CH=N); 1500, 1480, 1380 (C-Carom) cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz): δ 8.06 (s, CH=N), 7.38 (d, J = 1.3 Hz, H5), 6.72 (d, J = 3.3 Hz, =CHCH=), 6.38 (d, J = 3.3 Hz, =CHCH=), 6.35 (m, H3), 6.27 (dd, J = 3.0 Hz and J = 1.1 Hz, H4), 4.71 (s, CH_2Fur), 4.64 (s, CH_2OH), 2.17 (s, OH)

N-(5-hydroxymethyl)furfurylidene-tert-butylylamine **(2c)**

Y = 91%

Elem.anal: found: C-64.64; H-8.32; N-7.53% Calc: C-66.27; H-8.34; N-7.73%

IR (KBr): 3300 (OH), 1640 (CH=N), 1580, 1530, 1380 (C-Cfur) cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz): δ 8.08 (s, CH=N), 6.73 (d, J = 3.3 Hz, =CHCH=), 6.37 (d, J = 3.3 Hz, =CHCH=), 4.90 (s, OH), 4.65 (s, CH_2OH), 1.25 (s, CH_3)

N-(5-hydroxymethyl)furfurylidene-α-methylbenzylamine **(2d)**

Y = 75%, mp = 76–77°C

N-(5-hydroxymethyl)furfurylidene-(R)-(+)-α-methylbenzylamine **(2d(R))**

Y = 82%, yellow oil

N-(5-hydroxymethyl)furfurylidene-(S)-(−)-α-methylbenzylamine **(2d(S))**

Y = 80%, yellow oil

Elem.anal: found: C-73.15; H-6,67; N-6.14% Calctd: C-73.34; H-6.59; N-6.11%

IR (KBr): 3400 (OH); 1640 (CH=N); 1600, 1580, 1490 (C-Carom) cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz): δ 8.08 (d, J = 0.3 Hz, CH=N), 7.40-7.20 (m, 5H, Charom), 6.67 (d, J = 3.3 Hz, =CHCH=), 6.34 (d, J = 3.3 Hz, =CHCH=), 4.63 (s, CH_2OH), 4.51 (dquart, J = 6.6 Hz and J = 0.3 Hz, CH), 2.85 (s, OH), 1.62 (d, J = 6. Hz, CH_3).

Dialkyl amino-2-(5-hydroxymethyl)furylmethylphosphonates **4** *and* **5**

To the solution of imine **2** (10 mmol) in acetonitrile (25 mL), dialkyl phosphite **3** (15 mmol) and 10 drops of trifluoroacetic acid were added. After stirring at 80°C for 6 hrs; the mixture was evaporated. The residue was dissolved in 10% aqueous hydrochloric acid and ethanol (4:1) then washed with ether (3 × 25 mL); the aqueous layer was then made alkaline and extracted with dichloromethane (5 × 25 mL). Dichloromethane layers were dried and evaporated; the residue was chromatographed on silica gel (AcOEt-hexane, 5:1) to give a pure ester. The separation of diastereoisomers of 4db was carried out chromatographically on silica gel (AcOEt-hexane, 4:1).

O,O'-Diethyl 1-(N-benzylamino)-2-(5-hydroxymethyl)furylmethylphosphonate **(4a)**

Y = 71% (yellow oil)

Elem. anal. Found: C-57.36; H-6.50; N-4.35; P-7.54%

Calc: C-57.78; H-6.85; N-3.96; P-8.77%

IR (neat): 3350 (OH); 1600, 1490 (C-Carom); 1450, 1380 (C-Cfur); 1230 (P═O) cm^{-1}

^{31}P-NMR ($CDCl_3$, 81 MHz): δ 21.42 ^{1}H-NMR($CDCl_3$, 200 MHz): δ 7.31 (m, 5H, Charom), 6.28 (m, 2H, ═CHCH═), 4.56 (s, CH_2OH), 4.19 (dquart, J = 2.7 and 4.4 Hz, CH_2CH_3), 3.92 (dquart, J = 2.7 and 4.4 Hz, CH_2CH_3), 4.02 (d, $^{2}J_{HP}$ = 22.4 Hz, CHP), 3.87 (d, $^{2}J_{HH}$ = 13.3 Hz, CH_2N), 3.61 (d, $^{2}J_{HH}$ = 13.3 Hz, CH_2N), 3.05 (m, OH and NH), 1.32 (t, J = 7.1 Hz, CH_2CH_3), 1.18 (t, J = 7.1 Hz, CH_2CH_3).

O,O'-Diethyl 1-(N-furfurylamino)-2-(5-hydroxymethyl)furylmethylphosphonate **4b**

Y = 67% (yellow oil)

Elem. anal. Found: C-51.01; H-6.45; N-3.85; P-7.73% Calctd: C-52.48; H-6.46; N-4.08; P-9.02%

IR (neat): 3350 (OH); 1490, 1450, 1380 (C-Cfur); 1230 (P═O) cm^{-1}

^{31}P-NMR ($CDCl_3$, 81 MHz): δ 21.15 ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.34 (t, J = 1.0 Hz, 1H, Chfur), 6.32 (m, 2H, Chfur; 6.24 (d, J = 3.1 Hz, Chfur), 6.16 (d, J = 3.1 Hz, Chfur), 4.08 (d, $^{2}J_{HP}$ = 21.4 Hz, CHP), 4.24-3.90 (m, 4H, CH_2CH_3), 3.86 (d, $^{2}J_{HH}$ = 13.3 Hz, CH_2N), 3.75 (d, $^{2}J_{HH}$ = 13.3 Hz, CH_2N), 2.96 (m, OH and NH), 1.31 (t, J = 7.0 Hz, CH_2CH_3), 1.20 (t, J = 7.0 Hz, CH_2CH_3).

O,O'-Diethyl 1-(N-tert-butylamino)-2-(5-hydroxymethyl)furylmethylphosphonate **4c**

Y = 90% (yellow oil)

Elem. anal. Found: C-51.27; H-8.15; N-4.29; P-9.03%

Calc: C-52.66; H-8.21; N-4.39; P-9.70%

IR (neat): 3350 (OH); 2960 ($CH_{stretch}$); 1670 (NH); 1540, 1430, 1385 (C-Cfur); 1225 (P═O) cm^{-1}

^{31}P-NMR ($CDCl_3$, 81 MHz), δ 21.85. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 6.23 (m, 2H, ═CHCH═), 4.56 (s, CH_2OH), 4.20 (d, $^{2}J_{HP}$ = 21.4 Hz, CHP); 3.36 (s, OH), 4.08 − 3.82 (m, 4H, CH_2CH_3), 1.68 (s, NH), 1.32 (t, J = 7.0 Hz, CH_2CH_3), 1.19 (t, J = 7.0 Hz, CH_2CH_3), 1.02 (s, 9H, CH_3).

O,O'-Diethyl 1-(N-α-methylbenzylamino)-2-(5-hydroxymethyl)furylmethylphosphonate **4d**

(signals of product in minority are presented in italics)

Y = 69%

Elem. anal. Found: C-55.89; H-7.41; N-3.51; P-8.47%

Calc: C-58.85; H-7.13; N-3.81; P-8.43%

IR (neat): 3350 (OH); 1600, 1490 (C-Carom); 1450, 1380 (C-Cfur); 1230 (P═O) cm^{-1}

^{31}P-NMR ($CDCl_3$, 81 MHz): δ *21.74* and 22.17. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.33-7.20 (m, 5H, Charom), *6.23* and 6.14 (m, 2H, =CHCH=), *4.55* and 4.50 (s, CH_2OH), 4.26-3.62 (m, 8H, CH_2CH_3, CHPh, CHP, NH and OH), 1.35 (m, 3H, CH_2CH_3), 1.19 (m, 6H, CH_2CH_3, $CHCH_3$).

O,O'-Dibenzyl 1-(N-(S)-(-)-α-methylbenzylamino)-2-(5-hydroxymethyl)furylmethylphosphonate **5d**

Major product: Y = 47%

Elem. anal. Found: C-68.00; H-7.6.10; N-2.78; P-6.37%

Calc: C-68.42; H-6.15; N-2.85; P-6.30%

$[\alpha]_D^{20}$ = +6.33° (c = 1.07, MeOH).

IR (neat): 3380 (OH); 3060, 3020 (CH); 1600, 1500, 1450, (C-Cfur, C-Carom); 1250 (P=O) cm^{-1}

^{31}P-NMR ($CDCl_3$, 81 MHz): δ 22.82. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.37-7.18 (m, 15H, CHarom), 6.15 (m, 2H, =CHCH=), 5.24-5.02 (Part of ABX syst, $^{2}J_{HH}$ = 11.8 Hz, $^{3}J_{HP}$ = 8.4 Hz, $^{3}J_{HP}$ = 7.2 Hz, CH_2Ph), 5.02-4.79 (Part of ABX syst, $^{2}J_{HH}$ = 11.8 Hz, $^{3}J_{HP}$ = 8.2 Hz, $^{3}J_{HP}$ = 7.8 Hz, CH_2Ph), 4.46 (s, CH_2OH), 4.19 (d, $^{2}J_{HP}$ = 21.6 Hz, CHP); 3.86 (quart, J = 6.5 Hz, $CHCH_3$), 2.7-2.1 (large s, NH and OH), 1.25 (d, J = 6.5 Hz, $CHCH_3$)

Minor product: Y = 23%

$[\alpha]_D^{20}$ = −26.95° (c = 0.98, MeOH).

^{31}P-NMR ($CDCl_3$, 81 MHz): δ 22.39. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.34-7.13 (m, 15H, CHarom), 6.23 (d, J = 3.0 Hz, =CHCH=); 6.16 (dd, $^{3}J_{HH}$ = 3.2 Hz and $^{4}J_{HP}$ = 1.7 Hz, =CHCH=), 5.28-5.03 (Part of ABX syst, $^{2}J_{HH}$ = 12.7 Hz, $^{3}J_{HP}$ = 8.0 Hz, $^{3}J_{HP}$ = 6.7 Hz, CH_2Ph), 4.49-4.70 (Part of ABX syst, $^{2}J_{HH}$ = 12.7 Hz, $^{3}J_{HP}$ = 8.0 Hz, $^{3}J_{HP}$ = 6.8 Hz, CH_2Ph), 4.54 (s, CH_2OH), 3.90 (d, $^{2}J_{HP}$ = 21.6 Hz, CHP); 3.67 (dquart, $^{3}J_{HH}$ = 6.5 Hz and $^{4}J_{HP}$ = 1.1 Hz, $CHCH_3$), 2.7-2.1 (large s, NH and OH), 1.26 (d, J = 6.8 Hz, $CHCH_3$)

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