Hexafluoroacetone as Protecting and Activating Reagent: Site-Selective Functionalization of α-Amino Alkanedioic Acids

Thomas Rühl, Christoph Böttcher, Ksenia Pumpor, Lothar Hennig, Joachim Sieler, Klaus Burger

a Department of Organic Chemistry, University of Leipzig, Johannisallee 29, 04103 Leipzig, Germany
Fax +49(341)9736599; E-mail: burger@organik.chemie.uni-leipzig.de
b Department of Inorganic Chemistry, University of Leipzig, Linnéstraße 3, 04103 Leipzig, Germany

Received 7 July 2004; revised 30 August 2004

SYNTHESIS 2004, No. 18, pp 3065–3069

Abstract: Methodology for the site-selective functionalization of α-amino alkanedioic acids (Asp, Glu and homologues) using hexafluoroacetone as protecting and activating reagent is described. Via new types of dielectrophiles, alternative approaches to multifunctional non-natural amino acids and some of their conjugates become readily available.

Key words: hexafluoroacetone, fluorine, DAST, diacylation, α-carboxy-activation, amino acids

Site-selective derivatizations of multifunctional compounds like α-carboxy-α-amino acids (Asp, Glu and homologues) require sophisticated protection/activation concepts.1,2 Even relatively simple derivatives of aspartic acid like the sweetener aspartame3 (α-functionalization) and isopeptides4 (ω-functionalization) demand laborious multi-step procedures. Therefore, the development of new methodology is a challenge, where activation of the α-carboxylic group and protection of the adjacent amino group as well as peptide bond formation and deprotection of the amino group are performed as tandem reactions.5 This challenge can be met by using bidentate protective groups like phosgene,6 and certain aldehydes and ketones.7–9 However, on aminolysis of Leuchs anhydrides, formation of oligomers cannot be avoided. During aminolysis of the cyclic anhydride, the amino group of the newly formed dipeptide derivatives are so quickly deblocked, that they compete successfully with the amino acid ester as acyl acceptors. Furthermore, oxazolidinones derived from certain aldehydes like formaldehyde10 require additional N-protection and N-deprotection steps.

Recently, hexafluoroacetone (HFA) has been successfully applied for simultaneous protection and activation of α-amino-,11 α-hydroxy-,12 and α-mercapto acids13 without the need of additional protection and deprotection steps. On reaction of aspartic, malic, and thiomalic acid with HFA the α-functionality and the adjacent carboxy group are simultaneously protected. Concomitantly, the α-carboxy group is activated, while the α-carboxy group remains unaffected and can be derivatized selectively after separate activation. Remarkably, orthogonal protection and ω-activation can be achieved in only two steps.

We now report on the application of HFA as protecting and activating reagent for ω-derivatization of α-amino alkanedioic acids of different chain lengths (four to eight carbon atoms). HFA reacts with α-amino alkanedioic acids 1 in DMSO at room temperature to give 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-ones (2) in 67–90% yield. A second equivalent of HFA is necessary to trap the by-product formed. The extraction process with the biphasic system CH2Cl2–H2O to remove the hydrate can be avoided when DMF is used as a solvent. For work-up, DMF is distilled off in vacuo and HFA hydrate is removed by lyophilization (3 ×) to give 2 (90–98%; Scheme 1).

With the formation of the five-membered heterocyclic system – which is surprisingly stable toward acids under exclusion of moisture, but relatively sensitive toward bases14 – amino group protection and selective activation of the α-carboxy group are achieved in one step. Compounds 2 offer an efficient access to α-functionalized α-carboxy-α-amino acid derivatives demonstrated by a two-step aspartame synthesis in 72% overall yield.15
The first steps of the site-selective α- and ω-functionalization are identical (1 → 2, Scheme 1). Activation of the ω-carboxy group is achieved via acid halides. Acid chlorides 3 are readily available on treatment of 2 with an excess of thionyl chloride at room temperature. However, they can be isolated as stable compounds only in the case of certain chain lengths. The HFA-protected amino acid chlorides 3(17) and 3c can be purified by distillation in vacuo and stored over weeks on exclusion of moisture without decomposition. With 5 to 7 carbon atoms in the backbone the initially formed acid chlorides 3 spontaneously undergo ring closure to give lactams 5 (Scheme 1). Therefore, activation via acid chloride cannot be applied for HFA-protected glutamic-, α-amino adipic- and α-aminopimelic acid.

Open-chain and ring-closed products can be easily distinguished by IR, 1H and 19F NMR spectroscopy (Table 1). The δ-values of the geminal trifluoromethyl groups of the bicyclic systems are different compared to the open-chain species and show that the flexibility of the bicyclic lactams increases with the ring size (Δδ = 7.75 → 1.51, Table 1). To prove the bicyclic structure of the seven-membered lactam unequivocally we performed an X-ray structure analysis. Another serious disadvantage of the acid chloride route is its inability to handle tert-butyl-protected side chains. In contrast, the corresponding acid fluorides do not suffer such limitation. Acid fluorides, readily available from the corresponding carboxylates on reaction with cyanuric fluoride or DAST (diethylaminosulfur trifluoride) are less active than acid chlorides. Nevertheless, they are still useful acyl transfer reagents for both solution and solid phase peptide synthesis as well as for N-glycosylation reactions.

When HFA-protected glutamic acid (2b) was treated with DAST two products were formed in a 4:1 ratio, which are readily separable by column chromatography (silica gel; eluent: CH2Cl2). The assigned structures 4b and 5b are in agreement with the recorded NMR data. Surprisingly, 4b is distillable in vacuo without being transformed into the corresponding lactam 5b. However, on standing at room temperature after three days quantitative transformation 4b → 5b was observed. In the case of HFA-protected ω-amino adipic acid fluoride (4c) the amount of the corresponding by-product 5c is already well below 5%.

In summary, we found that acid fluorides 4 – except HFA-protected glutamic acid δ-fluoride – are perfectly stable dielectrophiles where two electrophilic centers of different reactivity are linked together with a spacer of variable length.

The protection/activation strategy disclosed above provides new methodology for site-selective ω-monofunctionalization, ω-monofunctionalization and α,ω-difunctionalization of α-amino alkanedioic acids. During the construction of the side chain the lactone moiety serves as protective group to give carboxy-activated species 7–9 which in the following step under appropriate conditions act as activated ester. Concomitantly, the α-amino group is deprotected and can be directly derivatized further. The above sequence enlarges the synthetic repertoire for histone deacetylases inhibitors (HDAC) considerably (Scheme 2).

Using the methodology disclosed above for site-selective ω-activation of α-amino alkanedioic acids 1 new routes to ω-isocyanato α-amino acids 6, ω-Fmoc-amino α-amino acids 7, isopeptides 8, multifunctional solid phase reagents 9 as well as to glycoconjugates, ω-keto-α-amino acids, ω-diazo α-amino acids, and lipid-modified α-amino acids with variable chain lengths now become readily available. Compounds 2–9 represent a new class of synthetically valuable building blocks, because they are α-carboxy-activated species, storable in a fridge for months on exclusion of moisture, and can be directly subjected to consecutive functionalizations without the need of extra activation or deprotection steps.

Table 1: 19F NMR Data of Compounds 2 and 5 (Solvent: CDCl3; Reference: TFA).

<table>
<thead>
<tr>
<th>Compound</th>
<th>δCF3 (ppm) of compounds 2</th>
<th>δCF3 (ppm) of compounds 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>b</td>
<td>-2.02, -2.96</td>
<td>-1.99, 5.76</td>
</tr>
<tr>
<td>c</td>
<td>-2.00, -2.91</td>
<td>0.05, 5.99</td>
</tr>
<tr>
<td>d</td>
<td>-2.64, -2.81</td>
<td>1.21, 2.72</td>
</tr>
</tbody>
</table>

The IR spectra were obtained with a Genesis ATI Mattson/Unicam FTIR spectrometer. NMR spectra were recorded with VARIAN Gemini 200, 2000 and 300, Bruker DRX 400 and 600 spectrometers. Chemical shifts are reported in ppm relative to CHCl3/CDCl3 (CHCl3, δ = 7.26 ppm/CDCl3, δ = 77.16 ppm). J values are given in Hz. 1H NMR spectra were recorded at 200 MHz, 300 MHz, 400 MHz and 600 MHz. 13C NMR spectra were recorded at 50 MHz, 76 MHz, 101 MHz and 151 MHz. 19F spectra were recorded at 188 MHz and 282 MHz with trifluoroacetic acid (TFA, δ = 0 ppm) as external standard. The signals were reported as real signals. Optical rotations ([α]D) were measured using a Polarotronic polarimeter (Schmidt & Haensch) in a 5 cm cell. For C, H, N analyses a CHNO-
Rapid-Elemental-Analyzer (Heraeus) and a VarioEL V2.6 (Elementar Analysensysteme GmbH) was used. MS spectra were obtained with an ESI, FAB and El spectrometer (Bruker Daltonics FT-ICR-MS Apex II; Fisons VG Autospec, ZAB-HSQ: Thermo Electron, Finnigan MAT, MAT 8230, MAT 212). For flash chromatography, silica gel (32–63 μm) was used with solvent systems given in the text. Organic solvents were dried and distilled prior to use. For the X-ray diffraction study crystals of the dimensions 0.20 × 0.10 × 0.20 mm were used. Crystallographic measurements were made at −60 °C using a SMART CCD area detector diffractometer (AXS BRUKER) (graphite monochromated MoKα, λ = 0.710730). The structure was solved by direct methods and subsequent Fourier difference techniques and refined using the program SHELXL-97. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were located by a Fourier difference map and refined using the program SHELXL. The structure was solved by direct methods and subsequent Fourier difference techniques and refined using the program SHELXL-97. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were located by a Fourier difference map and refined using the program SHELXL.

Protection of α-Amino Alkanedioic Acids with Hexafluoroacetone; General Procedure

Compound 1 (100 mmol) in DMF (50 mL) was reacted with an excess of hexafluoroacetone (> 2 equiv) in a t.t. in a glass apparatus equipped with a dry-ice condenser and sealed with a rubber bung. When the reaction was complete the solvent was removed under reduced pressure, and the residue was lyophilized. The crude product was redissolved in CHCl3, filtered and after removal of the solvent under reduced pressure the residue was lyophilized (3 ×).

(rac)-5-[2,2-Bis(trifluoromethyl)-5-oxo-1,3-oxazolidin-4-yl]pentanoic Acid (2d)

Yield: 31.65 g (98%); colorless crystals; mp 71–73 °C.

IR (KBr): 3352, 1818, 1707 cm⁻¹.

1H NMR (CDCl3): δ = 1.50 (m, 1 H), 1.58 (m, 1 H), 1.67–1.72 (m, 3 H), 1.91 (m, 1 H), 2.36–2.43 (m, 2 H), 3.05 (d, J = 7 Hz, 1 H), 3.96 (m, 1 H), 11.44 (br s, 1 H).

13C NMR (CDCl3): δ = 23.9, 24.7, 32.5, 33.6, 54.4, 88.4 (sept, J = 34 Hz), 120.3 (q, J = 285 Hz), 121.4 (q, J = 289 Hz), 171.2, 179.6.

19F NMR (CDCl3): δ = –2.64 (m, CF3), –2.81 (m, CF3).


Anal. Calcd for C14H10F6NO3: C, 37.41; H, 3.43; N, 4.33; Found: C, 37.54; H, 3.62; N, 4.57.

(rac)-6-[2,2-Bis(trifluoromethyl)-5-oxo-1,3-oxazolidin-4-yl]hexanoic Acid (2e)

Yield: 30.36 g (90%); colorless crystals; mp 79–80 °C.

IR (film): 3375, 1838 cm⁻¹.

1H NMR (CDCl3): δ = 1.33–1.47 (m, 3 H), 1.50 (m, 1 H), 1.60–1.78 (m, 3 H), 1.86 (m, 1 H), 2.89 (t, J = 7 Hz, 2 H), 3.27 (br s, 1 H), 3.95 (m, 1 H).

13C NMR (CDCl3): δ = 24.7, 24.8, 27.9, 32.5, 46.9, 54.5, 88.4 (sept, J = 34 Hz), 120.3 (q, J = 286 Hz), 121.3 (q, J = 289 Hz), 171.4, 174.0.

19F NMR (CDCl3): δ = –2.95 (m, CF3), –2.79 (m, CF3).

MS (ESI): mlz = 319 (M – HCl)+, 301 (20), 273 (8), 246 (4), 222 (50), 206 (9), 178 (16), 152 (13), 140 (12), 109 (39), 81 (66), 73 (100).

Anal. Calcd for C14H10F6ClNO3: C, 37.15; H, 3.40; N, 3.94; Found: C, 37.41; H, 3.34; N, 4.07.

Treatment of Compounds 2 with DAST; General Procedure

To a stirred solution of 2 (20 mmol) in anhyd CH2Cl2 (80 mL) DAST (3.45 g, 22 mmol) was added at 0 °C within 1 min. Stirring was continued at r.t. for 48 h. The progress of the reaction was monitored by 19F NMR spectroscopy. The excess of thionyl chloride was evaporated in vacuo; yield: 4.27 g (100%); bp 140 °C/0.2 torr (Kugelrohr).

(rac)-10,10-Bis(trifluoromethyl)-1-aza-9-oxabicyclo[5.3.0]decan-2,8-dione (5d)

Yield: 23.48 g (77%); colorless crystals; mp 102–103 °C; purification by sublimation.

IR (KBr): 1510, 1383 cm⁻¹.

1H NMR (CDCl3): δ = 1.80–1.85 (m, 1 H), 2.20–2.25 (m, 2 H), 2.27 (dd, J = 7 Hz, J = 15 Hz, 1 H), 2.75 (dd, J = 8 Hz, J = 15 Hz, 1 H), 4.41 (d, J = 11 Hz, 1 H).

13C NMR (CDCl3): δ = 22.7, 28.8, 33.0, 38.6, 57.51, 90.1 (sept, J = 36 Hz), 120.1 (q, J = 289 Hz), 120.3 (q, J = 290 Hz), 167.5, 171.6.

19F NMR (CDCl3): δ = 1.21 (q, J = 7 Hz, CF3), 2.72 (q, J = 7 Hz, CF3).

Synthesis 2004, No. 18, 3065–3069 © Thieme Stuttgart · New York
Anal. Calcd for C9H8F7NO3: C, 34.74; H, 2.60; N, 4.50. Found: C, 34.98; H, 2.67; N, 4.35.

1H NMR (CDCl3): 0.78–0.92 (m, 8 H), 1.86–2.03 (m, 4 H), 3.40–3.50 (m, 4 H), 3.61 (dd, J = 12 Hz, 1 H), 7.20–7.30 (m, 4 H).

13C NMR (CDCl3): 30.11; H, 1.68; N, 5.05.

1H NMR (CDCl3): 0.80–0.98 (m, 4 H), 1.86–2.05 (m, 4 H), 3.45–3.55 (m, 4 H), 3.68 (dd, J = 12 Hz, 1 H), 7.20–7.30 (m, 4 H).

13C NMR (CDCl3): 30.11; H, 1.68; N, 5.05.

1H NMR (CDCl3): 0.80–0.98 (m, 4 H), 1.86–2.05 (m, 4 H), 3.45–3.55 (m, 4 H), 3.68 (dd, J = 12 Hz, 1 H), 7.20–7.30 (m, 4 H).

13C NMR (CDCl3): 30.11; H, 1.68; N, 5.05.

rac-(Fluoren-9-yl)methyl-N-(3-[2,2-bis(trifluoromethyl)-5-oxo-1,3-oxazolidin-4-yl]pentanoyl) Fluoride (4d)
To a stirred solution of (fluoren-9-yl)methanol (216 mg, 1.1 mmol) in anhyd CHCl3 (10 mL), 6e (255 mg, 0.8 mmol) was added. Stirring was continued at reflux for 45 h. The progress of the reaction was monitored by TLC (elucent: petroleum ether–EtOAc, 4:1). After evaporation of the solvent in vacuo, the crude product was purified by flash chromatography (elucent: EtOAc–petroleum ether); yield 361 mg (88%); mp 101–102 °C.

IR (KBr): 3398, 1832, 1535 cm–1.

1H NMR (CDCl3): 0.80–0.99 (m, 4 H), 1.86–2.06 (m, 4 H), 3.45–3.55 (m, 4 H), 3.68 (dd, J = 12 Hz, 1 H), 7.20–7.30 (m, 4 H).

13C NMR (CDCl3): 30.11; H, 1.68; N, 5.05.

rac-(Fluoren-9-yl)methyl-N-(5-[2,2-bis(trifluoromethyl)-5-oxo-1,3-oxazolidin-4-yl]pen-tyl)carbamate (7e)
To a stirred solution of (fluoren-9-yl)methanol (343 mg, 1.8 mmol) in anhyd CHCl3 (10 mL), 6e (255 mg, 0.8 mmol) was added. Stirring was continued at reflux for 45 h. The progress of the reaction was monitored by TLC (elucent: petroleum ether–EtOAc, 4:1). After evaporation of the solvent in vacuo, the crude product was purified by flash chromatography (elucent: EtOAc–petroleum ether); yield 361 mg (88%); mp 101–102 °C.

IR (KBr): 3398, 1832, 1535 cm–1.

1H NMR (CDCl3): 0.80–0.99 (m, 4 H), 1.86–2.06 (m, 4 H), 3.45–3.55 (m, 4 H), 3.68 (dd, J = 12 Hz, 1 H), 7.20–7.30 (m, 4 H).

13C NMR (CDCl3): 30.11; H, 1.68; N, 5.05.

rac-(Fluoren-9-yl)methyl-N-(3-[2,2-bis(trifluoromethyl)-5-oxo-1,3-oxazolidin-4-yl]propyl) carbamate (7e)
To a stirred solution of (fluoren-9-yl)methyl-N-(3-[2,2-bis(trifluoromethyl)-5-oxo-1,3-oxazolidin-4-yl]propyl) carbamate (7e) in anhyd CHCl3 (10 mL), 6e (255 mg, 0.8 mmol) was added. Stirring was continued at reflux for 45 h. The progress of the reaction was monitored by TLC (elucent: petroleum ether–EtOAc, 4:1). After evaporation of the solvent in vacuo, the crude product was purified by flash chromatography (elucent: EtOAc–petroleum ether); yield 361 mg (88%); mp 101–102 °C.

IR (KBr): 3398, 1832, 1535 cm–1.

1H NMR (CDCl3): 0.80–0.99 (m, 4 H), 1.86–2.06 (m, 4 H), 3.45–3.55 (m, 4 H), 3.68 (dd, J = 12 Hz, 1 H), 7.20–7.30 (m, 4 H).

13C NMR (CDCl3): 30.11; H, 1.68; N, 5.05.

rac-(Fluoren-9-yl)methyl-N-3-[2,2-bis(trifluoromethyl)-5-oxo-1,3-oxazolidin-4-yl]pentyl Fluoride (4c)
To a stirred solution of (fluoren-9-yl)methanol (343 mg, 1.8 mmol) in anhyd CHCl3 (10 mL), 6e (255 mg, 0.8 mmol) was added. Stirring was continued at reflux for 45 h. The progress of the reaction was monitored by TLC (elucent: petroleum ether–EtOAc, 4:1). After evaporation of the solvent in vacuo, the crude product was purified by flash chromatography (elucent: EtOAc–petroleum ether); yield 361 mg (88%); mp 101–102 °C.

IR (KBr): 3398, 1832, 1535 cm–1.

1H NMR (CDCl3): 0.80–0.99 (m, 4 H), 1.86–2.06 (m, 4 H), 3.45–3.55 (m, 4 H), 3.68 (dd, J = 12 Hz, 1 H), 7.20–7.30 (m, 4 H).

13C NMR (CDCl3): 30.11; H, 1.68; N, 5.05.

rac-(Fluoren-9-yl)methyl-N-[3-[2,2-bis(trifluoromethyl)-5-oxo-1,3-oxazolidin-4-yl]pentyl Fluoride (4c)
To a stirred solution of (fluoren-9-yl)methanol (343 mg, 1.8 mmol) in anhyd CHCl3 (10 mL), 6e (255 mg, 0.8 mmol) was added. Stirring was continued at reflux for 45 h. The progress of the reaction was monitored by TLC (elucent: petroleum ether–EtOAc, 4:1). After evaporation of the solvent in vacuo, the crude product was purified by flash chromatography (elucent: EtOAc–petroleum ether); yield 361 mg (88%); mp 113–111 °C.

IR (KBr): 3359, 1830, 1539 cm–1.

1H NMR (CDCl3): 1.05–1.28 (m, 18 H), 1.38–1.44 (m, 14 H), 1.44–1.50 (m, 2 H), 2.46–2.52 (m, 1 H), 3.31–3.37 (m, 1 H), 7.30–7.36 (m, 4 H).

13C NMR (CDCl3): 30.11; H, 1.68; N, 5.05.

rac-(Fluoren-9-yl)methyl-N-3-[2,2-bis(trifluoromethyl)-5-oxo-1,3-oxazolidin-4-yl]pentyl Fluoride (4c)
To a stirred solution of (fluoren-9-yl)methanol (343 mg, 1.8 mmol) in anhyd CHCl3 (10 mL), 6e (255 mg, 0.8 mmol) was added. Stirring was continued at reflux for 45 h. The progress of the reaction was monitored by TLC (elucent: petroleum ether–EtOAc, 4:1). After evaporation of the solvent in vacuo, the crude product was purified by flash chromatography (elucent: EtOAc–petroleum ether); yield 361 mg (88%); mp 113–111 °C.

IR (KBr): 3359, 1830, 1539 cm–1.

1H NMR (CDCl3): 1.05–1.28 (m, 18 H), 1.38–1.44 (m, 14 H), 1.44–1.50 (m, 2 H), 2.46–2.52 (m, 1 H), 3.31–3.37 (m, 1 H), 7.30–7.36 (m, 4 H).

13C NMR (CDCl3): 30.11; H, 1.68; N, 5.05.
IR (KBr): 3305, 1835, 1730, 1660 cm⁻¹.

1H NMR (CDCl₃): δ = 1.40 (d, J = 7 Hz, 3 H), 2.56 (dd, J = 16 Hz, J = 9.5 Hz, 1 H), 2.91 (d, J = 16 Hz, J = 9 Hz, 1 H), 3.75 (s, 3 H), 4.05 (d, J = 7 Hz, 1 H), 4.40 (dd, J = 9.5 Hz, J = 7 Hz, 1 H), 4.55 (dd, J = 7 Hz, J = 7 Hz, 1 H), 6.48 (d, J = 7 Hz, 1 H).

13C NMR (CDCl₃): δ = 12.6 (CH₃), 120.2 (q, J = 288 Hz), 127.4, 128.7, 157.0, 171.7.

19F NMR (CDCl₃): δ = –2.27 (q, J = 9 Hz, CF₂), –2.27 (q, J = 9 Hz, CF₂).

IR (KBr): 3291–3025, 2935–2850, 1817, 1736, 1610 cm⁻¹.

Acknowledgement

We are grateful to Stiftung Volkswagenwerk, Hannover, for financial support.

References
