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Synthesis of diethyl 2-thioxo-1,2,3,4-tetrahydro- and hexahydropyrimidine-5-phosphonates

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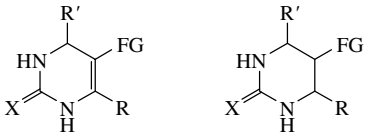
The reaction of sodium enolate of diethyl (2-oxoprop-1-yl)phosphonate with *N*-(1-tosylprop-1-yl)thiourea results in the stereoselective formation of diethyl (4*R,5*R**,6*R**)-6-ethyl-4-hydroxy-4-methyl-2-thioxohexahydropyrimidine-5-phosphonate, which is transformed into diethyl 4-ethyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-phosphonate and diethyl (4*R**,5*S**,6*R**)-4-ethyl-6-methyl-2-thioxohexahydropyrimidine-5-phosphonate by acid-catalysed dehydration and stereoselective reduction with $NaBH_4$–CF_3COOH, respectively.**

Hydrogenated pyrimidin-2-ones/thiones bearing functional groups at the 5-position (*e.g.*, **1** and **2**) are of interest because of their biological activity. For instance, 4-aryl-2-oxo(or 2-thioxo)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid esters (**1** R′ = aryl, FG = COOR″), Biginelli compounds, are inhibitors of kinesin Eg5,[1] selective antagonists of α_{1a} adrenoceptors;[2] they possess high antihypertensive activity.[3,4]



1 **2**

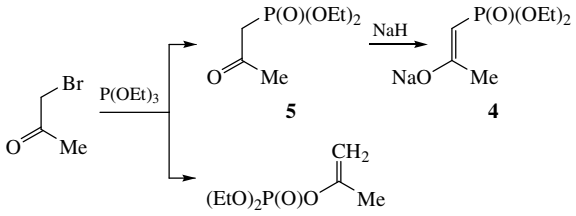
X = O, S

FG = functional group

Pyrimidines **1** bearing carboxamide (**1** FG = CONR″R‴),[5] carboxyl (**1** FG = COOH),[6] cyano (**1** FG = CN),[7] acyl (**1** FG = = COR″),[8] nitro (**1** FG = NO_2),[9] sulfonyl (**1** FG = SO_2R'')[10] groups and halogen atoms[11] at C(5) are also compounds with potential biological activity. However, 1,2,3,4-tetrahydro- and hexahydropyrimidin-2-ones/thiones **1** and **2**, respectively, bearing phosphorus atoms at the 5-position remain poorly studied. Gong *et al.*[12] described the synthesis of 4-aryl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-phosphonic acid esters [**1** R′ = aryl, FG = $PO(OEt)_2$] by the reaction of urea with diethyl (2-oxoprop-1-yl)phosphonate and aromatic aldehydes in the presence of ytterbium triflate. Thus, the development of general synthetic methods for the preparation of pyrimidines with organophosphorus moieties at the C(5) atom, particularly dialkoxyphosphoryl groups, is of considerable interest.

Diethyl 6-ethyl-4-hydroxy-4-methyl-2-thioxohexahydropyrimidine-5-phosphonate **3** served as a key heterocyclic compound. It was obtained by the reaction of enolates of α-functionalised aldehydes or ketones with α-tosyl-substituted ureas/thioureas.[13,14] We used sodium enolate **4** of diethyl (2-oxoprop-1-yl)phosphonate **5** as a nucleophile for the preparation of pyrimidine **3**. Compound **5** was obtained as described elsewhere[15,16] by heating bromoacetone with triethylphosphite at 165–170 °C without solvent (Scheme 1).

A considerable amount of ester **6** (up to 20% according to ^{1}H NMR data) forms in this reaction along with phosphonate **5**. The presence of **6** in **5** strongly decreased the yield of pyrimidine **3**. Therefore, it was necessary to develop a convenient procedure to purify phosphonate **5**. This problem was solved by the treatment of a diethyl ether solution of a mixture of **5** and **6** with a known ratio of the components by a calculated amount of NaH.† Precipitated sodium enolate **4** was filtered off, dried and used in further reactions without additional purification.‡



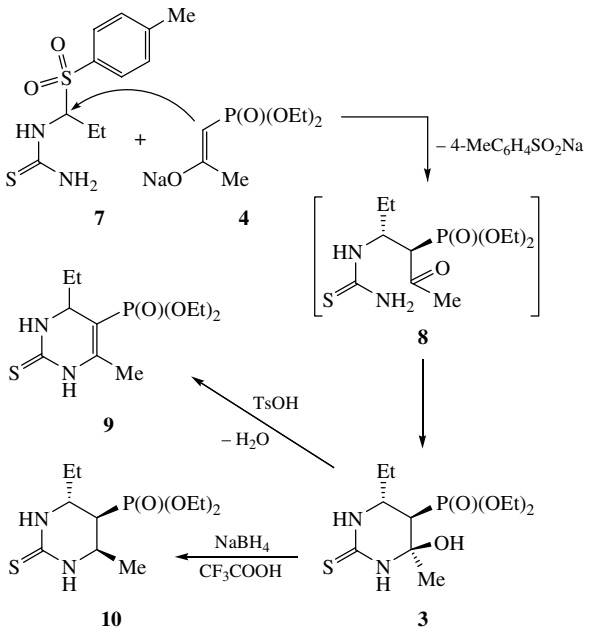
Scheme 1

We found that enolate **4** reacted with readily available *N*-(1-tosylprop-1-yl)thiourea **7**[14] in dry THF for 8 h at room temperature to produce expected hydroxypyrimidine **3** in 81% yield (Scheme 2).§

Note that both stages of compound **3** formation (nucleophilic substitution of tosyl group in **7** and subsequent heterocyclization of intermediate thiourea **8**) proceeded with high diastereoselectivity. The ^{1}H NMR spectrum of crude **3** showed a single diastereomer. The vicinal coupling constants of 6-H with 5-H and N(1)H¶ in this diastereomer ($J_{5\text{-H,6-H}}$ 11.7 Hz, $J_{N(1)H,6\text{-H}}$ 0 Hz) reveal a diequatorial orientation of ethyl and diethoxyphosphoryl groups. The orientation of substituents at the quaternary C(4)

† *Synthesis of* **4**. A mixture (1.150 g; 5.92 mmol) of phosphonate **5** and ester **6** in a ratio of 85:15 (according to ^{1}H NMR data) obtained as described in refs. 15, 16 and distilled *in vacuo* three times (bp 126–139 °C/ 12 Torr, n_D^{20} 1.4320) was dissolved in dry diethyl ether (15 ml). The solution was added dropwise to a NaH suspension (0.105 g, 4.38 mmol) in dry diethyl ether (15 ml) for 18 min away from air moisture with stirring. The formed mixture was vigorously stirred for 11 min; the white solid was then filtered off, promptly washed with dry diethyl ether and light petroleum and dried in a round-bottom flask under vacuum up to constant weight to give **4** (0.666 g; 70.4%), which was used immediately after preparation.‡

‡ Treatment of an aqueous solution of **4** with an equivalent amount of glacial acetic acid, extraction with diethyl ether, drying and removal of the solvent afforded pure **5** without the impurity of ester **6** (according to the ^{1}H NMR spectrum).



Scheme 2

atom was determined from the ^{1}H–^{1}H NOESY spectrum in [$^2H_6$]DMSO. Cross-peaks between the hydrogen of the OH group and axial hydrogen 6-H, as well as between the hydrogens of the 4-Me group and axial hydrogen 5-H, indicate that the orientation of the hydroxyl group is axial. This was confirmed by the presence of a distant coupling constant between the OH proton and the axial 5-H proton ($J_{OH,5\text{-}H}$ 1.2 Hz). Thus, the obtained compound has (4*R**,5*R**,6*R**)-configuration.

Hydroxypyrimidine **3** easily dehydrates in the presence of *p*-toluenesulfonic acid in refluxed ethanol for 1.5 h to give diethyl 1,2,3,4-tetrahydropyrimidine-5-phosphonate **9** in 89% yield (Scheme 2) (Method A).[††] The latter can also be obtained directly from sulfone **7** in 73% overall yield without isolation of **3**. For this purpose, *p*-toluenesulfonic acid was added to the reaction mixture formed by the reaction of **7** with **4** (THF, 20 °C, 7 h) followed by heating at reflux for 2 h (Method B).[††]

Previously, we found that $NaBH_4$–CF_3COOH readily reduces 5-unsubstituted 1,2,3,4-tetrahydro- and 4-hydroxy(or 4-alkoxy)-hexahydropyrimidin-2-ones/thiones.[18] This reducing agent was used for the preparation of diethyl hexahydropyrimidine-5-phosphonate **10** from **3**. Expected hexahydropyrimidine **10** was obtained after adding an excess of CF_3COOH to a mixture of pyrimidine **3** and $NaBH_4$ (molar ratio of 1:8) in THF at 0 °C followed by stirring the solution for 7 h at room temperature (Scheme 2). The yield of the recrystallised product was 65%.[‡‡]

Note that the reduction of **3** involving the chiral C(4) atom proceeded with high diastereoselectivity. Compound **10** formed as a single stereoisomer with (4*R**,5*S**,6*R**)-configuration according to the ^{1}H NMR spectrum of crude product. This follows from analysis of coupling constants between N(1)H, N(3)H, 4-H, 5-H and 6-H protons. In contrast to compound **3**, which exists in the conformation of a slightly flat chair, compound **10** in [$^2H_6$]DMSO has the conformation of a distorted chair with the pseudo-axial orientation of the 6-Me group and the pseudo-equatorial orientation of the 4-Et group. This conclusion is based on the following coupling constants: $J_{4\text{-}H,5\text{-}H}$ 7.0 Hz, $J_{5\text{-}H,6\text{-}H}$ 4.3 Hz, $J_{N(3)H,4\text{-}H}$ 2.3 Hz and $J_{N(1)H,6\text{-}H}$ 3.0 Hz.

The stereoselectivity of hydroxypyrimidine **3** reduction can be explained in terms of S_N1 mechanism *via* the formation of a practically planar acyliminium cation. Subsequent hydride ion transfer from bulky sodium tris(trifluoroacetoxy)borohydride,[19] which is formed by the reaction of $NaBH_4$ with an excess of CF_3COOH, occurs preferably from the side opposite to the diethoxyphosphoryl group.

§ *Synthesis of diethyl (4*R**,5*R**,6*R**)-6-ethyl-4-hydroxy-4-methyl-2-thioxohexahydropyrimidine-5-phosphonate* **3**. A mixture of enolate **4** (0.795 g, 3.68 mmol), sulfone **7** (0.904 g, 3.32 mmol) and dry THF (15 ml) was stirred for 8 h at room temperature. The reaction mixture containing a white precipitate was evaparated to dryness *in vacuo*. The residue was kept *in vacuo* for 20 min and triturated with heptane (5 ml). A saturated aqueous solution of $NaHCO_3$ (4 ml) was added to the obtained suspension. The mixture was allowed to stand for 3 h in a water bath (40 °C), cooled to 0 °C; the precipitate was filtered off, washed with ice water and heptane and dried to yield 0.837 g (81.3%) of chromatographically pure **3** (Silufol, chloroform–methanol, 9:1); mp 148.5 °C (ethanol; decomp.). ^{1}H NMR (Bruker DPX 300, 300.13 MHz, [$^2H_6$]DMSO) δ: 8.30 (dd, 1H, N(3)H, $J_{N(3)H,P}$ 4.1 Hz, $J_{N(3)H,N(1)H}$ 1.6 Hz), 7.97 (dd, 1H, N(1)H, $J_{N(1)H,P}$ 3.5 Hz, $J_{N(1)H,N(3)H}$ 1.6 Hz, $J_{N(1)H,6\text{-}H}$ 0 Hz), 6.12 (d, 1H, OH, $J_{OH,5\text{-}H}$ 1.2 Hz), 3.94–4.06 (m, 4H, OCH_2), 3.69 (m, 1H, 6-H, $J_{6\text{-}H,5\text{-}H}$ 11.7 Hz, $J_{6\text{-}H,P}$ 7.0 Hz, $J_{6\text{-}H,CH(A)}$ 3.6 Hz, $J_{6\text{-}H,CH(B)}$ 3.6 Hz, $J_{6\text{-}H,N(1)H}$ 0 Hz), 1.98 (ddd, 1H, 5-H, $J_{5\text{-}H,P}$ 17.3 Hz, $J_{5\text{-}H,6\text{-}H}$ 11.7 Hz, $J_{5\text{-}H,OH}$ 1.2 Hz), 1.85 [m, 1H, CH(A) in 6-CH_2, $J_{CH(A),CH(B)}$ 14.6 Hz, $J_{CH(A),Me}$ 7.3 Hz, $J_{CH(A),6\text{-}H}$ 3.6 Hz], 1.68 [m, 1H, CH(B) in 6-CH_2, $J_{CH(B),CH(A)}$ 14.6 Hz, $J_{CH(B),Me}$ 7.3 Hz, $J_{CH(B),6\text{-}H}$ 3.6 Hz], 1.69 (s, 3H, 4-Me), 1.21 (t, 3H, Me in OEt, J_{Me,CH_2} 7.1 Hz), 1.20 (t, 3H, Me in OEt, J_{Me,CH_2} 7.1 Hz), 0.79 (t, 3H, Me in 6-Et, J_{Me,CH_2} 7.3 Hz). ^{13}C NMR (Bruker DPX 300, 75.48 MHz, [$^2H_6$]DMSO) δ: 174.89 (s, C=S), 78.41 [s, C(4)], 61.53 (d, OCH_2, *J* 6.0 Hz), 60.62 (d, OCH_2, *J* 6.2 Hz), 49.45 [s, C(6)], 42.63 [d, C(5), *J* 143.1 Hz], 27.54 (s, 4-Me), 23.23 (s, CH_2 in 6-Et), 16.09 (d, Me in OEt, *J* 6.0 Hz), 16.01 (d, Me in OEt, *J* 6.6 Hz), 6.93 (s, Me in 6-Et). ^{31}P NMR (Bruker DPX 300, 121.49 MHz, [$^2H_6$]DMSO, using 85% H_3PO_4 as an external standard) δ: 26.61. IR (FT-IR Bruker 'Equinox 55/S') (Nujol, ν/cm^{-1}): 3294 (m), 3261 (s), 3192 (s), 3111 (m) (ν_{N-H}, ν_{O-H}), 1577 (s), 1534 (s) ('thioamide-II'), 1226 (vs, $\nu_{P=O}$), 1211 (m, δ_{N-H}), 1047 (s), 1020 (s, ν_{P-O-C}). Found (%): C, 42.47; H, 7.69; N, 9.10. Calc. for $C_{11}H_{23}N_2O_4PS$ (%): C, 42.57; H, 7.47; N, 9.03.

¶ Previously,[17] we proposed a convenient criterion for the determination of substituents orientation at C(4) and C(6) in hexahydropyrimidin-2-ones/thiones, which is based on the coupling constants between C(4)H and N(3)H, C(6)H and N(1)H.

†† *Synthesis of diethyl 4-ethyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-phosphonate* **9** *(Method A)*. A stirred solution of hydroxypyrimidine **3** (0.381 g, 1.23 mmol) and $TsOH·H_2O$ (0.072 g, 0.38 mmol) in ethanol (6 ml) was refluxed for 1.5 h, the solvent was removed *in vacuo*, and the solid residue was treated with a saturated aqueous solution of $NaHCO_3$ (2 ml). The obtained suspension was cooled to 0 °C, the precipitate was filtered off, washed with ice water and heptane and dried to yield 0.318 g (88.6%) of chromatographically pure **9** (Silufol, chloroform–methanol, 9:1); mp 169–169.5 °C (acetonitrile). ^{1}H NMR (Bruker DPX 300, 300.13 MHz, [$^2H_6$]DMSO) δ: 10.04 [br. d, 1H, N(1)H, $J_{N(1)H,P}$ 3.6 Hz], 9.08 [br. m, 1H, N(3)H], 3.85–4.03 (m, 4H, OCH_2), 3.80 (m, 1H, 4-H, $J_{4\text{-}H,P}$ 8.3 Hz, $J_{4\text{-}H,CH_2}$ 5.4 Hz, $J_{4\text{-}H,N(3)H}$ 3.6 Hz), 2.05 (d, 3H, 6-Me, $J_{Me,P}$ 2.5 Hz), 1.44 (dq, 2H, CH_2 in 4-Et, $J_{CH_2,Me}$ 7.4 Hz, $J_{CH_2,4\text{-}H}$ 5.4 Hz), 1.22 (t, 6H, Me in OEt, J_{Me,CH_2} 7.0 Hz), 0.80 (t, 3H, Me in 4-Et, J_{Me,CH_2} 7.4 Hz). ^{13}C NMR (Bruker DPX 300, 75.48 MHz, [$^2H_6$]DMSO) δ: 175.27 (s, C=S), 145.26 [d, C(6), *J* 20.4 Hz], 95.24 [d, C(5), *J* 202.4 Hz], 60.87 (d, OCH_2, *J* 5.4 Hz), 60.80 (d, OCH_2, *J* 5.4 Hz), 52.48 [d, C(4), *J* 14.3 Hz], 29.48 (s, CH_2 in 4-Et), 16.83 (d, 6-Me, *J* 3.4 Hz), 16.07 (d, Me in OEt, *J* 6.2 Hz), 7.96 (s, Me in 4-Et). ^{31}P NMR (Bruker DPX 300, 121.49 MHz, [$^2H_6$]DMSO, using 85% H_3PO_4 as an external standard) δ: 20.43. IR (FT-IR Bruker 'Equinox 55/S') (Nujol, ν/cm^{-1}): 3176 (s, ν_{N-H}), 1644 (s, $\nu_{C=C}$), 1578 (s, 'thioamide-II'), 1227 (s, $\nu_{P=O}$), 1210 (s, δ_{N-H}), 1038 (sh), 1029 (s, ν_{P-O-C}). Found (%): C, 45.03; H, 7.01; N, 9.61. Calc. for $C_{11}H_{21}N_2O_3PS$ (%): C, 45.20; H, 7.24; N, 9.58.

Synthesis of **9** *(Method B).* A mixture of enolate **4** (0.706 g, 3.27 mmol), sulfone **7** (0.806 g, 2.96 mmol) and dry THF (14.5 ml) was stirred for 7 h at room temperature. Then, $TsOH·H_2O$ (0.314 g, 1.65 mmol) was added, and the mixture was refluxed with stirring for 2 h. The solvent was removed *in vacuo*, the residue was kept *in vacuo* for 20 min and triturated with heptane (5 ml). A saturated aqueous solution of $NaHCO_3$ (4 ml) was added to the obtained suspension. The mixture was allowed to stand at room temperature overnight and then cooled to 0 °C; the precipitate was filtered off, washed with ice water and heptane and dried to give **9** (0.633 g, 73.2%).

Thus, we developed a synthetic method for the preparation of previously unknown derivatives of 2-thioxo-1,2,3,4-tetrahydro- and 2-thioxohexahydropyrimidine-5-phosphonic acids. This method includes the stereoselective formation of diethyl 4-hydroxy-2-thioxohexahydropyrimidine-5-phosphonates and their subsequent transformations.

‡‡ *Synthesis of diethyl (4R*,5S*,6R*)-4-ethyl-6-methyl-2-thioxohexahydropyrimidine-5-phosphonate* **10**. CF_3COOH (12 ml) was added dropwise for 37 min with the protection from air moisture to a stirred, cooled in an ice bath suspension of finely powdered $NaBH_4$ (0.612 g, 16.18 mmol) and hydroxypyrimidine **3** (0.634 g, 2.04 mmol) in dry THF (6 ml). The obtained solution was stirred for 7 h at room temperature, evaporated *in vacuo* at 50–60 °C, the viscous oil formed was neutralised with a saturated aqueous solution of K_2CO_3. The product was extracted with $CHCl_3$ (5×10 ml); the combined organic layers were washed with water and a saturated aqueous solution of NaCl and dried over Na_2SO_4. The solvent was removed *in vacuo*; the solid residue was triturated with dry diethyl ether and cooled to –10 °C; the white precipitate was filtered off, washed with cooled dry diethyl ether and dried to give product (0.535 g) containing 80 mol% **10** and 20 mol% unidentified organophosphorus compound according to ^{1}H NMR data. After recrystallization of this mixture from ethyl acetate (24 ml), pure **10** (0.393 g, 65.4%) was obtained; mp 166–168 °C (ethyl acetate). ^{1}H NMR (Bruker Avance 600, 600.13 MHz, [$^2H_6$]DMSO) δ: 8.13 [br. d, 1H, N(1)H, $J_{N(1)H,6\text{-}H}$ 3.0 Hz], 7.95 [br. d, 1H, N(3)H, $J_{N(3)H,4\text{-}H}$ 2.3 Hz], 3.98–4.07 (m, 4H, OCH_2), 3.59 (m, 1H, 6-H, $J_{6\text{-}H,P}$ 19.3 Hz, $J_{6\text{-}H,Me}$ 6.7 Hz, $J_{6\text{-}H,5\text{-}H}$ 4.3 Hz, $J_{6\text{-}H,N(1)H}$ 3.0 Hz), 3.53 (m, 1H, 4-H, $J_{4\text{-}H,P}$ 8.9 Hz, $J_{4\text{-}H,5\text{-}H}$ 7.0 Hz, $J_{4\text{-}H,CH(A)}$ 5.3 Hz, $J_{4\text{-}H,CH(B)}$ 5.3 Hz, $J_{4\text{-}H,N(3)H}$ 2.3 Hz), 2.22 (ddd, 1H, 5-H, $J_{5\text{-}H,P}$ 19.9 Hz, $J_{5\text{-}H,4\text{-}H}$ 7.0 Hz, $J_{5\text{-}H,6\text{-}H}$ 4.3 Hz), 1.67 [m, 1H, CH(A) in 4-CH_2, $J_{CH(A),CH(B)}$ 14.1 Hz, $J_{CH(A),Me}$ 7.3 Hz, $J_{CH(A),4\text{-}H}$ 5.3 Hz], 1.55 [m, 1H, CH(B) in 4-CH_2, $J_{CH(B),CH(A)}$ 14.1 Hz, $J_{CH(B),Me}$ 7.3 Hz, $J_{CH(B),4\text{-}H}$ 5.3 Hz], 1.24 (t, 6H, Me in OEt, J_{Me,CH_2} 7.0 Hz), 1.22 (d, 3H, 6-Me, $J_{Me,6\text{-}H}$ 6.7 Hz), 0.83 (t, 3H, Me in 4-Et, J_{Me,CH_2} 7.3 Hz). ^{13}C NMR (Bruker DPX 300, 75.48 MHz, [$^2H_6$]DMSO) δ: 175.15 (s, C=S), 61.44 (d, OCH_2, *J* 6.6 Hz), 61.21 (d, OCH_2, *J* 6.7 Hz), 49.95 [s, C(4)], 44.58 [d, C(6), *J* 1.6 Hz], 35.17 [d, C(5), *J* 142.9 Hz], 26.34 (d, CH_2 in 4-Et, *J* 6.5 Hz), 18.39 (d, 6-Me, *J* 1.9 Hz), 16.23 (d, Me in OEt, *J* 5.9 Hz), 16.19 (d, Me in OEt, *J* 5.9 Hz), 8.17 (s, Me in 4-Et). ^{31}P NMR (Bruker DPX 300, 121.49 MHz, [$^2H_6$]DMSO, using 85% H_3PO_4 as an external standard) δ: 27.67. IR (FT-IR Perkin-Elmer Spectrum BX) (KBr, ν/cm^{-1}): 3434 (br. s), 3183 (s), 3107 (m, ν_{N-H}), 1579 (s), 1564 (s), 1544 (s, 'thioamide-II'), 1246 (s, $\nu_{P=O}$), 1210 (s, δ_{N-H}), 1046 (s), 1020 (s), 967 (s, ν_{P-O-C}). Found (%): C, 44.81; H, 7.88; N, 9.37. Calc. for $C_{11}H_{23}N_2O_3PS$ (%): C, 44.89; H, 7.88; N, 9.52.

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