Hexafluoroacetone as protecting and activating reagent: Site-selective functionalization of iminodiacetic acid[*]

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Summary. Hexafluoroacetone was applied as a bidentate protecting and activating agent for the syntheses of RGD-peptide mimetics starting from iminodiacetic acid in solution and on solid phase.

Introduction

The development of new, efficient methodology for the construction of chemical libraries is of current interest (Cheng et al., 1996). In this context, we studied a series of multifunctional hexafluoroacetone-protected model compounds, including aspartic acid and its homologues (Rühl et al., 2004), to evaluate the applicability of hexafluoroacetone as protecting and activating agent for concise site-selective functionalizations. We found, that HFA-Asp is a reagent with highly interesting synthetic potential. The new concept offers alternative routes *i.a.* to numerous natural and non-natural amino acids (Fehn and Burger, 1997; Burger et al., 1992), antibiotics (Winkler and Burger, 1996; Golubev et al., 1993); small peptides (Burger et al., 2003) and glycoconjugates (Böttcher et al., 2004).

Now, we report on a successful application of the new strategy for the incorporation of imino diacetic acid moiety as a scaffold for peptide surrogates using liquid phase and solid phase techniques.

Integrins are the major family of cell surface receptors that mediate attachment to the extracellular matrix. There have been considerable efforts aimed at the design of RGD (Arg-Gly-Asp) containing peptides and RGD mimetics as integrin antagonists (Engleman et al., 1996). Liquid phase parallel synthesis (Sewald and Jakubke, 2002, Molteni et al., 1998; Gravert et al., 1997; Park et al., 1996; Han et al., 1996; Douglas et al., 1991) has been applied to synthesize small libraries of iminodiacetic acid derivatives (Cheng et al., 1996; Cheresh and Mecham, 1994; Ruoslahti et al., 1987). After each step of the reaction sequence, the PEG bound products were precipitated selectively and the excess of the reagents and the by-products were removed by simple filtration (Mutter and Bayer, 1994). Applying this technique, a library of integrin antagonists was constructed *via* a six step sequence starting from iminodiacetic acid (Scheme 1) (Cheng et al., 1999).

Materials and methods

General

IR spectra were obtained with a FTIR spectrometer (Genesis ATI Mattson/Unicam). NMR spectra were recorded with Varian Gemini 200/300 or Bruker DRX 400/600 spectrometers. [1]H chemical shifts were referenced to residual protic solvent (CDCl$_3$, $\delta_H = 7.26$ ppm; CD$_3$OD, $\delta_H = 3.35$ ppm; ^{13}C chemical shifts to solvent signals (CDCl$_3$, $\delta_C = 77.16$; CD$_3$OD, $\delta_C = 49.00$ ppm) and ^{19}F chemical shifts to CF$_3$COOH (external, $\delta_F = 0.00$ ppm). High resolution mass spectra were obtained with a Bruker Daltonics Apex II ESI-FT-ICR mass spectrometer. For flash chromatography silica gel (32–63 μm) was used with

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[*] Dedicated to Prof. Dr. Horst Wilde on the ocassion of his 65th birthday.
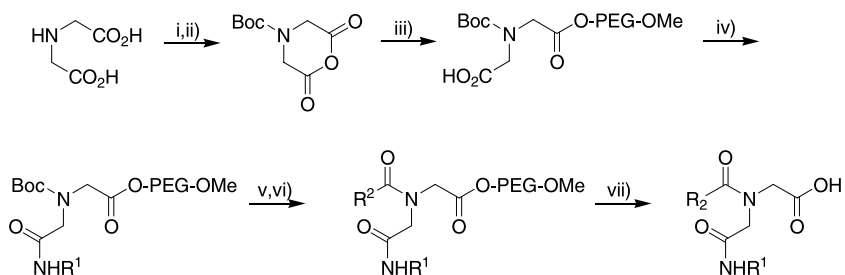
Scheme 1. i) Boc protection; ii) DCC; iii) MeO-PEG-OH, pyridine; iv) R^1NH_2, PyBOP, DIEA; v) TFA; vi) R^2CO_2H, PyBOP, DIEA; vii) 0.1 N NaOH

solvent systems given in the text. Organic solvents were dried and distilled prior to use.

Liquid phase synthesis

Methyl N'-[N-(carboxymethyl)glycyl]-N''-(benzyloxycarbonyl)lysinate (**3**)

To a stirred suspension of H-Lys(Cbz)-OMe·HCl (1.07 g, 3.23 mmol) in DMF (10 mL) DMAP (395 mg, 3.23 mmol) was added. After 30 min **2** (908 mg, 3.23 mmol) (Burger et al., 1993) was added and the mixture stirred at room temperature until TLC (eluent: MeOH) showed complete consumption of the starting material (2 d). DMF was distilled off and the residue purified by flash chromatography (eluent: CHCl$_3$/MeOH 1:1).

Yield: 1.20 g (91%), colorless solid. ^{1}H NMR (200 MHz, CD$_3$OD): $\delta = 1.35$–1.60 (m, 4H), 1.65–1.95 (m, 2H), 3.14 (t, J = 7.0 Hz, 2H), 3.60 (s, 2H), 3.74 (s, 3H), 3.90 (s, 2H), 4.49 (m, 1H), 5.10 (s, 2H), 7.35–7.39 (m, 5H) ppm. ^{13}C NMR (50 MHz, CD$_3$OD): $\delta = 23.9$, 30.4, 32.1, 41.4, 49.0, 50.5, 52.8, 53.8, 67.3, 128.8, 129.0, 129.5, 138.4, 158.9, 167.4, 171.3, 173.7 ppm. IR (KBr): ν 1735, 1683, 1634, 1539 cm^{-1}. MS (ESI): calcd. for C$_{19}$H$_{28}$N$_3$O$_7$ [M + H]$^+$: 410.19218, found: 410.19257.

Methyl N'-{N-(carboxymethyl)-N-[(4-trifluoromethyl)benzoyl]glycyl}-N''-(benzyloxycarbonyl)lysinate (**4a**)

3 (205 mg, 0.5 mmol) and NaHCO$_3$ (126 mg, 1.50 mmol) were suspended in dioxane (2.5 mL) and water (5 mL). A solution of 4-(trifluoromethyl)benzoyl chloride (104 mg, 0.5 mmol) in dioxane (2.5 mL) was slowly added under vigorous stirring. Stirring was continued for 18 h at room temperature. The solvents were evaporated *in vacuo* and the remaining residue was partitioned between ethyl acetate and 1 M HCl (each 10 mL). The aqueous phase was extracted twice with ethyl acetate (10 mL). The combined organic phases were dried over MgSO$_4$, filtered and evaporated. The crude product was purified by flash chromatography (gradient elution: CHCl$_3$/MeOH 10:1 → 4:1).

Yield: 171 mg (59%), colorless solid. ^{1}H NMR (600 MHz, CD$_3$OD, 298 K, COSY): rotational isomers (ratio 1.3:1); $\delta = 1.35$–1.60 (m, γ,δ-CH$_2$^{Lys}), 1.65–1.95 (m, β-CH$_2$^{Lys}), 3.12–3.17 (m, ε-CH$_2$^{Lys}), 3.73/3.77 (2s, OMe), 3.94–4.25 (m, 2CH$_2$^{Nasn}), 4.41 (m, α-CH^{Lys}-*minor rotamer*), 4.50 (m, α-CH^{Lys}-*major rotamer*), 5.09 (s, CH$_2$^{Cbz}), 7.31–7.39 (m, 2,3,4,5,6-CH^{Cbz}), 7.73–7.80 (m, 2,3,5,6-CH^{benzoyl}) ppm. ^{13}C NMR (150 MHz, CD$_3$OD, 298 K): $\delta = 24.0/24.2$, 30.3, 31.7/32.3, 41.4/41.5, 52.8, 53.2, 53.7/54.0, 55.3, 67.3/67.4, 125.3 (q, J = 273 Hz), 126.6/126.7, 128.7, 128.9, 129.5, 132.9 (q, J = 32 Hz), 138.4, 140.5/140.7, 158.9, 171.3, 171.6, 173.3, 174.0/174.1 ppm. ^{19}F NMR (282 MHz, CD$_3$OD, 298 K): $\delta = 13.4$ (s) ppm. MS (ESI): calcd. for C$_{27}$H$_{31}$F$_3$N$_3$O$_8$ [M + H]$^+$: 582.20578, found: 582.20524.

Methyl N'-[N-(carboxymethyl)-N-(4-benzoylbenzoyl)glycyl]-N''-(benzyloxycarbonyl)lysinate (**4b**)

3 (205 mg, 0.5 mmol), NaHCO$_3$ (126 mg, 1.5 mmol) and 4-benzoylbenzoyl chloride (122 mg, 0.5 mmol) were reacted according to the previous procedure under exclusion of light. The crude product was purified by flash chromatography (gradient elution: CHCl$_3$/MeOH 10:1 → 4:1).

Yield: 167 mg (54%), colorless solid. ^{1}H NMR (300 MHz, CD$_3$OD, 298 K, COSY): rotational isomers (ratio 1.3:1); $\delta = 1.35$–1.60 (m, γ,δ-CH$_2$^{Lys}), 1.65–1.95 (m, β-CH$_2$^{Lys}), 3.12 (t, J = 6.6 Hz, ε-CH$_2$^{Lys}), 3.72 (s, 3H, OMe), 3.98–4.27 (m, 2CH$_2$^{Nasn}), 4.42 (m, α-CH^{Lys}-*minor rotamer*), 4.52 (m, α-CH^{Lys}-*major rotamer*), 5.05 (s, CH$_2$^{Cbz}), 7.28–7.35 (m, 2,3,4,5,6-CH^{Cbz}), 7.51–7.57 (m, 2H, CH^{arom}), 7.64–7.72 (m, 3H, CH^{arom}), 7.74–7.86 (m, 4H, CH^{arom}) ppm. ^{13}C NMR (75 MHz, CD$_3$OD, 298 K): $\delta = 24.0/24.2$, 30.2, 31.7/32.2, 41.5, 52.8, 53.3, 53.7, 54.0, 55.4, 56.4, 67.3/67.4, 128.2, 128.7, 128.8, 128.9, 129.4, 129.6, 131.1, 131.2, 134.1, 138.3, 140.0, 140.1, 140.4, 140.6, 158.9, 171.4, 171.7, 173.7, 174.0, 174.2, 197.4 ppm. MS (ESI): calcd. for C$_{33}$H$_{36}$N$_3$O$_9$ [M + H]$^+$: 618.24461, found: 618.24441.

4-Methoxybenzyl [5-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolidine-3-yl]acetate (**6**)

To a stirred solution of 4-methoxybenzyl alcohol (1.00 g, 7.24 mmol) and DMAP (45 mg, 0.37 mmol) in pyridine (10 mL) **5** (2.61 g, 8.71 mmol) (Burger et al., 1993) was slowly added at 0°C. Stirring was continued for 2 h at 0°C and for 16 h at room temperature. The volatiles were evaporated *in vacuo* and the residue redissolved in ethyl acetate (100 mL). The organic phase was extracted twice with ice water (50 mL), dried over MgSO$_4$, filtered and evaporated. The crude product was purified by flash chromatography (eluent: petroleum ether/ethyl acetate 9:1).

Yield: 1.87 g (64%), colorless solid. ^{1}H NMR (200 MHz, CDCl$_3$): $\delta = 3.81$ (s, 5H), 3.93 (s, 2H), 6.89 (d, 2H, J = 8.5 Hz), 7.28 (d, 2H, J = 8.5 Hz) ppm. ^{13}C NMR (50 MHz, CDCl$_3$): $\delta = 48.6$, 48.7, 55.5, 67.5, 89.9 (sept, J = 33 Hz), 114.3, 121.1 (q, J = 289 Hz), 127.0, 130.6, 160.2, 166.7, 167.9 ppm. ^{19}F NMR (188 MHz, CDCl$_3$): $\delta = -0.11$ (s) ppm. IR (KBr): ν 1846, 1749, 1610, 1515, 1452 cm^{-1}.

Methyl N'-[N-(4-methoxybenzyloxycarbonylmethyl)glycyl]-N''-(benzyloxycarbonyl)lysinate (**7**)

To a stirred suspension of H-Lys(Cbz)-OMe·HCl (165 mg, 0.50 mmol) in pyridine (2 mL) DMAP (61 mg, 0.50 mmol) was added. After 30 min **6** (100 mg, 0.25 mmol) was added and the mixture stirred at room temperature until TLC (eluent: ethyl acetate) showed complete consumption of the starting material (2 d). After addition of water (25 mL) the mixture was freeze dried and the remaining residue purified by flash chromatography (eluent: ethyl acetate).

Yield: 116 mg (88%), slightly yellow oil. ^{1}H NMR (200 MHz, CDCl$_3$): $\delta = 1.30$–1.90 (m, 6H), 3.13–3.21 (m, 2H), 3.33 (s, 2H), 3.43 (s, 2H), 3.72 (s, 3H), 3.80 (s, 3H), 4.60 (m, 1H), 4.90 (s br., 1H), 5.10 (s, 4H), 6.88 (d, 2H, J = 8.5 Hz), 7.29 (d, 2H, J = 8.5 Hz), 7.29–7.34 (m, 5H), 7.64 (d, 1H, J = 9.0 Hz) ppm. ^{13}C NMR (50 MHz, CDCl$_3$): $\delta = 22.6$, 29.5, 32.1, 40.7, 50.9, 51.5, 52.3, 52.5, 55.4, 66.7, 66.8, 114.2, 127.6, 128.2, 128.6, 130.4, 136.8, 156.5, 160.2, 171.1, 172.8 ppm. IR (KBr): ν 1734, 1670, 1520 cm^{-1}.

Methyl N'-{N-(4-methoxybenzyloxycarbonylmethyl)-N-[4-(trifluoromethyl)benzoyl]glycyl}-N''-(benzyloxy-carbonyl)lysinate (**8**)

7 (106 mg, 0.20 mmol) and DMAP (3 mg, 0.02 mmol) were dissolved in pyridine (2 mL) and chilled in an ice bath. 4-(Trifluoromethyl)benzoyl chloride (63 mg, 0.30 mmol) was slowly added under stirring at 0°C and

stirring was continued at room temperature until TLC (eluent: ethyl acetate) showed complete consumption of the starting material (2 h). Water (25 mL) was added and the mixture stirred for 15 min. After freeze drying the crude product was purified by flash chromatography (eluent: petroleum ether/ethyl acetate 1:1).

Yield: 76 mg (54%), colorless solid. ^{1}H NMR (400 MHz, CDCl$_3$, 298 K, COSY): rotational isomers (ratio 1.3:1); $\delta = 1.20-1.40$ (m, γ-CH$_2^{Lys}$), 1.40–1.55 (m, δ-CH$_2^{Lys}$), 1.70–1.90 (m, β-CH$_2^{Lys}$), 3.12–3.19 (m, ε-CH$_2^{Lys}$), 3.71 (s, OMe), 3.76 (s, OMe), 3.89–4.32 (m, 2CH$_2^{Nasn}$), 4.52 (m, α-CH^{Lys}), 4.83 (s br., ε-NH^{Lys}-major rotamer), 4.97 (s, CH$_2^{Cbz}$, ε-NH^{Lys}-minor rotamer), 5.06 (s, CH$_2^{PMB}$-minor rotamer), 5.14 (s, CH$_2^{PMB}$-major rotamer), 6.85 (d, J = 8.4 Hz, 3,5-CH^{PMB}), 7.11 (d, J = 7.2 Hz, α-NH^{Lys}-minor rotamer), 7.19 (d, J = 8.4 Hz, 2,6-CH^{PMB}-minor rotamer) 7.26–7.32 (m, 2,3,4,5,6-CH^{Cbz}, 2,6-CH^{PMB}-major rotamer), 7.42/7.50 (2d, J = 7.6 Hz, 2,6-/3,5-CH^{benzoyl}-minor rotamer), 7.65 (s, 2,3,5,6-CH^{benzoyl}-major rotamer), 7.88 (d, J = 7.2 Hz, α-NH^{Lys}-major rotamer) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 298 K): $\delta = 22.5/22.9$, 29.7, 31.1/31.9, 40.7, 50.6, 51.6, 52.3, 52.7, 54.9, 55.6, 66.9, 67.9, 114.3, 124.2 (q, J = 273 Hz), 126.1, 127.5, 127.9, 128.3, 128.8, 130.6/130.8, 133.0 (q, J = 32 Hz), 136.9, 137.9, 138.3, 156.9, 160.2, 168.2/168.4, 169.7, 170.5, 171.6, 172.6/172.8 ppm. ^{13}C NMR (282 MHz, CDCl$_3$, 298 K): $\delta = 14.7$ (s) ppm. IR (KBr): ν 1739, 1690, 1657, 1615, 1542, 1516 cm^{-1}. MS (ESI): calcd. for C$_{35}$H$_{39}$F$_3$N$_3$O$_9$ [M + H]$^+$: 702.26329, found: 702.26278.

Methyl N'-[N-(carboxymethyl)-N-(4-trifluoromethylbenzoyl) glycyl]-N''-(benzyloxycarbonyl)lysinate (**4a**)

8 (70 mg, 0.10 mmol) was dissolved in CH$_2$Cl$_2$ (2 mL) and trifluoroacetic acid (2 mL) and water (0.05 ml) were added. The mixture was stirred at room temperature for 45 min. The volatiles were evaporated *in vacuo* and the remaining residue purified by flash chromatography (eluent: CHCl$_3$/MeOH 5:1). Yield: 55 mg (95%), analytical data in accordance with those previously reported.

Solid phase synthesis

Preparation of **4a** on Wang resin

10a: Wang resin (1.00 g, 0.5–0.6 mmol/g, 200–400 mesh, Acros) was swollen in pyridine (10 mL) for 30 min. DMAP (7 mg, 0.06 mmol) and **5** (360 mg, 1.2 mmol) were added under vigorous stirring and stirring was continued for 18 h at room temperature. The resin was filtered off, washed carefully with pyridine (3 × 50 mL) and ethyl acetate (3 × 50 mL) and dried *in vacuo*. Loading: 0.55 mmol/g, as determined by elemental analysis of nitrogen. IR (KBr): ν 3419 (br.), 3061, 3020, 2908, 2848, 1846, 1745, 1603, 1506, 1446 cm^{-1}.

11a: H-Lys(Cbz)-OMe · HCl (397 mg, 1.20 mmol) and DMAP (147 mg, 1.20 mmol) were dissolved in pyridine (10 mL) and stirred. After 30 min the resin was added and stirring was continued at room temperature for

2 d. The resin was filtered off, washed carefully with pyridine (2 × 50 mL), CH$_2$Cl$_2$ (2 × 50 mL) and water (2 × 50 mL) and dried *in vacuo*.

12a: The resin was swollen in pyridine (10 mL) for 30 min and the mixture chilled in an ice bath. DMAP (7 mg, 0.06 mmol) followed by 4-(trifluoromethyl)benzoyl chloride (250 mg, 1.20 mmol) were added at 0°C under vigorous stirring and stirring was continued at room temperature for 24 h. The resin was filtered off, washed with pyridine (2 × 50 mL), ethyl acetate (2 × 50 mL) and water (2 × 50 mL) and dried *in vacuo*.

4a: The resin was swollen in dichloromethane (10 mL) for 30 min. Trifluoroacetic acid (10 mL) and water (0.25 mL) were added and the mixture stirred for 4 h at room temperature. The resin was filtered off and washed with CH$_2$Cl$_2$ (3 × 50 mL) and methanol (3 × 50 mL). The filtrate was evaporated *in vacuo* and the remaining residue purified by flash chromatography (eluent: chloroform/methanol 5:1). Yield: 144 mg (45%), analytical data in accordance with those previously reported.

Preparation of **4b** on HMPA PEGA resin

10b: HMPA PEGA resin (1.40 g, 0.2–0.4 mmol/g, Novabiochem) was swollen in pyridine (20 mL) for 30 min. DMAP (7 mg, 0.06 mmol) and **5** (360 mg, 1.2 mmol) were added under vigorous stirring and stirring was continued at room temperature for 24 h. The resin was filtered off and washed carefully with pyridine (3 × 50 mL). The loading procedure was repeated and the resin finally washed with ethyl acetate (3 × 50 mL) and dried *in vacuo*. Loading: 0.51 mmol/g, as determined by elemental analysis of fluorine. IR (KBr): ν 3448 (br.), 2929, 2885, 1848, 1749, 1639 cm^{-1}.

11b: H-Lys(Cbz)-OMe · HCl (473 mg, 1.43 mmol) and DMAP (175 mg, 1.43 mmol) were dissolved in pyridine (20 mL) and stirred. After 30 min the resin was added and stirring was continued for 2 d at room temperature. The resin was filtered off, washed carefully with pyridine (2 × 50 mL), ethyl acetate (2 × 50 mL) and water (2 × 50 mL) and dried *in vacuo*.

12b: The resin was swollen in pyridine (20 mL) for 30 min and the mixture chilled in an ice bath. DMAP (7 mg, 0.06 mmol) followed by 4-benzoylbenzoyl chloride (350 mg, 1.43 mmol) were added at 0°C under vigorous stirring and stirring was continued at room temperature for 24 h. The resin was filtered off, washed with pyridine (2 × 50 mL), ethyl acetate (2 × 50 mL) and water (2 × 50 mL) and dried *in vacuo*.

4b: The resin was stirred in a mixture of TFA (20 mL) and water (1 mL) for 4 h at room temperature. The resin was filtered off and washed carefully with methanol (3 × 50 mL). The filtrate was evaporated *in vacuo* and the remaining residue purified by flash chromatography (eluent: chloroform/methanol 5:1). Yield: 57 mg (13%), analytical data in accordance with those previously reported.

Results and discussion

We now disclose that the above mentioned strategy provides access to RGD mimetics in only three steps starting from iminodiacetic acid (Scheme 2).
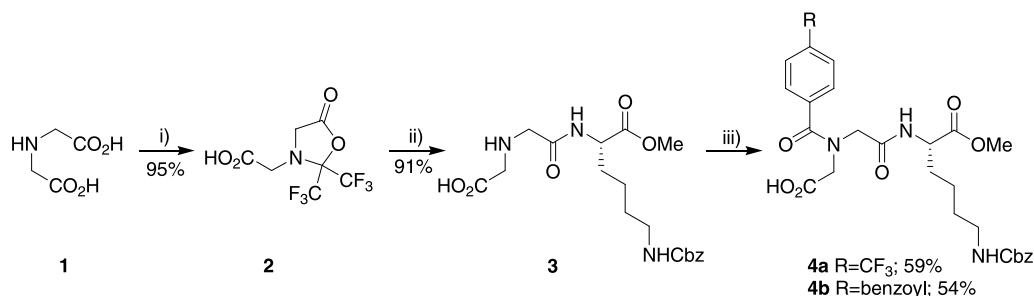
Scheme 2. i) 2 HFA, DMF; ii) H-Lys(Cbz)-OMe · HCl, DMAP, pyridine; iii) 4-substituted benzoyl chloride, NaHCO$_3$, dioxane/water 1:1

First, iminodiacetic acid **1** was transformed into lactone **2** on reaction with HFA in DMSO at room temperature (Weygand et al., 1966; Burger et al., 1993). To get optimal yields, two equivalents of HFA have to be added, because one equivalent is necessary for trapping the water eliminated during lactonization. Nearly quantitative yield was obtained when the reaction of iminodiacetic acid with HFA was performed in DMF (Rühl and Burger, unpublished). A modified work-up is the reason for the improvement: After distilling off DMF under reduced pressure, the HFA hydrate was removed by repeated lyophilization (3×). The heterocyclization process includes simultaneous functionalization of the imino and one of the carboxy groups. The second carboxy group remains unaffected.

The lactone moiety represents an activated ester and therefore can be derivatized site selectively with various nucleophiles. The cleavage of the lactone ring is coupled with the deprotection of the imino group which can be derivatized in a consecutive step. Structural diversity can be achieved on reaction of **3** with different acid chlorides in the presence of a tertiary base like *N*-methyl morpholine, using 4-dimethylamino pyridine as catalyst (5–10%) (Hoefle et al., 1978) or under base-free conditions in the presence of propene oxide. We found that protection of the carboxy group in general is not necessary for *N*-acylation, *N*-sulfonylation and *N*-phosphorylation reactions. In certain cases it may be advantageous to protect the carboxy moiety with 4-methoxyphenylmethanol (**5 → 6**). Deprotection is achieved on treatment with diluted TFA at room temperature (**8 → 4**).

Products **4** are analytically pure after flash chromatography. If trifunctionalization is required the unprotected carboxy group can be selectively activated and derivatized.

SPS of compounds **4** needs three additional steps, namely carboxy group activation and attachment of the HFA-protected iminodiacetic acid to the nucleophilic surface of the resin preferencially *via* acid chloride **5** in the presence of pyridine and catalytic amounts of 4-dimethylamino pyridine. In the final step products **4** have to be cleaved from the resin by acid hydrolysis (**12 → 4**).

SPS was performed with two different types of resins (Wang and PEGA resin) which exhibit different swelling properties. Water is not suitable for Wang resin, but it is optimal in the case of PEGA resin. The option to work in aqueous systems can be essential for certain biochemical processes. The loading of the resin was determined by elemental analysis (N%).

The advantage of the above reaction sequence is, that already activated species are bound to the resin. Therefore, carboxy group activation has not to be performed at the resin. This guarantees that 100% of the resin-bound iminodiacetic acid are activated. The resin-bound HFA-protected and activated derivative of iminodiacetic acid represents a useful universal solid phase reagent suitable *i.a.* for covalent immobilization of biomolecules, especially amino acids, peptides and proteins, for generation of libraries *via* combinatorial techniques and for affinity labeling (Jenssen et al., 2004) and affinity purification (Rühl et al., 2000; 2001) of certain biologically relevant species.

The aminolytic ring opening of the lactone moiety gave excellent yields when an excess of the nucleophile (3–5 equiv.) was used. Concomitantly, with the regioselective derivatization of the carboxy group, the secondary amino group is deprotected. The excess of the nucleophile and of the HFA hydrate formed during the cleavage of the lactone moiety can be readily removed by washing the resin
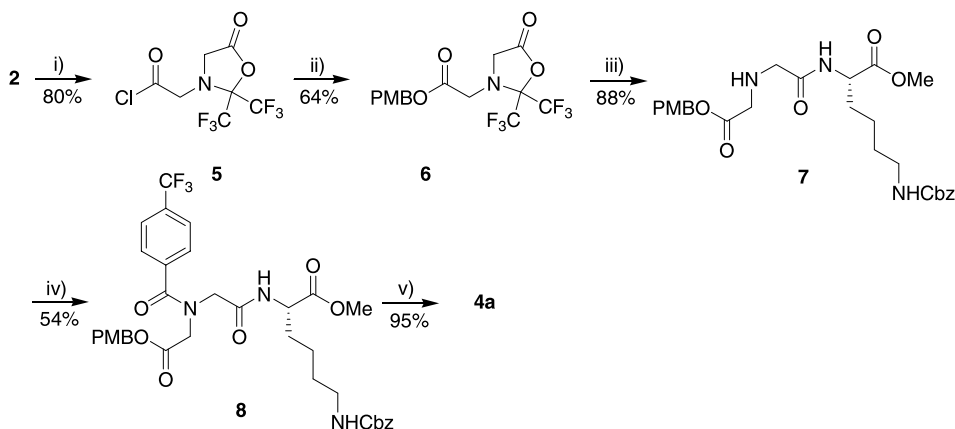
Scheme 3. i) PCl$_5$; ii) p-methoxybenzyl (PMB) alcohol, DMAP, pyridine; iii) H-Lys(Cbz)-OMe · HCl, DMAP, pyridine; iv) 4-(trifluoromethyl)benzoyl chloride, DMAP, pyridine; v) TFA, H$_2$O
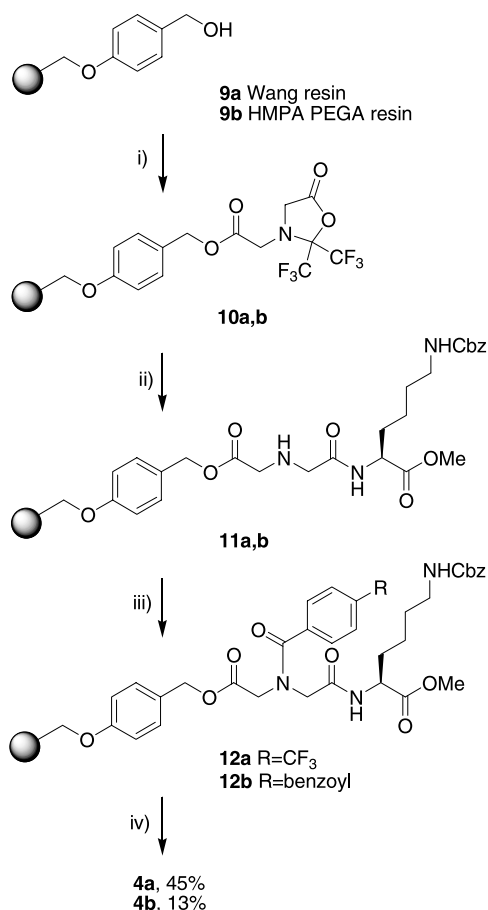
Scheme 4. i) **5**, DMAP, pyridine; ii) H-Lys(Cbz)-OMe · HCl, DMAP, pyridine; iii) 4-substituted benzoyl chloride, DMAP, pyridine; iv) TFA, H₂O

with an appropriate solvent and water. Next, the secondary amino group is *N*-acylated with the corresponding acid chlorides (3–5 equiv.) in the presence of tertiary amine/4-dimethylamino pyridine (5–10%), furnishing the corresponding resin-bound RGD surrogate in excellent yields. After removing the excess of the acylation reagent by washing the resin with pyridine, ethyl acetate and water the resin was dried *in vacuo*. Finally compounds **4a**, **b** were cleavaged from the resin. Standard conditions for cleavage of the Wang linker have been applied (TFA/H₂O, 95:5). The overall yield ranged from 13–45%.

HFA-protected iminodiacetic acid represents a valuable building block for the construction of peptidomimetics and apeptides.

Acknowledgements

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