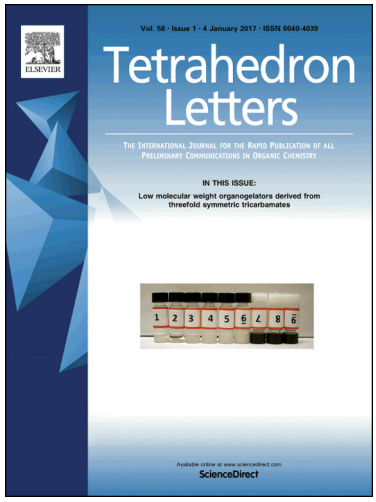

Fmoc-OPhth, the reagent of Fmoc protection

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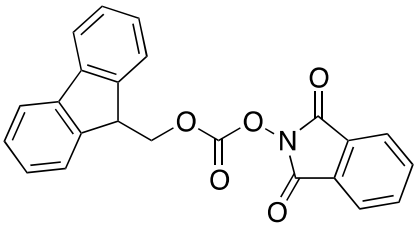

Fmoc-OPhth

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Fmoc-OPhth, the reagent of Fmoc protection

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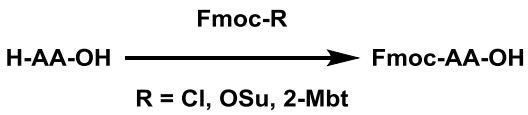
ABSTRACT

Fmoc-OSu has been widely used for Fmoc protection of amino groups, especially amino acids, in solid phase peptide synthesis. However, it has been recognized that Fmoc-βAla-OH is formed as a by-product via the Lossen rearrangement during the reaction. Since we reconfirmed the formation of Fmoc-βAla-OH during the preparation of Fmoc-AA-OH by Fmoc-OSu, Fmoc-OPhth was designed and synthesized as a new Fmoc reagent to avoid the formation of Fmoc-βAla-OH. Furthermore, Fmoc protection by Fmoc-OPhth and Fmoc-SPPS were evaluated. The various Fmoc-amino acids prepared by Fmoc-OPhth were carried out in good yields and these are applicable in Fmoc-SPPS.

Introduction

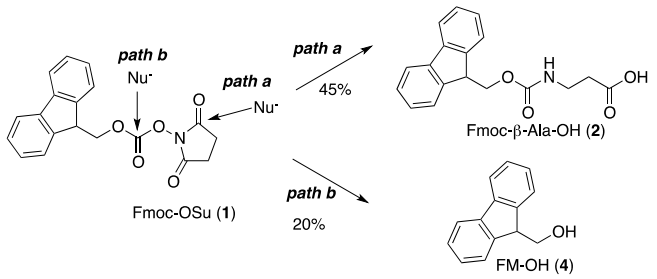
Fmoc-protection is widely used as an efficient way to mask the nucleophilicity of amine functionality in organic synthesis. In fact, it is one of the most versatile protecting groups in solid phase peptide synthesis (SPPS). Therefore, a variety of leaving groups has been considered to overcome any side reactions; chloride,[1] azide,[2] 1,2,2,2-tetrachloroethyl,[3] 5-norbornene-2,3-dicarboximido,[4] pentafluorophenyl,[5] pyrocarbonate.[6] Although hydroxysuccineimide (HO-Su) ester has been used as a promising group, Fmoc-OSu (**1**)[7,8] also has serious problems. Commercial Fmoc-amino acids prepared with Fmoc-OSu (**1**) were found to contain Fmoc-β-Ala-OH (**2**) and Fmoc-β-Ala-AA-OH as contaminants (0.1-0.4%).[9] These impurities may cause highly troublesome. For this reason, Albericio et al. reported a mechanism for the formation of Fmoc-β-Ala-OH (**2**) and Fmoc-β-Ala-AA-OH during the protection of amino acids, and moreover preparation and application of Fmoc-2-mercaptobenzothiazole (Mbt) to introduce an Fmoc moiety free of side reactions in 2007.[10] However the acylation reaction when using Fmoc-2-Mbt is much slower compared with the reaction with Fmoc-OSu (**1**). Recently, Rao group reported Fmoc-O-3-azaspiro[5,5]undecane-2,4-dione (ASUD) as a new reagent for the preparation of Fmoc-amino acids.[11] Although HO-ASUD is free from impurities resulting from Lossen rearrangement, it was needed to prepare starting from cyclohexanone following Stevens et al.[12,13] Unfortunately, the Fmoc formation of β-methoxytyrosine (β-MOY) with Fmoc-OSu (**1**) we prepared gave Fmoc-β-Ala-OH (**2**) in 10% yield.[14,15] Because it is difficult to remove the by-product, peptide purity in the coupling with Fmoc-β-MOY reduced the synthesis of callipeltin E, B and M. Herein, we report that a reconfirmation of the reaction process of Fmoc-OSu (**1**) and the merit of Fmoc-O-phthalimide (Phth) (**3**),[7] a cheap and simple reagent for Fmoc-protection (Scheme 1).



Scheme 1. Preparation of Fmoc-amino acids. AA=amino acids, R=leaving groups

Result and discussion

At first, we attempted to prove the sequence of the Lossen rearrangement.[9,10] The treatment of Fmoc-OSu (**1**) with potassium carbonate in 50% MeCN for 2h at room temperature followed by an extractive work-up gave mainly Fmoc-β-Ala-OH (**2**) and Fluorenyl methanol (FM-OH) (**4**) in 45% and 20%, respectively. This experiment proves that the basic condition in an aqueous solvent, namely the Schotten-Baumann condition, derives from Fmoc-OSu to Fmoc-β-Ala-OH (**2**) via a Lossen type reaction (path a) and simultaneously to FM-OH (**4**) by hydrolysis (path b). The putative mechanism for the formation of Fmoc-β-Ala-OH (**2**) from Fmoc-OSu (**1**) by the Lossen rearrangement reaction has already been shown by Albericio's[10] and Dick's[9] groups independently, and we support their analogical reaction sequence. In contrast, we also need to keep in mind the yield of FM-OH (**4**) by hydrolysis, because this also decreases the chemical yield. As treatment of Fmoc-OSu (**1**) with Et_3N in CH_2Cl_2 has scarcely detect Fmoc-β-Ala-OH (**2**) and FM-OH (**4**), these reactions proceed in an aqueous condition (Scheme 2).



Scheme 2. Fmoc-β-Ala-OH (**2**) and FM-OH (**4**) derived from Fmoc-OSu (**1**). Reagents and conditions: Fmoc-OSu (**1**), K_2CO_3 (2.0 eq), 50% MeCN (0.1 M), 2h, rt.

For the next confirmation, Fmoc-OSu (**1**) in the presence of leucine (1.0 equivalent) was stirred with 2 equivalents of K_2CO_3 in 50% MeCN. The reaction was monitored by HPLC. The Fmoc formation of leucine proceeded within 20 min and simultaneously production of Fmoc-βAla-OH (**2**) and FM-OH (**4**) were suppressed in ~3% yield. In this case, 10% of the contaminating Fmoc-β-Ala-OH (**2**) was found in the crude product and the yield of FM-OH (**4**) was 22% after 6 h. The chemical yield (70%) of the desired Fmoc-Leu-OH (**5**) was not satisfactory and recrystallization was necessary to reduce the amount of these impurities. As the Fmoc-protection of phenylalanine was carried out by the similar condition shown in Figure 1, only 0.1% Fmoc-β-Ala-OH (**2**) was identified in the crude product after the isolation; however, Fmoc-Phe-OH (**6**) was produced in 86% yield. To increase the yield from 86% to 96% of Fmoc-Phe-OH (**6**), 1.2 equivalent of Fmoc-OSu (**1**) was needed. However, 5% Fmoc-β-Ala-OH (**2**) was detected in the crude product, therefore removal of impurity was a laborious task. In both cases, hydrolysis of Fmoc-OSu (**1**) proceeded to give FM-OH (**4**) about 10% yield. These results suggested that hydrolysis of Fmoc-OSu (**1**) afforded FM-OH (**4**) in a ratio of ~10%, although the Lossen rearrangement of Fmoc-OSu (**1**) was suppressed by carbamate formation. This means that excess reagent is needed for the Fmoc-protection of amino functionality (Figure 1). Fmoc-βAla-Leu-OH and Fmoc-βAla-Phe-OH were not detected other by-products mentioned by Albericio et al (Figure 1).[10]

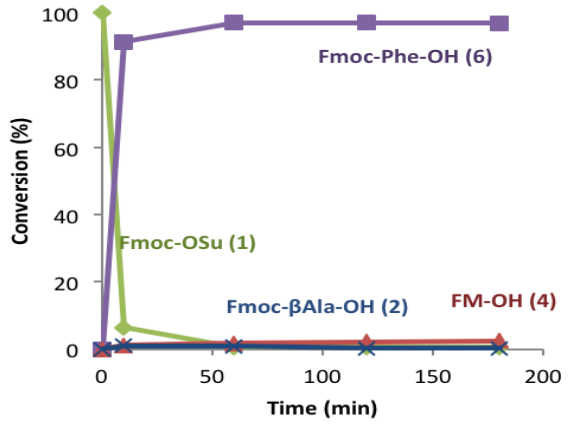
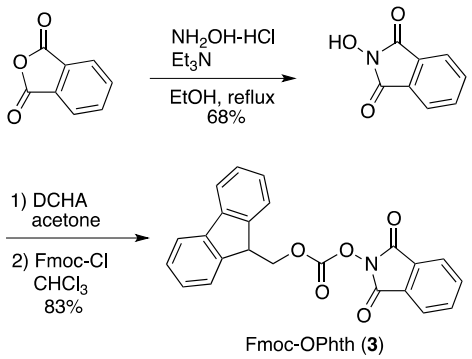


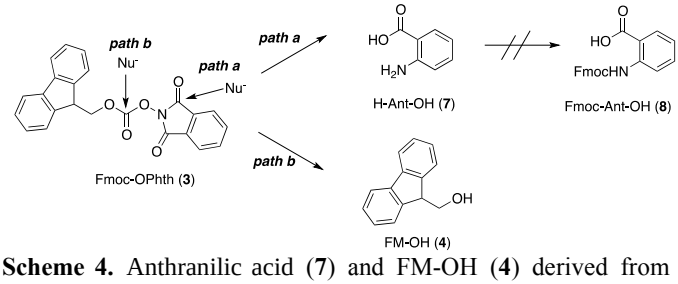
Figure 1. Time course of Fmoc-protection of phenylalanine. Reagents and conditions: phenylalanine, Fmoc-OSu (**1**) (1.0 eq), K_2CO_3 (2.0 eq), 50% MeCN (0.1 M). HPLC profile for Rt = 13.1 min of Fmoc-Phe-OH (**5**), Rt = 9.7 min of FM-OH (**4**), Rt = 8.9 min of Fmoc-βAla-OH (**2**) and Rt = 12.2 min of Fmoc-OSu (**1**) (Condition: equipped with nacalai tesque cosmosil $5C_{18}$-ARII; WL = 256 nm, Flow 1 mL/min, 0~20 min 30~90% MeCN/H_2O). Conversions (%) were estimated from HPLC.

To avoid Fmoc-βAla-OH (**2**) formation, we recommend the design and synthesis of a new Fmoc reagent to apply a variety of substrates. We focused on the phthalimide (Phth) framework, which is used in the protection of primary amine. In spite of the similar structure between succinimide and phthalimide, we expected that the Lossen rearrangement of Fmoc-OPhth (**3**) barely occurred. The pKa of *N*-hydroxy group of phthalimide (pKa = 6.10) was lower than that of succinimide (pKa = 7.81), making the phthalimide derivatives potentially more reactive than those bearing OSu as the leaving group. However, reactivity is suppressed by the steric effect of a phenyl ring. We speculated that phthalimide could be a reasonable leaving group. As a pioneer contribution, preparation and application of Fmoc-OPhth (**3**) for Fmoc protection have been reported alongside Fmoc-OSu (**1**) by the Sigler group.[7] However, the reaction mechanism and its side reaction, that is the Lossen rearrangement and hydrolysis, have not been investigated in detail. An undeniable advantage of phthalimide derivatives lies in their availability at low cost for phthalic anhydride and easy preparation. To attempt the preparation of Fmoc-OPhth (**3**) derivatives derived from phthalic anhydride derivatives, we selected Fmoc-OPhth (**3**), which is stable under normal storage. As depicted in Scheme 3, the treatment of phthalic anhydride and hydroxylamine hydrochloric acid with Et_3N in EtOH reflux gave *N*-hydroxyphthalimide in 68% yield. After the formation of *N*-hydroxyphthalimide DCHA salt, Fmoc-Cl was mixed in $CHCl_3$ to afford Fmoc-OPhth (**3**) in 83% yield. Chemical assignment of the synthesized Fmoc-OPhth (**3**) was achieved by ^{1}H- and ^{13}C-NMR and mass spectra (Scheme 3).



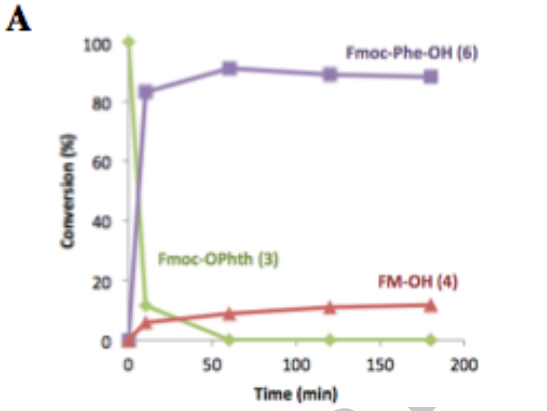
Scheme 3. Preparation of Fmoc-OPhth (**3**).

To investigate the side reactions via the Lossen rearrangement, synthesized Fmoc-OPhth (**3**) was treated with K_2CO_3 in 50% MeCN for 2h at room temperature as mentioned above. As expected, FM-OH (**4**) by hydrolysis was detected on HPLC analysis (path b). Though anthranilic acid via the Lossen rearrengement was generated about 20% yield, there was no detection as Fmoc-Ant-OH (**8**) (path a). Fmoc formation of anthranilic acid under the conditions was extremely slow because of weak nucleophilicity of amine of aniline derivatives (Scheme 4).



Scheme 4. Anthranilic acid (**7**) and FM-OH (**4**) derived from Fmoc-OPhth (**3**). Reagents and conditions: Fmoc-OPhth (**3**), K_2CO_3 (2.0 eq), 50% MeCN (0.1 M), 2h, rt.

To compare the reaction times for the Fmoc formation, Fmoc-OSu (**1**) or Fmoc-OPhth (**3**) in the present of phenylalanine (1.0 equivalent) was stirred with 2.0 equivalent of K_2CO_3 in 50% MeCN. As shown in Figure 2A, the reaction using Fmoc-OPhth (**3**) was monitored by HPLC. It should be noted that no significant deviations in the reaction time were observed. The Fmoc protection of phenylalanine by Fmoc-OPhth (**3**) predictably avoided anthranilic acid (**7**) and Fmoc-Ant-OH (**8**) formation to give Fmoc-Phe-OH (**6**) in 89%, but hydrolysis proceeded to afford FM-OH (**4**) at a ratio of 11%. It spent 2h to achieve total conversion of Fmoc-OPhth (**3**) under this condition. In this case, the Fmoc protection by Fmoc-OPhth (**3**) afforded Fmoc-Phe-OH (**6**) (84%) and *N*-hydroxyphthalimide after the usual work-up (Figure 2A). To increase the chemical yield for the Fmoc protection, we optimized the reaction conditions using Fmoc-OPhth (**3**). As a result, we found that Fmoc-Phe-OH (**6**) was obtained in 97% yield using 1.6 equivalent of Fmoc-OPhth (**3**) (Figure 2B). However it was difficult to remove the impurity *N*-hydroxyphthalimide (39%) and anthranilic acid (2%) and subsequently a careful separation step by silica gel column chromatography was needed. The *N*-hydroxyphthalimide impurity is fortunately used as a coupling reagent for peptide synthesis. Therefore, inclusion of *N*-hydroxyphthalimide might be scarcely needed to be sensitive toward the SPPS (Figure 2).



entry	Fmoc-OPhth (**3**)	Yield (%)[c]
1	1.0[a]	84
2	1.2[a]	88
3	1.4[a]	95 (99:1)
4	1.6[b]	97 (97:3)

[a] 2 eq. K_2CO_3, 0.1M 50% MeCN
[b] 4 eq. K_2CO_3, 0.05 M 50% MeCN
[c] Chemical yields after the usual work-up

Figure 2. Fmoc protection of phenylalanine with Fmoc-OPhth (**3**). (**A**) Time course of the Fmoc protection of phenylalanine. Reagents and conditions: phenylalanine, Fmoc-OPhth (**3**) (1.0 eq), K_2CO_3 (2.0 eq), 50% MeCN (0.1 M). HPLC profile for Rt = 13.1 min of Fmoc-Phe-OH (**6**), Rt = 9.7 min of FM-OH (**4**), Rt = 15.7 min of Fmoc-OPhth (**3**) and Rt = 2.7 min of antranilic acid (Condition: equipped with nacalai tesque cosmosil $5C_{18}$-ARII; WL = 256 nm, Flow 1 mL/min, 0~20 min 30~90% MeCN/H_2O). Conversions (%) were estimated from HPLC. (**B**) Comparison of the amount of Fmoc-OPhth (**3**) for Fmoc protection.

In addition, we performed Fmoc protection of several amino acids by Fmoc-OPhth (**3**). Treatment of Gly, Ala, Val, Leu and Ile with 1.0 equivalent of Fmoc-OPhth (**3**) reacted smoothly to afford the corresponding Fmoc-amino acids in 86~91% yields. By-products excluding FM-OH (**4**) were not detected on the HPLC profiles and therefore the purification process was easy (enties 1-5). On the other hand, primary amines of Glu and Gln with active side chains were protected with Fmoc group in 85% and 76% yields, respectively (enties 6, 7). There were similar results using Ser and Thr in good yields (enties 8, 9). Fmoc-OPhth (**3**)-assisted protection of Pro was caused by a secondary amine to give the 92:8 mixture of Fmoc-Pro-OH and anthranilic acid (**7**) in 81% yield (entry 10). Next, Fmoc-protection of unusual amino acids was attempted. Sarcosine (*N*-methylglycine) was protected to give Fmoc-Sar-OH in 88% yield (entry 11). Although treatment of 2-aminoisobutyric acid (Aib), β-methoxytyrosine (β-MOY)[14] or β-methoxythreonine (β-MOT)[15] with similar conditions gave the corresponding Fmoc-amino acids and anthranilic acid (H-Ant-OH; **7**) as a mixture at moderate yields, respectively (entries 12-14). On the other hand, 2-amino-3-hydroxy-4,5-dimethylhexanoic acid (AHDH)[16] was not protected by Fmoc-OPhth (**3**) in the presence of K_2CO_3 in 50% MeCN. Because this condition gives the retro-aldol adduct. In an attempt to optimize the conditions, Fmoc-OPhth (**3**)/Na_2CO_3 in dioxane/H_2O was chosen to give Fmoc-AHDH-OH in 74% yield without by-products (entry 15). Unfortunately, protection of β-hydroxyphenylalanine (β-HYF) was not proceeded by Fmoc-OPhth (**3**) instead of Fmoc-OSu (**1**), which was inability to afford Fmoc-βHYF-OH (entry 16). Though these reactions using 1.6 equivalents of Fmoc-OPhth (**3**) proceeded to give the corresponding Fmoc-amino acids in high yields, anthranilic acid was detected about 2~15% yields on ^{1}H NMR analyses. Therefore these products were carefully separated by silica gel column chromatography. Although increased chemical yields can be expected using excess Fmoc-OPhth (**3**), there are easy operations by 1.0 equivalent of the reagent to give pure Fmoc-AA-OH (Table 1).

Table 1. Fmoc protection of selected amino acids with Fmoc-OPhth (**3**).

H-AA-OH —Fmoc-OPhth (**3**), K_2CO_3, 0.1 M 50% MeCN→ Fmoc-AA-OH

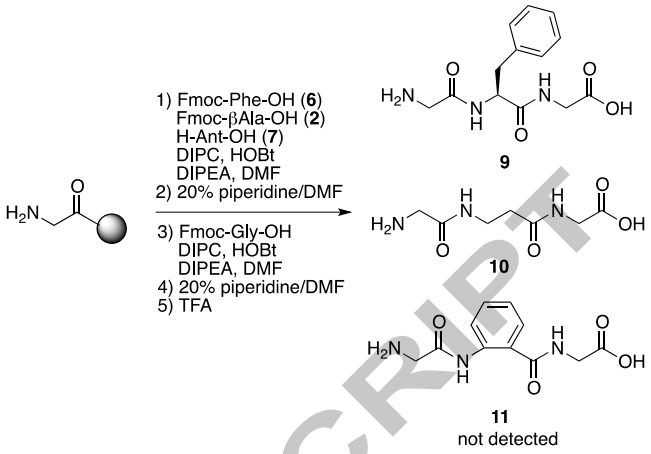
entry	AA	% (1.0 eq)[a,f]	% (1.6 eq)[b,f]	entry	AA	% (1.0 eq)[a,f]	% (1.6 eq)[b,f]
1	Gly	88	97 (91:9)[c]	9	Thr	80	93 (94:6)[c]
2	Ala	91	98 (95:5)[c]	10	Pro	81 (92:8)[c]	86 (85:15)[c]
3	Val	86	94 (89:11)[c]	11	Sar	88	91 (95:5)[c]
4	Leu	88	88 (93:7)[c]	12	Aib	67 (92:8)[c]	67 (93:7)[c]
5	Ile	88	89 (96:4)[c]	13	βMOY	64(87:13)[c]	80 (85:15)[c]
6	Gln	85	90	14	βMOT	61 (95:5)[c]	82 (87:13)[c]
7	Glu	76	85 (97:3)[c]	15	AHDH	74[d]	99 (98:2)[c,e]
8	Ser	90	94 (96:4)[c]	16	βHYF	trace	trace

[a] 2 eq K_2CO_3, 0.1 M 50% MeCN
[b] 4 eq K_2CO_3, 0.05 M 50% MeCN
[c] The ratio of Fmoc-AA-OH and anthranilic acid detected by ^{1}H NMR.
[d] 2 eq Na_2CO_3, 0.1 M 50% dioxane
[e] 4 eq Na_2CO_3, 0.05 M 50% dioxane
[f] Chemical yields after the usual work-up

In order to evaluate the utility of this methodology with Fmoc formation, we designed a tripeptide, Gly-Phe-Gly (**9**), to compere reactivity of Phe, βAla and Ant. The designed tripeptide was synthesized using ordinary Fmoc-SPPS. After the Fmoc group of Fmoc-glycine-2-chlorotrityl resin was removed with 20% piperidine/DMF, the resultant resin with Fmoc-Phe-OH (**6**) (3 eq.) contaminated with H-Ant-OH shown at entry 4 in Figure 2B, DIPC (3 eq.), HOBt (3 eq.), DIPEA (3 eq.) in DMF for 2h at

room temperature was treated. Additionally, the Fmoc deprotection and coupling with Fmoc-Gly-OH by DIPC/HOBt/DIPEA in DMF were carried out. Finally, the Fmoc deprotection followed by cleavage from resin with TFA gave the crude tripeptide, which was one major product of Gly-Phe-Gly (**9**) by HPLC analysis. Ant-containing peptides, Gly-Ant-Gly (**11**) and Ant-Gly, were not observed by HPLC analysis.

Next, we demonstrated the glycine-2-chlorotrityl resin with Fmoc-Phe-OH (**6**) (3 eq.), Fmoc-βAla-OH (**2**) (0.5 eq.), H-Ant-OH (**7**) (0.5 eq.), DIPC (3 eq.), HOBt (3 eq.), DIPEA (4 eq.) in DMF for 2h at room temperature was treated. After the elongation of Gly and cleavage from resin, the corresponding crude tripeptides, which were two major products of Gly-Phe-Gly (**9**) and Gly-βAla-Gly (**10**), were detected by HPLC analysis. Nevertheless 3 equivalents of Fmoc-Phe-OH (**6**) and 0.5 equivalent of Fmoc-βAla-OH (**2**) as the second coupling reaction were used in Fmoc-SPPS, approximately 2:1 mixture of Gly-Phe-Gly (**9**) and Gly-βAla-Gly (**10**) was appeared. It means that coupling of Fmoc-βAla-OH (**2**) proceed quickly and therefore contamination of Fmoc-βAla-OH (**2**) is extremely risky. In contrast, Ant-containing peptides, Gly-Ant-Gly (**11**) and Ant-Gly, were not observed by HPLC analysis in spite of the mixing of H-Ant-OH (**7**) into the reaction mixture. Even if there is the impurity of H-Ant-OH (**7**) and/or the corresponding Fmoc-Ant-OH, it is possible to decrease the by-product formation (Scheme 5).



Scheme 5. Synthesis of tripeptides Gly-Phe-Gly (**9**) to compere reactivity of Phe, βAla and Ant. Conversions (%) were estimated from HPLC.

In conclusion, we investigated the availability of Fmoc-OPhth (**3**) to avoid formation of Fmoc-βAla-OH (**2**) by the Lossen rearrangement. Fmoc-OPhth (**3**) was synthesized from cheap phthalic anhydride in 3 steps. Fmoc protection of amino acids by Fmoc-OPhth (**3**) was carried out in good yields. In contrast, the reaction times of Fmoc formation were similar to those of Fmoc-OSu (**1**); therefore, we recommend Fmoc-OPhth (**3**) as the reagent for Fmoc protection as Fmoc-βAla-OH (**2**) is contamined by Fmoc-OSu (**1**).

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Highlights

Fmoc-OPhth, the reagent of Fmoc protection

Ryo Yoshino, Yoshinori Tokairin, Mari Kikuchi and Hiroyuki Konno*

Department of Biochemical Engineering, Graduate School of Science and Engineering, Yamagata University, Yonezawa, Yamagata 992-8510, Japan

A new Fmoc reagent to avoid the formation of Fmoc-βAla-OH

Easy and cheap preparation of the reagent

The reagent gives Fmoc-amino acid in good yields