Synthesis of β-Amino and β-Hydroxy Phosphonates

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Abstract: Two alternative routes to methyl and trifluoromethyl substituted β-amino and β-hydroxy phosphonates via hydrogenation of vinylphosphonates and via aldol-type addition of ethylphosphonate to trifluoromethyl substituted imines and carbonyl compounds are described.

Key Words: hydrogenation, aldol reactions, fluorinated imines, fluorinated ketones, phosphonates

During the last decade there has been a steadily growing interest in phosphonic acids and their derivatives, because of their widespread applications in organic synthesis,1 medicinal2 and agricultural chemistry.3 Since the discovery of biologically active aminophosphonic acids and phosphonopeptides4 in living organisms, much effort has been devoted to develop preparatively simple and efficient routes to aminophosphonic acids and their derivatives, especially phosphonopeptides.5

Several syntheses of multifunctional phosphonates are described.6 For example, it was reported that α-vinyl phosphonates were obtained by a modified Morita–Baylis–Hillman (MBH) procedure.7 However, when we applied this protocol to the reaction of fluoroalkyl substituted imines and ketones with vinyl phosphonates we found that the reaction proceeds slowly, giving unsatisfactory yields because of the high tendency of the substrates to polymerize and/or hydrolize. Recently, the synthesis of MBH adducts on reaction of vinyl phosphonates with carbonyl compounds in the presence of LDA was reported.8 When we applied this protocol to acylimines of hexafluoroacetone we found that reduction of the C=N bond was the main reaction pathway (Scheme 1, Pg = protective group). Therefore, we started to test alternative approaches to compounds of the Morita–Baylis–Hillman type, which we intended to use as precursors for syntheses of β-fluoroalkyl substituted β-amino and β-hydroxy phosphonates via catalytic hydrogenation.

The trifluoromethyl substituted imines 1a,b readily reacted with diethyl 2-(N,N-dimethylamino)-ethylphosphonate in the presence of n-BuLi in THF at –78 °C to give (1:1) adducts 2a,b in 60–75% yield. Compounds 2a,b on treatment with m-chloroperbenzoic acid in dichloromethane at elevated temperatures (bath temperature, 55 °C) were converted into β-trifluoromethyl substituted vinylphosphonates 3a,b (Scheme 2, Table 1).

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acid surrogate. The parent compound, 2-amino-3-
phosphonopropionic acid (APPA) was first isolated by
Kittredge et. al. from Zoanthus sociatus.12 APPA is a bio-
synthetic precursor of AEP (2-aminoethylphosphonic ac-
id) and has been found in humans, protozoa and marine
organisms. APPA is a selective, potent modulator of the
metabotropic excitatory amino acid receptor subtype.12
The above-described procedure can be applied also to
alkyl- and fluoroalkyl-substituted ketones 4a–c. Some mi-
nor modifications are necessary to obtain optimal yields.
In the case of 4b and 4c, 2 equivalents of the starting ma-
terials are required (Scheme 3, Table 2).

Noteworthy, the crude adducts 5a–c are already pure
enough for subsequent reactions. Due to their high polari-
ty, purification by column chromatography is problemat-
ic. Like in the case of the above described imines, we were
not able to isolate the intermediates of the reactions 5a–
c→6a–c, the corresponding N-oxides. Compounds 6a–c
are already pure enough for subsequent reactions. Due to their high polari-
ty, purification by column chromatography is problemat-
ic. Like in the case of the above described imines, we were
not able to isolate the intermediates of the reactions 5a–
c→6a–c, the corresponding N-oxides. Compounds 6a–c
can be formally classified as highly substituted malic acid
derivatives.

Transformation of the α-methylidene-β-amino phospho-
mates 3a,b into α-methyl-β-amino phosphonates 7a,b and
of α-methylidene-β-hydroxy phosphonates 6a–c into α-
methyl-β-hydroxy phosphonates 8a–c was accomplished
by catalytic hydrogenation. The highest diastereoselectiv-
ity was obtained for the transformation 3b→7b
(Scheme 4, Table 3).

An alternative route to compounds of type 7 and 8a is the
direct base-catalyzed aldol-like addition (Scheme 5) of
ethyl phosphonate to imines 1 and ketones 4, respectively.
However, diastereomers are formed in 1:1 ratio.

---

Table 2 Derivatives 5 and 6 Obtained from Carbonyl Compounds 4

<table>
<thead>
<tr>
<th>Compound</th>
<th>R¹</th>
<th>R²</th>
<th>Yields, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>Me</td>
<td>CF₃</td>
<td>75 a</td>
</tr>
<tr>
<td>5b</td>
<td>Me</td>
<td>Me</td>
<td>65 a</td>
</tr>
<tr>
<td>5c</td>
<td>Et</td>
<td>H</td>
<td>65 a</td>
</tr>
<tr>
<td>6a</td>
<td>Me</td>
<td>CF₃</td>
<td>65</td>
</tr>
<tr>
<td>6b</td>
<td>Me</td>
<td>Me</td>
<td>74</td>
</tr>
<tr>
<td>6c</td>
<td>Et</td>
<td>H</td>
<td>72</td>
</tr>
</tbody>
</table>

* Yields were determined by NMR spectroscopy.

Table 3 Compounds 7,8 Obtained by Hydrogenation from 3,6 and
by Aldol-type Condensation from 1,4a

<table>
<thead>
<tr>
<th>Compound</th>
<th>de, % (hydrogenation)</th>
<th>Yield, % (hydrogenation)</th>
<th>Yield, % (condensation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>–</td>
<td>98</td>
<td>72</td>
</tr>
<tr>
<td>7b</td>
<td>89:11</td>
<td>91</td>
<td>68</td>
</tr>
<tr>
<td>8a</td>
<td>50:50</td>
<td>98</td>
<td>77</td>
</tr>
<tr>
<td>8b</td>
<td>71:29</td>
<td>94</td>
<td>–</td>
</tr>
<tr>
<td>8c</td>
<td>60:40</td>
<td>82</td>
<td>–</td>
</tr>
</tbody>
</table>

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Scheme 5

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A growing number of reports focus on peptidomimetics built from two or more different monomers. The resistance to proteolytic degradation by peptidases and the immense structural diversity renders peptide hybrids promising candidates for pharmaceutical applications. In this context, compounds of type 3, 6, 7 and 8 are of interest as building blocks for peptide, β-peptide and depsipeptide modification for the construction of highly constrained side chains to stabilize secondary structure motifs, which may be crucial for biological activity.

Solvants were purified and dried prior to use. Reagents were used as purchased. Mps were determined on a Boetius heating table. MS were recorded on a VG-250 (Masslab) EI spectrometer (70 eV) or by a VG ZAB-HSQ FAB spectrometer. 1H (200 MHz or 300 MHz), 13C (50 or 75 MHz), 19F NMR (188 or 282 MHz) and 31P NMR spectra (121.5 MHz) were recorded on a Varian Gemini 2000 or a Varian Gemini 300 spectrometer. TMS was used as reference standard for 1H and 13C NMR spectra (internal), TFA for 19F NMR and phosphoric acid for 31P NMR spectra (external). Flash chromatography was performed by using silica gel (32–63 µm, ICN Biomedicals) with solvent systems given in the text.

2a,b and 5a: General Procedure

To a soln of n-BuLi (3.0 mL, 1.6 M in hexane) in THF (70 mL) diethyl(N,N-dimethylamino)ethylphosphonate (1.0 g, 3.82 mmol) was added at –78 °C. The mixture was stirred for ca. 15 min, then compounds 1a or 4a (3.64 mmol) were added dropwise. Stirring was continued for 3–4 h at –78 °C. Then the reaction mixture was cooled to r.t., then it was quenched with sat. NH4Cl soln (25 mL). The organic layer was washed with sat. NaHCO3 soln (2×15 mL) and the organic phase was dried with MgSO4. The volatiles were removed in vacuo to give crude 2a,b and 5a. Compounds 2a,b were purified by column chromatography (hexanes–EtOAc, 1:1). Compound 5a was not purified by column chromatography due to the high polarity and was used as crude product for the next step of transformations.

2-Benzylimino-1-dimethylaminoethyl-3,3,3-trifluoro-2-trifluoromethyl-propyl-phosphonic Acid Diethyl Ester (2a)

Yield: 75% (1.31 g); column chromatography (hexanes–EtOAc, 1:1); mp 78 °C; Rf 0.32.

1H NMR (200 MHz, CDCl3): δ = 1.21 (t, JHH = 7.1 Hz, 3 H), 1.29 (t, JHH = 7.1 Hz, 3 H), 2.23 (s, 6 H), 2.52 (m, 1 H), 2.94 (m, 1 H), 3.74 (m, 1 H), 4.08 (m, 4 H), 7.81 (m, 3 H), 7.96 (br, 1 H).

13C NMR (50 MHz, CDCl3): δ = 16.2 (t, JCP = 7.4 Hz, 3 C), 16.3 (t, JCP = 6.4 Hz, 3 C), 36.4 (d, JCP = 140.6 Hz, 44.9), 55.6, 62.6 (d, JCP = 6.5 Hz, 68.1 (sept., JCP = 29 Hz, 122.7 (q, JCP = 291 Hz)), 123.1 (dq, JCP = 289 Hz), 127.4, 128.7, 132.2, 134.2, 167.6.

19F NMR (282 MHz, CDCl3): δ = 13.72 (br, 3 F), 9.61 (q, J = 9 Hz, 3 F).

31P NMR (121.5 MHz): δ = 21.48 (br).

HRMS: m/z [M + H+] calcd for C18H25F6N2O4P, 479.15289; found, 479.15294.

2-(1-Butoxycarbonylamino)-4-dimethylamino-3-(diethoxycarbonyl)-2-trifluoromethyl-butyric Acid Methyl Ester (2b)

Yield: 60% (1.02 g); diasteromeric mixture; mp 68 °C for one of the diastereomers; column chromatography (hexanes–EtOAc, 1:1); Rf 0.34.

The spectroscopic data, melting point, and Rf are given for one diastereomer.

1H NMR (200 MHz, CDCl3): δ = 1.25 (t, JHH = 7.1 Hz, 3 H), 1.27 (t, JHH = 7.2 Hz, 3 H), 1.36 (s, 9 H), 2.27 (s, 6 H), 2.55 (m, 1 H), 3.10 (m, 1 H), 3.13 (m, 1 H), 3.81 (s, 3 H), 4.04 (m, 4 H), 9.62 (br, 1 H).

13C NMR (50 MHz, CDCl3): δ = 16.3 (d, JCP = 5.0 Hz, 16.4 (d, JCP = 5.9 Hz, 28.3, 39.6 (d, JCP = 137.4 Hz, 44.6, 53.2, 56.8 (d, JCP = 2.5 Hz, 62.5 (d, JCP = 7.5 Hz), 62.7 (d, JCP = 6.7 Hz), 68.1 (m), 79.8, 124.6 (q, JCP = 287 Hz), 153.8, 166.3.

19F NMR (282 MHz, CDCl3): δ = 8.45 (br, 3 F).

31P NMR (121.5 MHz): δ = 20.65 (br).
31P NMR (121.5 MHz): δ = 12.37 (br).

HRMS: m/z [M + H+] calcd for C16H20F6NO4P, 436.11069; found, 436.11086.

2-(tert-Butyloxyacarbonylamo)-3-(diethoxypyrophosphoryl)-2-trifluoromethylbutyric Acid Methyl Ester (7b)

Yield: 91% (464 mg); colorless oil; column chromatography hexanes–EtOAc, 1:1; Rf 0.6.

1H NMR (200 MHz, CDC13, major diastereomer): δ = 1.17 (dd, 3JHH = 7.5 Hz, 2JHF = 16 Hz, 3 JHF = 16 Hz, 31H, 1 H), 1.28 (t, 3JHH = 7.5 Hz, 2JHF = 16 Hz, 31H, 3 JHF = 7 Hz, 3 H), 1.37 (s, 9 H), 2.56 (dq, 3JHH = 7.5 Hz, 2JHF = 23.3 Hz, 1 H), 1.79 (s, 3 H), 4.45 (m, 4 H), 7.41 (br, 1 H).

13C NMR (50 MHz, CDC13, major diastereomer): δ = 10.6 (m), 16.2 (d, 3JCP = 16.2 Hz, 6.4 (d, 3JCP = 6.2 Hz), 28.2, 36.8 (d, 3JCP = 141 Hz), 53.1, 62.6 (d, 3JCP = 6.5 Hz), 63.1 (d, 3JCP = 7.3 Hz), 65.6 (q, 3JCP = 29 Hz), 80.7, 124.3 (dq, 3JCP = 288 Hz, 3JCP = 4.5 Hz), 153.8, 166.0 (d, 3JCP = 17 Hz).

19F NMR (282 MHz, CDC13): δ = 8.66 (s, 3 F).

31P NMR (121.5 MHz): δ = 24.93 (s).

HRMS: m/z [M + H+] calcd for C15H27F3NO7P, 422.15500; found, 422.15494.

3-(Diethoxypyrophosphoryl)-2-hydroxy-2-trifluoromethyl-butyric Acid Methyl Ester (8a)

Yield: 98% (379 mg); column chromatography (EtOAc), colorless oil; Rf 0.53.

The spectroscopic data are given for one diastereomer.

1H NMR (200 MHz, CDC13): δ = 1.24–1.36 (m, 9 H), 2.61 (dq, 3JHH = 7.3 Hz, 3JHP = 20.9 Hz, 1 H), 3.84 (s, 3 H), 4.11 (m, 4 H), 5.49 (s, 1 H).

13C NMR (50 MHz, CDC13): δ = 10.6 (d, 3JCP = 3.4 Hz), 16.2 (d, 3JCP = 6.8 Hz), 16.4 (d, 3JCP = 6.5 Hz), 35.5 (d, 3JCP = 141 Hz), 53.7, 62.7 (d, 3JCP = 6.9 Hz), 63.1 (d, 3JCP = 6.9 Hz), 78.6 (dq, 3JCP = 29 Hz, 3JCP = 3.0 Hz), 123.2 (dq, 3JCP = 287.5 Hz, 3JCP = 14.5 Hz), 168.0 (d, 3JCP = 9.9 Hz).

19F NMR (188 MHz, CDC13): δ = 1.80 (br, 3 F).

31P NMR (81 MHz): δ = 28.70 (q, 3JPP = 1.8 Hz).

HRMS: [M + Na+] calcd for C16H28F3NO8P, 323.08652; found, 323.08652.

3-(Diethoxypyrophosphoryl)-2-hydroxy-2-trifluoromethyl-butylc Acid Methyl Ester (8b)

Yield: 94% (302 mg); column chromatography (EtOAc), colorless oil; Rf 0.48.

The spectroscopic data are given for the diastereomeric mixture (ratio 2:5).

1H NMR (300 MHz, CDCl3): δ = 1.20 (dd, 3JHH = 7.4 Hz, 3JHP = 17.3 Hz, 3JHP = 17.3 Hz, 1.21 (dd, 3JHH = 7.4 Hz, 3JHP = 19.2 Hz, 3 JHP = 19.2 Hz, 1.26–1.31 (m, 12 H), 1.33–1.38 (m, 6 H), 2.29 (dq, 3JHH = 7.4 Hz, 3JHP = 20.3 Hz, 1 H), 2.48 (dq, 3JHH = 7.4 Hz, 3JHP = 20.4 Hz, 1 H), 3.75 (s, 3 H), 3.76 (s, 3 H), 4.01–4.15 (m, 8 H).
Yield: 77% (1.59 g); colorless oil.

8a

Yield: 68% (1.83 g); colorless oil.

7b

Yield: 72% (2.0 g); mp 50 °C.

- 50 °C. Then the reaction mixture was allowed to warm up to 0 °C and stirred for 1.5 h. It was quenched with HCl (20 mL, 1%) and extracted with CH2Cl2 (3 × 10 mL). The combined organic layers were dried with MgSO4. The volatiles were removed in vacuo to give crude 7a and 8a. Compounds 7a, 7b and 8a were purified by column chromatography (hexanes–EtOAc, 1:1) and EtOAc, respectively.

7a

Yield: 72% (2.0 g); mp 50 °C.

7b

Yield: 68% (1.83 g); colorless oil.

8a

Yield: 77% (1.59 g); colorless oil.

Acknowledgments

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References


(16) Ethyl glyoxylate (50% soln in toluene) was distilled prior to use according to literature: Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. J. Am. Chem. Soc. 2000, 122, 7936.