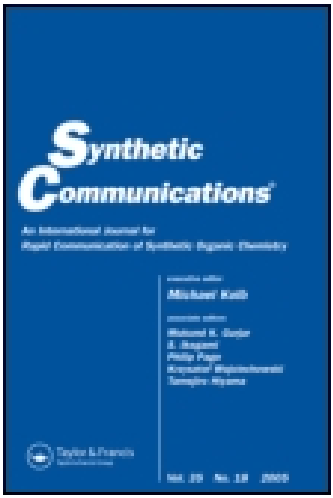

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SYNTHESIS OF NOVEL PYRONE, CHROMONE AND COUMARIN DERIVATIVES OF AMINOMETHANEPHOSPHONIC ACID

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Abstract: Novel pyrone, chromone and coumarin derivatives of aminomethanephosphonic acid were obtained in a one-step process, by treatment of a mixture of heterocyclic aldehyde and amine with tris(trimethylsilyl)phosphite, and a subsequent solvolysis of the formed silylated product with methanol.

Phosphonic analogs of various aminoacids, known as „aminophosphonic acids" are presently recognized as a very important class of compounds, due to their great biological activity [1]. Chemical literature concerning synthetic methods for preparation of the aminophosphonic acids is now very extensive. So far, a large number of the phosphonic analogs of most natural aminoacids, some peptides and related compounds are synthesized and characterized [2].

Aminophosphonic acids containing oxygen heterocycles, such as pyrones, chromones and coumarins are not described in literature [4]. These derivatives are very interesting and would have a potential biological activity, due to the fact that

various oxygen heterocycles (i.e. pyrones, chromones and coumarins) have a widespread occurence amongst the vegetable kingdom.

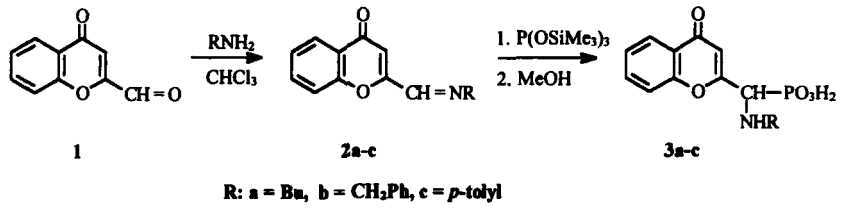
We tried to obtain several chromone derivatives of aminomethanephosphonic acid by an application of some classical methods of synthesis of aminophosphonates toward chromone aldehydes. These methods are depended mainly on an addition of dialkyl esters of phosphorous acids to imines (formed from the corresponding aldehydes and primary amines). In addition, the amidoalkylation reaction [3] and its modifications are frequently used for synthesis of various aminophosphonates. The mentioned methods worked well only in the case of 3-formylchromones [4]. Application of these methods for synthesis with other heterocyclic aldehydes, i.e. 2-formylpyrones, 2-formylchromones and 4-formylcoumarins, has failed completely.

We found, that the title acids can be easily obtained in a one-pot synthesis, by using silylated ester of phosphorous acid, namely $P(OSiMe_3)_3$, as a reagent of choice. When the imine (obtained *in situ*) was treated in chloroform solution with $P(OSiMe_3)_3$, the corresponding silylated aminophosphonate ester was formed. The formed silylated esters were not isolated, but transformed immediately to the desired aminophosphonic acids, by means of an addition of methanol or ethanol. The final products **3**, **5** and **7** were separated out as the amorphous powders from reaction mixture and collected by filtration. The products were obtained in a pure state.

The advantage of this method is as follows: The reaction of $P(OSiMe_3)_3$ with aldimines proceeds smoothly and clean at room temperature. The desired silylated

agent, i.e. $P(OSiMe_3)_3$ can be easily obtained *in situ*, from commercially available reagents, namely; trimethyl phosphite and Me_3SiBr.

The synthesis of new chromone-2, coumarin-4 and pyrone-2 derivatives of the aminomethanephosphonic acid is shown in Schemes 1-3, respectively.



1 **2a-c** **3a-c**

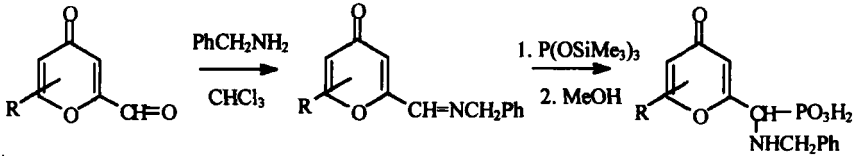
R: a = Bu, b = CH_2Ph, c = *p*-tolyl

Scheme 1

4a,b **R: a = H, b,c = OMe** **5a,b,c**

R': a, b = CH_2Ph, c = Bu

Scheme 2



6a-c **7a-c**

R: a = 3-OMe, b = 5-OMe, c = 5-OCH_2Ph

Scheme 3

Yields of the aminophosphonic acids (**3**, **5** and **7**) were moderate, due to a slow crystallization of these acids from reaction mixture.

EXPERIMENTAL

NMR spectra were recorded on a Bruker Avance TM DRX 300 MHz in DMSO-d_6 or D_2O solutions, using 300.13 MHz for ^1H NMR and 121.51 MHz for ^{31}P NMR spectra. Elemental analyses were done in the laboratory of Instrumental Analysis, in the Institute. Melting points were measured on a Digital Melting Point Apparatus Electrothermal 9200, and were uncorrected.

All commercially available reagents were used as received from the supplier (Aldrich Company). 2-Formylchromone (**1**) was prepared from methyl chromone-2-carboxylate, according to the published method [5]. 2-Formylpyrones (**6a-c**) were synthesized according to the described methods [6, 7]. 4-Formylcoumarins (**4a,b**) were obtained by using the procedures published in [8, 9].

Synthesis of Chromone, Coumarin and Pyrone Derivatives of Aminomethanephosphonic Acid; General Procedure:

Heterocyclic aldehyde (**1**, **4** or **6**) (3 mmol) was dissolved in dry, freshly distilled chloroform (50 mL) and the appropriate amine (3 mmol) was added. The solution was stirred for 24 hr in the presence of anh. sodium carbonate (~ 1g). Next day the mixture was filtered and to the filtrate, containing aldimine *in situ*, the fresh by prepared solution of $P(OSiMe_3)_3$ in dry chloroform was added. [The $P(OSiMe_3)_3$ was obtained by dissolving $P(OMe)_3$ (0.38g, 3 mmol) and Me_3SiBr (1.5g, 10 mmol) in dry chloroform (50 mL), and the solution was left for 24 hr]. The final mixture was kept for 24 hr at room temperature and the solvent was evaporated. The oily residue was was dissolved in methanol or ethanol (10 mL) and cooled. After several hours, the precipitated aminophosphonic acid (**3**, **5** or **7**) was collected by filtration, washed with diethyl ether and dried.

Chromone-2-[α-(N-butylamino)]methanephosphonic Acid (**3a**): Yield: 21%. M.p. 143-145°C(dec.). ^1H NMR(DMSO): 8.00(d, 1H, J=7.8 Hz, H-8, chrom.), 7.73(m, 2H, chrom.), 7.46(m, 1H, chrom.), 6.59(s, 1H, H-3, chrom.), 4.33(d, 1H, J=16.56 Hz, CH-P), 2.95(m, 2H, NCH_2), 1.63(m, 2H, CH_2), 1.18(m, 2H, CH_2), 0.72(t, 3H, J=7.4 Hz, CH_3). ^{31}P NMR(DMSO): 4.444(s). Anal. ($C_{14}H_{18}NO_5P$) (311.265) Found: N 4.32, P 9.87, calc. N 4.50, P 9.95.

Chromone-2-[α-(N-benzylamino)]methanephosphonic Acid (**3b**): Yield: 36%. M.p. 161-163°C(dec.). ^1H NMR(DMSO): 8.01(d, 1H, J=7.9 Hz, H-8, chrom.), 7.75(m, 1H, chrom.), 7.73(1H, chrom.), 7.61-7.23(m, 7H, arom.), 6.48(s, 1H, H-3, chrom.), 4.21(bs, 2H, NCH_2Ph), 4.09(d, 1H, J=17.6 Hz, CH-P). ^{31}P NMR(DMSO): 7.329(s). Anal. ($C_{17}H_{16}NO_5P$) (345.279) Found: N 3.92, P 9.15, calc. N 4.06, P 8.97.

Chromone-2-[α-(N-p-tolylamino)]methanephosphonic Acid (**3c**): Yield: 24%. M.p. 179-182°C(dec.). ^1H NMR(DMSO): 8.00(d, 1H, J= 7.9 Hz, H-8, chrom.),

7.78(t, 1H, J= 8.6 Hz, chrom.), 7.60(d, 1H, J= 8.3 Hz, chrom.), 7.46(t, 1H, J= 7.3 Hz, chrom.), 6.89(d, 2H, J= 8.25 Hz, tolyl), 6.71(d, 2H, J= 8.3 Hz, tolyl), 6.49(d, 1H, J= 2.85 Hz, H-3, chrom.), 4.66(d, 1H, J=24.57 Hz, CH-P), 2.11(s, 3H, $ArCH_3$ ^{31}P NMR(DMSO): 14.787(s). Anal. ($C_{17}H_{16}NO_5P$) (345.279) Found: N 4.01, P 8.88, calc. N 4.06, P 8.97.

Coumarin-4-[α-(N-benzylamino)]-methanephosphonic Acid (**5a**): Yield: 53%. M.p. 181-183°C. ^1H NMR(DMSO): 7.60-7.15(m, 9H, arom), 6.93(s, 1H, H-3, coum.), 4.57(d, 1H, J= 12.6 Hz, CH-P), 4.23(bs, 2H, NCH_2Ph). ^{31}P NMR (DMSO): 6.749(s). Anal. ($C_{17}H_{16}NO_5P$) (345.279) Found: N 3.90, P 9.02, calc. N 4.06, P 8.97.

7-Methoxy-Coumarin-4-[α-(N-benzylamino)]-methanephosphonic Acid (**5b**): Yield: 34%. M.p. 221-224°C. ^1H NMR(DMSO): 7.46-7.17(m, 6H, arom), 6.96(s, 1H, arom), 6.84(m, 1H, arom), 6.72(s, 1H, H-3, coum.), 4.48(d, 1H, J=17.4 Hz, CH-P), 4.20(bs, 2H, NCH_2Ph), 3.83(s, 3H, $ArOCH_3$). ^{31}P NMR (DMSO): 7.004(s). Anal. ($C_{18}H_{18}NO_6P$) (375.305) Found: N 3.63, P 8.30, calc. N 3.73, P 8.25.

7-Methoxy-Coumarin-4-[α-(N-butylamino)]-methanephosphonic Acid (**5c**): Yield: 25%. M.p. 190-195°C(dec.). ^1H NMR(DMSO): 7.91(d, 1H, J= 8.9 Hz, H-8, coum.), 6.93(m, 2H, coum.), 6.69(s, 1H, H-3, coum.), 4.73(d, 1H, J= 16.9 Hz, CH-P), 3.84(s, 3H, $ArOCH_3$), 2.98(m, 2H, NCH_2), 1.61(m, 2H, CH_2), 1.18(m, 2H, CH_2), 0.77(t, 3H, J= 7.3 Hz, CH_3). ^{31}P NMR (DMSO): 5.599(s). Anal. ($C_{15}H_{20}NO_6P$) (341.291). Found: N 3.96, P 9.12, calc. N 4.10, P 9.08.

3-Methoxy-4-Oxo-4H-Pyran-2-[α-(N-benzylamino)]-methanephosphonic Acid (**7a**): Yield: 36%. M.p. 170-171°C(dec.). ^1H NMR(DMSO): 8.03(d, 1H, J=5.6 Hz, H-6, pyrone), 7.45(m, 2H, arom.), 7.30(m, 3H, arom.), 6.31(d, 1H, J=5.6 Hz, H-5, pyrone),4.35(d, 1H, J=17.6 Hz, CH-P), 4.08(dd, 2H, $NHCH_2Ph$, J=13.5 Hz), 3.60(s, 3H, OCH_3). ^{31}P NMR(DMSO): 6.217(s). Anal. ($C_{14}H_{16}NO_6P$) (325.249) Found: N 4.17, P 9.41, calc. N 4.31, P 9.52.

5-Methoxy-4-Oxo-4H-Pyran-2-[α-(N-benzylamino)]-methanephosphonic Acid (**7b**): Yield: 41%. M.p. 180-182°C(dec.). ^1H NMR(DMSO): 8.01(s, 1H, H-6, pyrone), 7.45(m, 2H, arom.), 7.31(m, 3H, arom.), 6.50(s, 1H, H-3, pyrone), 4.10(dd, 2H, NCH_2Ph, J=13.5 Hz), 3.88(d, 1H, J= 17.55 Hz, CH-P), 3.62(s, 3H, OCH_3). ^{31}P NMR(DMSO): 6.779(s). Anal. ($C_{14}H_{16}NO_6P$) (325.249) Found: N 4.15, P 9.39, calc. N 4.31, P 9.52.

5-Benzyloxy-4-Oxo-4H-Pyran-2-[α-(N-benzylamino)]-methanephosphonic Acid (**7c**): Yield: 59%. M.p. 151-153°C(dec.). ^1H NMR(DMSO): 8.10(s, 1H, H-6, pyrone), 7.36(m, 10H, 2xPh), 6.55(s, 1H, H-3, pyrone), 4.89(s, 2H, OCH_2Ph), 4.11(m, 2H, NCH_2Ph), 3.89(d, 1H, J= 17.55 Hz, CH-P). ^{31}P NMR(DMSO): 6.566(s). Anal. ($C_{20}H_{20}NO_6P$) (401.341) Found: N 3.21, P 7.64, calc. N 3.49, P 7.72.

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