Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 596

www.rsc.org/obc

PAPER

DBU-Catalyzed transprotection of *N*-Fmoc-cysteine di- and tripeptides into *S*-Fm-cysteine di- and tripeptides†

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Received 3rd September 2010, Accepted 21st September 2010
DOI: 10.1039/c0ob00663g

The transprotection of *N*-Fmoc-cysteine containing di- and tripeptides possessing a free SH group to produce the corresponding *S*-Fm-cysteine di- and tripeptides bearing a free amino group is accomplished efficiently with DBU in dry THF. The *N*-Fmoc to *S*-Fm transformation mechanism is discussed. *S*-Fm-Cysteine di- and tripeptides readily form amide bonds on coupling with *N*-(Pg-α-aminoacyl)-benzotriazoles and *N*-(Pg-α-dipeptidoyl)benzotriazoles to give larger peptides.

Introduction

Protecting groups play important roles in organic synthesis and the development of new selective methodologies for the protection and deprotection of sensitive functionalities is ongoing.[1] 9-Fluorenylmethyloxycarbonyl (Fmoc) is widely used as a protecting group in peptide chemistry, since it is easily removed by base, provides good orthogonality and is inexpensive with many Fmoc-protected amino acids sold commercially. The 9-fluorenylmethyl (Fm) group is used for thiol protection[2] and has been preferred for the orthogonal protection of cysteine in Boc/benzyl-based synthetic strategies.[3]

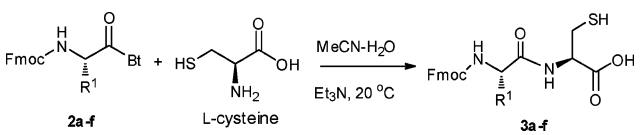
Transprotections, which combine deprotection and protection into a single step, can be highly valuable in organic synthesis. Known transprotections include the well-known, useful transformation of enol ethers into ketals,[4] the conversions of allyl carbamates into amides or dipeptides,[5] thioesters into thioethers or thioketals,[6] silyl ethers into benzyl ethers or esters,[7] enol ethers into thioketals,[8] and nucleosidic silyl ethers into acetates.[9] We now report transprotections of *N*-Fmoc-protected cysteine peptides possessing free sulfhydryl groups into *S*-Fm-protected cysteine peptides having free amino groups corresponding to simultaneous *N*-Fmoc deprotection of the amino group and *S*-Fm protection of the thiol group.

Results and discussion

1. Preparation of *N*-Fmoc-protected cysteine dipeptides 3a–f

The starting *N*-(protected-α-aminoacyl)benzotriazoles **2a–i** (*N*-Fmoc-L-Phe-Bt **2a**, *N*-Fmoc-L-Met-Bt **2b**, *N*-Fmoc-L-Ala-Bt **2c**, *N*-Fmoc-L-Leu-Bt **2d**, *N*-Fmoc-Gly-Bt **2e**, *N*-Fmoc-L-Lys(*N*-Boc)-Bt **2f**, *N*-Cbz-L-Ala-Bt **2g**, *N*-Cbz-Gly-Bt **2h**, *N*-Cbz-L-Leu-Bt **2i** were prepared from corresponding *N*-protected amino acids following our previously published one-step procedure.[10]

Peptide coupling of *N*-(Fmoc-α-aminoacyl)benzotriazoles **2a–f** with L-cysteine in partially aqueous solution (MeCN–H_2O 7 : 3) in the presence of Et_3N for one hour at room temperature gave novel *N*-Fmoc-protected cysteine dipeptides **3a–f** (78–98%), which were characterized by ^1H, ^{13}C NMR spectroscopy and elemental analyses (Scheme 1, Table 1).[11]



Scheme 1 Synthesis of *N*-Fmoc-cysteine dipeptides **3a–f**.

Table 1 Preparation *N*-Fmoc- Cysteine dipeptides **3a–f**

2	Product **3**	Yield[a] (%)	Mp/°C
2a	*N*-Fmoc-Phe-L-Cys-OH **3a**	98	164–166
2b	*N*-Fmoc-Met-L-Cys-OH **3b**	88	110–111
2c	*N*-Fmoc-Ala-L-Cys-OH **3c**	84	167–169
2d	*N*-Fmoc-Leu-L-Cys-OH **3d**	86	68–70
2e	*N*-Fmoc-Gly-L-Cys-OH **3e**	84	90–91
2f	*N*-Fmoc-Lys(*N*-Boc)-L-Cys-OH **3f**	78	88–90

[a] Isolated yield.

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† Electronic supplementary information (ESI) available: (1) characterization data for compounds **3b–f**, **4b–f**, **9b–d**, **10a–c** and **11**, and (2) ^1H NMR, ^{13}C NMR spectra of compounds. See DOI: 10.1039/c0ob00663g

Table 2 Transprotection of *N*-Fmoc-dipeptides **3a–f** to form *S*-Fm-dipeptides **4a–f**

3	Product **4**	Yield[a] (%)	Mp °C
3a	H-L-Phe-L-Cys(*S*-Fm)-OH **4a**	81	233–235
3b	H-L-Met-L-Cys(*S*-Fm)-OH **4b**	76	205–207
3c	H-L-Ala-L-Cys(*S*-Fm)-OH **4c**	70	202–204
3d	H-L-Leu-L-Cys(*S*-Fm)-OH **4d**	87	207–209
3e	H-Gly-L-Cys(*S*-Fm)-OH **4e**	78	230–232
3f	H-L-Lys(*N*-Boc)-L-Cys(*S*-Fm)-OH **4f**	69	165–167

[a] Isolated yield

2. Transprotection of *N*-Fmoc-protected cysteine dipeptides 3a–f

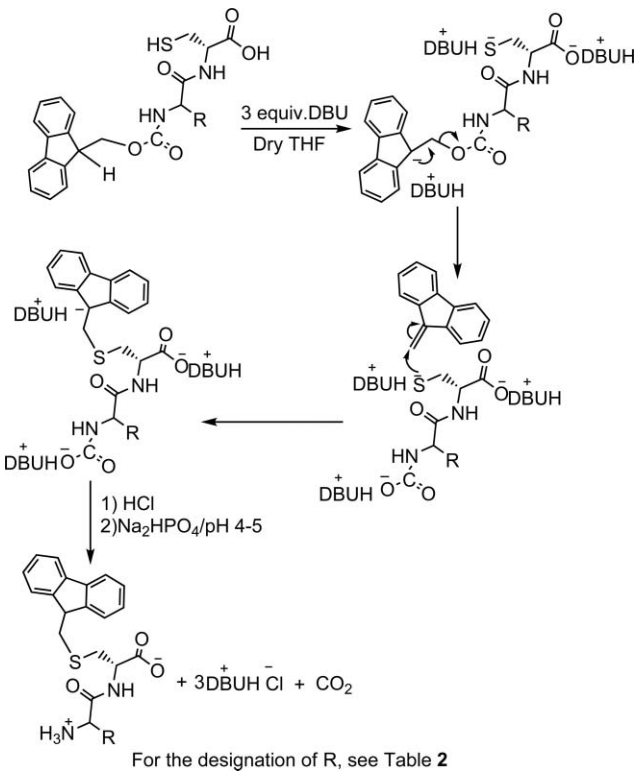
N-Fmoc-protected cysteine dipeptides **3a–f** were each treated with three equivalents of DBU in dry THF at 0 °C for 15 min to afford the corresponding *S*-Fm-transprotected dipeptides **4a–f** in (69–87%) yields (Scheme 2, Table 2). These compounds were characterized by ^{1}H, ^{13}C- NMR spectroscopy and elemental analyses.

Scheme 2 Transprotection of *N*-Fmoc-dipeptides **3a–f** to form *S*-Fm-dipeptides **4a–f**.

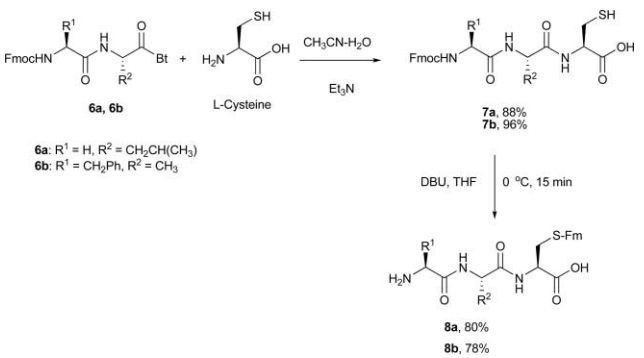
The mechanism of the transprotection (Scheme 3) involves three steps: (i) one equivalent of DBU catalyses the $E^{1}cB$ reaction, which liberates dibenzofulvene (DBF) and forms DBU carbamate, two additional equivalents of DBU are consumed in formation of DBU mercaptide and DBU carboxylate; (ii) the mercaptide anion adds by Michael reaction to dibenzofulvene (DBF); (iii) carbamic acid is formed and rapidly decarboxylated on acidification with HCl. When less than three equivalents of DBU was used, the reaction rate was decreased. The successful transprotection of **3f** into **4f** where the lysine side chain is protected with N-Boc acid labile group extends the scope of this methodology to examples of amino acids which require side chain protection by an acid labile group. One step deprotection of amino group of **3a–f** and protection of thiol group was thus achieved to afford *S*-Fm-protected dipeptides **4a–f**.

3. Transprotection of N-Fmoc-cysteine tripeptides 7a,b

N-(Fmoc-Dipeptidoyl)benzotriazoles **6a,b**, which were prepared by our previously published procedure[12] are reacted with L-cysteine in acetonitrile–water (3 : 1) in the presence of one equivalent of TEA to give *N*-Fmoc-cysteine tripeptides **7a,b** in 88%, 96% yields respectively (Scheme 4). Then, treatment of **7a,b** with three equivalents of DBU in dry THF at 0 °C for 15 min afforded transprotected *S*-Fm-cysteine tripeptides **8a,b** in 80%, 78% yields respectively (Scheme 4). *S*-Fm-Cysteine tripeptides **8a,b** were characterized by ^{1}H, ^{13}C-NMR spectroscopy and elemental analyses.



Scheme 3 Mechanism of *N*-Fmoc to *S*-Fm transformation.



Scheme 4 Synthesis of *N*-Fmoc cysteine tripeptides **7a,b** and their transprotection into *S*-Fm cysteine tripeptides **8a,b**.

4. Utility of the *S*-Fm protecting group

The Fm-group is stable towards hydrogenation,[13] and several reagents frequently used in solid-phase synthesis including HF and diisopropylethylamine (DIPEA).[14] However, Fm is readily cleaved by ammonia in methanol or organic bases, *e.g.* a 20% piperidine in dimethylformamide,[13] and hence *S*-Fm-protected cysteine peptides having a free amino group could be valuable building blocks in peptide synthesis in solid or solution phase. Indeed, the *S*-Fm protected cysteine residues have served as reliable thiol precursors during the synthesis of cyclic tripeptides,[15] cyclic disulfide-peptides such as oxytocin,[16] bicyclo[2,3]-Leu-enkephalin analogues,[17] and bis-cystine peptides.[14]

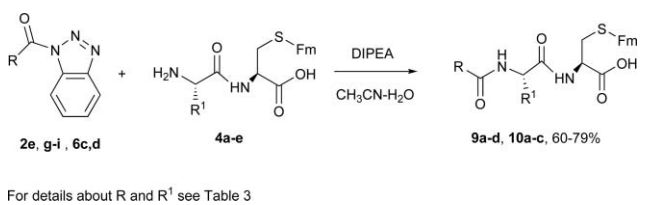
Table 3 Peptide coupling reactions of *S*-Fm-cysteine peptides **4a–e** with *N*-(Pg-α-aminoacyl)benzotriazoles **2e,g–i** and *N*-(Pg-dipeptidoyl)benzotriazole **6c,d**

Entry	RCOBt **2** or **6**	*S*-Fm-peptide **4**	*N*-Pg-*S*-Fm-Cysteine peptide **9** or **10**, Yield[a] (%)
1	*N*-Fmoc-Gly-Bt **2e**	H-Phe-Cys(*S*-Fm)-OH **4a**	Fmoc-Gly-Phe-Cys(*S*-Fm)-OH **9a**, 75
2	*N*-Cbz-Ala-Bt **2g**	H-Gly-Cys(*S*-Fm)-OH **4e**	Cbz-Ala-Gly-Cys(*S*-Fm)-OH **9b**, 70
3	*N*-Cbz-Gly-Bt **2h**	H-Ala-Cys(*S*-Fm)-OH **4c**	Cbz-Gly-Ala-Cys(*S*-Fm)-OH **9c**, 60
4	*N*-Cbz-Leu-Bt **2i**	H-Met-Cys(*S*-Fm)-OH **4b**	Cbz-Leu-Met-Cys(*S*-Fm)-OH **9d**, 65
5	*N*-Cbz-Leu-Met-Bt **6c**	H-Gly-Cys(*S*-Fm)-OH **4e**	Cbz-Leu-Met-Gly-Cys(*S*-Fm)-OH **10a**, 75
6	*N*-Cbz-Ala-Phe-Bt **6d**	H-Ala-Cys(*S*-Fm)-OH **4c**	Cbz-Ala-Phe-Ala-Cys(*S*-Fm)-OH **10b**, 72
7	*N*-Cbz-Ala-Phe-Bt **6d**	H-Leu-Cys(*S*-Fm)-OH **4d**	Cbz-Ala-Phe-Leu-Cys(*S*-Fm)-OH **10c**, 79

[a] Isolated yield.

5. Solution-phase peptide coupling reactions of *S*-Fm-cysteine peptides 4a–e, 8a with *N*-(protected-*α*-aminoacyl)benzotriazoles 2e, 2g–i and *N*-(protected-dipeptidoyl)benzotriazole 6c,d

S-Fm-Protected dipeptides **4a–e** on treatment with *N*-(Pg-α-aminoacyl)benzotriazoles **2e,g–i** and *N*-(Cbz-α-dipeptidoyl)benzotriazoles **6c,d** (compounds **6c,d** were prepared by our previously published procedure[12]) in the presence of diisopropyl ethylamine at 20 °C in acetonitrile–water afforded cysteine tripeptides **9a–d** (65–75%) and tetrapeptides **10a–c** (72–79%) respectively (Scheme 5, Table 3). *N*-Pg-*S*-Fm-Cysteine containing tri- and tetrapeptides were characterized by ^{1}H, ^{13}C NMR spectroscopy and elemental analyses.

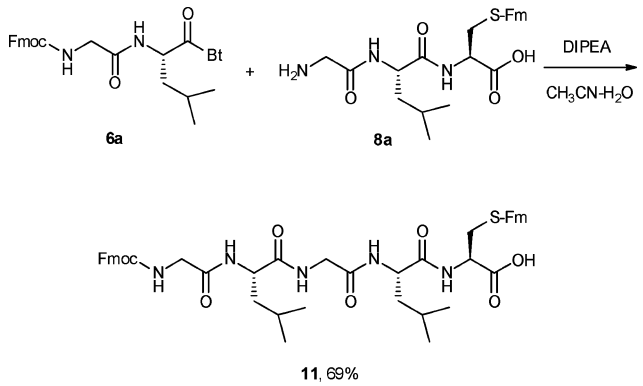


Scheme 5 Solution-phase peptide coupling reactions of *S*-Fm-cysteine peptides **4a–e** with *N*-(Pg-α-aminoacyl)benzotriazoles **2e,g–i** and *N*-(Pg-dipeptidoyl)benzotriazole **6c,d**.

Similarly, treatment of *S*-Fm-protected tripeptide **8a** with *N*-(Fmoc-α-dipeptidoyl)benzotriazole **6a** in the presence of diisopropyl ethylamine at 20 °C in acetonitrile–water afforded cysteine containing pentapeptide **11** in 69% yield (Scheme 6). Pentapeptide **11** was characterized by ^{1}H, ^{13}C NMR spectroscopy and elemental analysis.

Conclusion

In conclusion we have demonstrated useful and convenient transprotections of *N*-Fmoc-cysteine di- and tripeptides containing a free SH group into *S*-Fm-cysteine di- and tripeptides bearing free amino and carboxylic groups under mild conditions. The base-induced cleavage of the Fmoc protecting group of a *N*-Fmoc-cysteine di- or tripeptide provides dibenzofulvene, which is then attacked by the highly nucleophilic sulfur of a cysteine side chain to provide *S*-Fm-cysteine di- and tripeptides bearing free amino and carboxylic groups. Thus, in the present method, we not only deprotected the *N*-Fmoc group in a peptide, but also free SH group was protected with Fm group in the same peptide in a single step. This could be an efficient alternative to the usual two step process



Scheme 6 Preparation of cysteine containing pentapeptide **11**.

of the introduction of *S*-Fm protection with 9-fluorenylmethanol[18] or using expensive amino acids such as H-cysteine(*S*-Fm)-OH. These free amino *S*-Fm-cysteine di- and tripeptides can be readily used to form amide bonds in the synthesis of larger peptides.

Experimental

Starting materials and solvents were purchased from commercial sources and used without further purification. Melting points were determined on a Fisher melting apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a 300 MHz NMR spectrometer with $CDCl_3$ or DMSO-d_6 as solvents. *J* values are given in Hz. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed on a Carlo Erba–1106 instrument.

General procedure for preparation of *N*-Fmoc-cystiene dipeptides 3a–f and tripeptides 7a,b

N-(Protected-α-aminoacyl)benzotriazoles **2a–f** and *N*-Fmoc-dipeptidoylbenzotriazole **6a,b** were suspended in acetonitrile and a solution of cysteine in water containing equivalent amount of triethylamine was added. The mixture was stirred at 20 °C until the TLC revealed complete consumption of the starting materials. After acidifiacation with HCl (4 N) acetonitrile was removed under reduced pressure and the residue formed was taken in ethyl acetate, extracted with HCl (2 N) and brine. Ethyl acetate was concentrated under reduced pressure and hexanes were added. The turbid solution was left to crystallize overnight at –20 °C. The solid obtained was filtered, dried to give the corresponding di- or tripeptides.

***N*-Fmoc-L-Phe-L-Cys-OH (3a)[11a].** (0.19 g, 98%). White microcrystals; mp 164.0–166.0 °C (EtOAc/hexanes). $[\alpha]_D^{23}$ −13.0 (*c* 1.0 in MeOH). (Found: C, 65.98; H, 5.41; N, 5.51%. Calcd for $C_{27}H_{26}N_2O_5S$: C, 66.10; H, 5.34; N, 5.71%). δ_H (300 MHz; DMSO-d_6; Me_4Si) 8.37 (1 H, d, *J* 7.7), 7.87 (2 H, d, *J* 7.6), 7.71–7.62 (3 H, m), 7.43–7.16 (9H, m), 4.50–4.44 (1H, m), 4.38–4.32 (1 H, m), 4.19–4.15 (3 H, m), 3.06 (1 H, dd, *J* 13.6, 3.3), 2.97–2.77 (3 H, m), 2.44 (1 H, t, *J* 8.1); δ_C (75 MHz; DMSO-d_6; Me_4Si) 171.6, 171.4, 155.7, 143.7, 143.6, 140.6, 138.0, 129.1, 127.9, 127.5, 127.0, 126.2, 125.3, 125.2, 120.0, 65.6, 55.9, 54.3, 46.5, 37.3 and 25.5.

General procedure for transprotection of *N*-Fmoc-cystiene di- and tripeptides 3a–f, 7a,b into *S*-Fm-protected cysteine di- and tripeptides 4a–f, 8a,b

N-Fmoc-Di- or tripeptide (0.5 mmol) was dissolved in dry THF (5 mL) under argon at 0 °C. DBU (152 mg, 1 mmol) was dissolved in (1 mL) THF and added dropwise over 5 min to the Fmoc-dipeptide solution. The solution was left to stir for 10 more minutes and a sticky solid was precipitated. THF was evaporated under reduced pressure and the solid was dissolved in 1 N HCl (3 mL) under cooling. When the pH of the solution was adjusted to 5 using Na_2HPO_4 solution (1M), a solid precipitated. The solid was collected by filtration, washed with water (1 × 3 mL), ether (3 × 5 mL), dried to give the corresponding *S*-Fm-protected cysteine di- or tripeptide.

H-L-Phe-L-Cys(*S*-Fm)-OH (4a). (0.18 g, 81%). White microcrystals; mp 233.0–235.0 °C. $[\alpha]_D^{23}$ −13.0 (*c* 1.0 in MeOH). (Found: C, 65.15; H, 5.82; N, 5.66%. Calcd for $C_{26}H_{26}N_2O_3S{\cdot}2H_2O$: C, 64.71; H, 6.27; N, 5.80%). δ_H (300 MHz; DMSO-d_6; Me_4Si) 8.52 (1H, br s), 7.85 (2H, d, *J* 7.5), 7.75 (2H, d, *J* 6.9), 7.42–7.25 (9H, m), 4.91 (2H, br s), 4.36 (1H, br s), 4.14 (1H, t, *J* 6.2), 3.78–3.71 (1H, m), 3.17–2.81 (5H, m), 2.77–2.69 (1H, m); δ_C (75 MHz; DMSO-d_6; Me_4Si) 171.8, 171.2, 145.9, 140.3, 137.0, 129.3, 128.1, 127.2, 126.8, 126.3, 124.9, 121.2, 119.8, 54.8, 52.8, 46.3, 35.8 and 34.6.

General procedure for peptide coupling reaction between *S*-Fm protected cysteine peptides 4a–e and *N*-(Pg-α-aminoacyl)-benzotriazole 2e,2g–i or *N*-(Cbz-α-dipeptidoyl)benzotriazole 6c–d

S-Fm protected cysteine di- or tripeptide (0.25 mmol) was dissolved in water (1 mL) and *N*,*N*-diisopropyl-*N*-ethyl amine (0.043 mL, 0.25 mmol). Then acetonitrile (7 mL) and *N*-(Pg-α-aminoacyl)benzotriazole or *N*-(Cbz-α-dipeptidoyl)benzotriazole (0.25 mmol) were added. The heterogeneous mixture was left to stir at room temperature till the TLC shows complete consumption of *N*-acylbenzotriazole (1–3 h). After that, 6 N HCl was used to acidify the solution to pH 1 and acetonitrile was removed under reduced pressure. Ethyl acetate was added and the organic layer was extracted with 4 N HCl (2 × 2 mL). Ethyl acetate was dried over sodium sulfate and concentrated under reduced pressure. Hexanes were added and the solution was left to crystallize over night at −20 °C. The solid formed was filtered out and dried under reduced pressure to give the corresponding coupling products.

Fmoc-Gly-L-Phe-Cys(*S*-Fm)-OH (9a). (0.15 g, 75%). White micrcrystals; mp 103.0–105.0 °C (EtOAc/hexanes). $[\alpha]_D^{23}$ −15.0 (*c* 1.0 in MeOH). (Found: C, 65.97; H, 5.76; N, 5.05%. Calcd for $C_{43}H_{39}N_3O_6S{\cdot}3H_2O$: C, 66.22; H, 5.82; N, 5.39%). δ_H (300 MHz; DMSO-d_6; Me_4Si) 9.06 (1 H, d, *J* 8.1), 8.24 (2 H, br s), 7.88 (4 H, t, *J* 7.8), 7.77–7.70 (3 H, m), 7.65 (1 H, t, *J* 6.6), 7.45–7.31 (12 H, m), 4.53–4.49 (1 H, m), 4.31–4.18 (4 H, m), 4.09 (1 H, br s), 3.67 (2 H, d, *J* 6.3), 3.21 (2 H, d, *J* 6.3), 3.15 (1 H, d, *J* 5.1), 3.01–2.85 (3 H, m); δ_C (75 MHz; DMSO-d_6; Me_4Si) 171.5, 171.3, 168.1, 156.5, 145.8, 143.8, 140.7, 140.5, 134.8, 129.7, 128.4, 127.6, 127.4, 127.1, 127.0, 125.2, 125.0, 120.1, 120.0, 65.7, 53.2, 52.7, 46.6, 46.4, 42.1, 36.7, 35.9 and 33.9.

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