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Synthesis of diethyl (aryl)(4-oxopiperidin-1-yl)methylphosphonates

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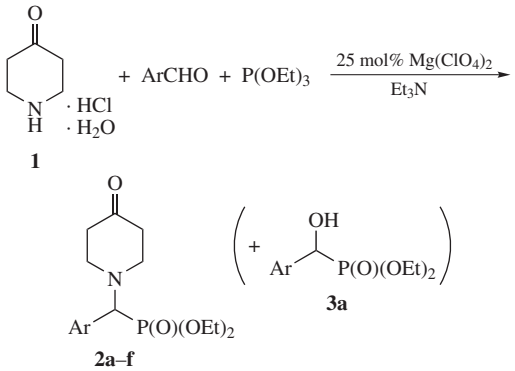
The Kabachnik–Fields reaction of 4-piperidone hydrochloride monohydrate, an aromatic aldehyde and triethyl phosphite in the presence of triethylamine and magnesium perchlorate affords diethyl (aryl)(4-oxopiperidin-1-yl)methylphosphonates in moderate yields.

γ-Piperidones, especially their N-derivatives, reveal versatile biological activities[1] including neurotropic[2] and anticancer properties.[3] On the other hand, phosphorus-containing modifiers are of special importance as they improve solubility and bioavailability of biologically active compounds and drugs and facilitate the delivery of a pharmacophore to a biological target.[4] In this regard, attaching phosphonate group to piperidone framework will result in piperidone-containing amino phosphonates that may be considered as phosphorus analogues of amino acid esters and, therefore, become prospective drug candidates.[5] Previously, we prepared diethyl β-aminoethyl-, γ-aminopropyl- and δ-aminobutylphosphonates bearing 4-piperidone fragment.[6] The aim of the present work was to obtain their lower homologue of α-aminomethylphosphonate type.

The Kabachnik–Fields reaction[7] between aldehydes, amines and dialkyl phosphites is the most general, convenient and straightforward way to dialkyl α-aminomethylphosphonates.[8,9] In another version, trialkyl phosphites can be used as phosphorus components instead of dialkyl phosphites.[10,11]

Herein, we describe the straightforward synthesis of novel diethyl (aryl)(4-oxopiperidin-1-yl)methylphosphonates **2a–f** from commercially available 4-piperidone hydrochloride monohydrate **1**, an aromatic aldehyde and $(EtO)_3P$ in the presence of catalytic amounts of anhydrous $Mg(ClO_4)_2$ (Scheme 1).† Triethylamine was used as a base in equimolar amount to amine hydrochloride **1**.



a Ar = 4-FC_6H_4 **d** Ar = 2-thienyl
b Ar = Ph **e** Ar = 2,3-$(MeO)_2C_6H_3$
c Ar = 4-$MeOC_6H_4$ **f** Ar = 2,3,4-$(MeO)_3C_6H_2$

Scheme 1

Application of catalytic amounts (5 mol%) of convenient anhydrous $Mg(ClO_4)_2$ for similar purpose was described previously, both $(EtO)_2P(O)H$ and $(EtO)_3P$ having been equally

† *Compounds* **2a–f** *(general procedure).* A mixture of 4-piperidone hydrochloride **1** (0.77 g, 5 mmol), aromatic aldehyde (5 mmol), Et_3N (0.5 g, 5 mmol), anhydrous $Mg(ClO_4)_2$ (0.28 g, 1.25 mmol, 25 mol%), and $(EtO)_3P$ (0.83 g, 5 mmol) was stirred for 20 h at room temperature. Water and CH_2Cl_2 were added to the mixture, the organic phase was separated, the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with aqueous Na_2CO_3 solution, separated, dried over Na_2SO_4, filtered and evaporated on a rotary evaporator to give crude product as an oil. Column chromatography (30×2 cm) using gradient elution starting with light petroleum and continuing with light petroleum–acetone mixtures (gradient from 10:1 to 10:2.5) afforded the desired compounds as viscous oils. Oily products gradually transformed in white solids in the case of compounds **2a**,**c**,**e**.

Diethyl (4-fluorophenyl)(4-oxopiperidin-1-yl)methylphosphonate **2a**: white solid, mp 77.5–79.5 °C, yield 51%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05 and 1.34 (2t, 3H, $POCH_2Me$, $^3J_{HH}$ 7.1 Hz), 2.37–2.46 [m, 4H, $N(CH_2)_2$], 2.71–2.77 (m, 2H), 3.10–3.16 (m, 2H), 3.68–3.78 (m, 1H, 0.5$POCH_2$), 3.88–3.98 (m, 1H, 0.5$POCH_2$), 4.04 (d, 1H, PCH, $^2J_{PH}$ 22.9 Hz), 4.16–4.29 (m, 2H, $POCH_2$), 7.02 (dd, 2H, C_6H_4, $^3J_{HH}$ 8.6 Hz, $^3J_{FH}$ 8.6 Hz), 7.43–7.46 (dd, 2H, C_6H_4, $^3J_{HH}$ 8.6 Hz, $^4J_{FH}$ 5.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.08 and 16.48 (2d, $POCH_2Me$, $^3J_{PC}$ 5.8 Hz), 41.53 (NCH_2CH_2), 50.88 (d, NCH_2CH_2, $^3J_{PC}$ 8.7 Hz), 62.29 and 62.97 (2d, $POCH_2$, $^2J_{PC}$ 7.3 Hz), 65.97 (d, PCH, $^1J_{PC}$ 161 Hz), 115.13 (d, *o*-$C_{Ar}H$ to F, $^2J_{FC}$ 21.0 Hz), 128.06 (t, PCH–C_{Ar}, $^2J_{PC}$ 3.0 Hz, $^4J_{FC}$ 3.0 Hz), 131.79 (t, PCH–C_{Ar}–$C_{Ar}H$, $^3J_{PC}$ 8.0 Hz, $^3J_{FC}$ 8.0 Hz), 162.50 (d, C_{Ar}–F, $^1J_{FC}$ 246 Hz), 207.92 (C=O). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.41. Found (%): C, 55.85; H, 6.77; N, 3.94; P, 8.90. Calc. for $C_{16}H_{23}FNO_4P$ (%): C, 55.97; H, 6.75; N, 4.08; P, 9.02.

Diethyl (4-oxopiperidin-1-yl)(phenyl)methylphosphonate **2b**: viscous liquid, yield 32%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.02 and 1.34 (2t, 3H, $POCH_2Me$, $^3J_{HH}$ 7.0 Hz), 2.37–2.47 [m, 4H, $N(CH_2)_2$], 2.73–2.79 (m, 2H), 3.12–3.18 (m, 2H), 3.63–3.73 (m, 1H, 0.5$POCH_2$), 3.86–3.96 (m, 1H, 0.5$POCH_2$), 4.01 (d, 1H, PCH, $^2J_{PH}$ 22.6 Hz), 4.17–4.28 (m, 2H, $POCH_2$), 7.25–7.32 (m, 3H, Ph), 7.43–7.45 (m, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.13 and 16.58 (2d, $POCH_2Me$, $^3J_{PC}$ 5.4 Hz), 41.67 (NCH_2CH_2), 51.05 (d, NCH_2CH_2, $^3J_{PC}$ 8.8 Hz), 62.35 and 62.90 (2d, $POCH_2$, $^2J_{PC}$ 7.0 Hz), 67.03 (d, PCH, $^1J_{PC}$ 161 Hz), 128.28 (overlapped $C_{Ph}H$ and $C_{Ph}CHP$), 130.17 (d, PCH–C_{Ph}–$C_{Ph}H$, $^3J_{PC}$ 8.6 Hz), 132.17 ($C_{Ph}H$), 208.35 (C=O). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.74. Found (%): C, 58.78; H, 7.09; N, 4.06; P, 9.52. Calc. for $C_{16}H_{24}NO_4P$ (%): C, 59.07; H, 7.44; N, 4.31; P, 9.52.

Diethyl (4-methoxyphenyl)(4-oxopiperidin-1-yl)methylphosphonate **2c**: white solid mp 79.5–81.5 °C, yield 32%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.04 and 1.34 (2t, 3H, $POCH_2Me$, $^3J_{HH}$ 7.0 Hz), 2.34–2.44 [m, 4H, $N(CH_2)_2$], 2.69–2.75 (m, 2H), 3.11–3.17 (m, 2H), 3.65–3.74 (m, 1H, 0.5$POCH_2$), 3.78 (s, 3H, OMe), 3.87–3.94 (m, 1H, 0.5$POCH_2$), 3.97 (d, 1H, PCH, $^2J_{PH}$ 22.6 Hz), 4.17–4.29 (m, 2H, $POCH_2$), 6.85 (d, 2H, C_6H_4, $^3J_{HH}$ 8.4 Hz), 7.37 (d, 2H, C_6H_4, $^3J_{HH}$ 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.96 and 16.35 (2d, $POCH_2Me$, $^3J_{PC}$ 5.4 Hz), 41.43 (NCH_2CH_2), 50.71 (d, NCH_2CH_2, $^3J_{PC}$ 8.7 Hz), 54.92 (OMe), 62.08 and 62.64 (2d, $POCH_2$, $^2J_{PC}$ 6.9 Hz), 66.00 (d, PCH, $^1J_{PC}$ 162 Hz), 113.36 ($C_{Ph}H$), 123.71 ($C_{Ph}CHP$), 131.17 (d, PCH–C_{Ph}–$C_{Ph}H$, $^3J_{PC}$ 8.8 Hz), 159.24 (C_{Ph}–OMe), 208.21 (C=O). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.96. Found (%): C, 57.14; H, 7.48; N, 3.87; P, 8.89. Calc. for $C_{17}H_{26}NO_5P$ (%): C, 57.46; H, 7.37; N, 3.94; P, 8.72.

effective as phosphorus components.[12] Taking into consideration that hydrogen chloride and water contained in the starting amine salt **1** may bring some complications, we initially studied the outcome of a model reaction between $(EtO)_2P(O)H$ and $(EtO)_3P$, amine **1** and 4-fluorobenzaldehyde (which allows one to perform ^{19}F NMR monitoring of the reaction).

No reaction occurred when equimolar amounts of 4-piperidone hydrochloride monohydrate, diethyl phosphite and 4-fluorobenzaldehyde were treated with 5 mol% of $Mg(ClO_4)_2$: within 6 h, the mixture contained only starting diethyl phosphite (δ_P 7.3 ppm) and 4-fluorobenzaldehyde (δ_F –103.5 ppm). However, on moving to triethyl phosphite, a mixture of α-(4-fluorophenyl)-α-hydroxymethylphosphonate **3a** (51 mol%) (δ_P 20.7 ppm, δ_F –114.7 ppm) and the desired amino phosphonate **2a** (22 mol%) (δ_P 21.3 ppm, δ_F –114.1 ppm) was obtained. Generally, in the ^{31}P NMR spectra chemical shifts of α-amino(aryl)methylphosphonates were located approximately 0.3–0.5 ppm downfield of those of α-hydroxy(aryl)methylphosphonates. The reaction mixture also contained $(EtO)_3P$ (2.5 mol%), $(EtO)_2P(O)H$ (4.3 mol%), and product resulting from oxidation and hydrolysis of triethyl phosphite (8.5 mol%) (δ_P –1.54 ppm). Other by-products had phosphonate nature (δ_P in the range 33.3–22.4 ppm) and were present in small amounts (11.7 mol% in total).

When triethylamine was introduced to liberate free base from salt **1** (with molar ratio **1** : Et_3N being 1:1), different results were obtained for diethyl and triethyl phosphites. In the case of diethyl phosphite with equimolar amounts of compound **1**, 4-fluorobenzaldehyde, Et_3N and 5 mol% of $Mg(ClO_4)_2$, the Abramov reaction proceeded giving exclusively hydroxymethylphosphonate **3a** (δ_P 21.12 ppm, doublet with $^6J_{PF}$ 4.4 Hz; δ_F –115.4 ppm, doublet with $^6J_{FP}$ = 4.8 Hz). The similar reaction with triethyl phosphite occurred more slowly than the above considered reactions, and after 6 h the mixture consisted of $(EtO)_3P$ (27 mol%), $(EtO)_2P(O)H$ (1.5 mol%), α-amino phosphonate **2a** (47 mol%), and corresponding hydroxy phosphonate **3a** (15 mol%). The increase in reaction time from 6 to 24 h caused a decrease in residual amount of triethyl phosphite down to ~5 mol% with a slight increase in amounts of phosphonate **2a** and α-hydroxymethylphosphonate and strong increase in amounts of above mentioned by-products of phosphonate nature.

Thus, triethylamine was found to be an essential component for the successful outcome of the synthesis of amino phosphonates **2**. When Et_3N was replaced by K_2CO_3 as a base, only hydroxy phosphonates **3** were formed. Raising the amounts of $P(OEt)_3$ resulted in growth of the fraction of above by-products containing $C–P(O)(OEt)_2$ bond.

The optimum conditions in terms of satisfactory yields of compounds **2a–f** involve using 25 mol% of $Mg(ClO_4)_2$. Further raising its amounts caused dropping the yields of the products. The use of acetonitrile as a solvent in the case of solid aldehydes (2,3-dimethoxy- or 2,3,4-trimethoxybenzaldehyde) to ensure better contact of reagents led to noticeable decrease in the yield. Finally, in contrast to the above cited work[12] where reactions with morpholine or piperidine were completed in 10–20 min, significantly longer reaction times were required in the case of compound **1** to consume entirely starting triethyl phosphite. Typically, after 20 h of reaction, remaining amounts of $P(OEt)_3$ did not exceed 5%, being even lower in many cases.

According to the ^{31}P NMR data, the crude mixtures contained approximately 42–60% of compounds **2a–f**, 15–21% of the above mentioned admixtures with phosphonate structure, 15–20% of hydroxy phosphonates **3**, and 7–15% of a compound that was a product of oxidation and/or hydrolysis of $P(OEt)_3$. Final column chromatography afforded the desired α-amino phosphonates **2a–f** in moderate yields (32–51%).

In conclusion, this study has demonstrated that(aryl)(4-oxopiperidin-1-yl)methylphosphonates can be obtained in moderate yields through the Kabachnik–Fields reaction between 4-piperidone hydrochloride monohydrate, an aromatic aldehyde and triethyl phosphite in the presence of triethylamine and magnesium perchlorate as a catalyst.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.05.026.

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Diethyl (4-oxopiperidin-1-yl)(2-thienyl)methylphosphonate **2d**: yellowish viscous liquid, yield 35%. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.14 and 1.37 (2t, 3H, $POCH_2Me$, $^3J_{HH}$ 7.0 Hz), 2.46 [t, 4H, $N(CH_2)_2$, $^3J_{HH}$ 5.9 Hz], 2.78–2.85 (m, 2H), 3.19–3.26 (m, 2H, CH_2), 3.85–3.95 (m, 1H, 0.5$POCH_2$), 3.99–4.07 (m, 1H, 0.5$POCH_2$), 4.21–4.30 (m, 2H, $POCH_2$), 4.35 (d, 1H, PCH, $^2J_{PH}$ 24.4 Hz), 7.02 (dd, 1H, $^3J_{HH}$ 3.6 Hz, $^3J_{HH}$ 5.0 Hz), 7.24 (m, 1H), 7.8 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.08 and 16.46 (2d, $POCH_2Me$, $^3J_{PC}$ 5.6 Hz), 41.61 (NCH_2CH_2), 50.50 (d, NCH_2CH_2, $^3J_{PC}$ 8.0 Hz), 61.36 (d, PCH, $^1J_{PC}$ 164 Hz), 62.39 and 63.16 (2d, $POCH_2$, $^2J_{PC}$ 7.1 Hz), 125.73 (d, $^4J_{PC}$ 1.5 Hz), 126.88, 128.44 (d, $^3J_{PC}$ 6.3 Hz), 133.38 (d, $^2J_{PC}$ 7.3 Hz), 208.06 (C=O). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.57. Found (%): C, 50.54; H, 7.01; N, 4.25. Calc. for $C_{14}H_{22}NO_4PS$ (%): C, 50.75; H, 6.69; N, 4.23.

For characteristics of compounds **2e**,**f**, see Online Supplementary Materials.