

Novabiochem® Letters 3^{Vol.} 15

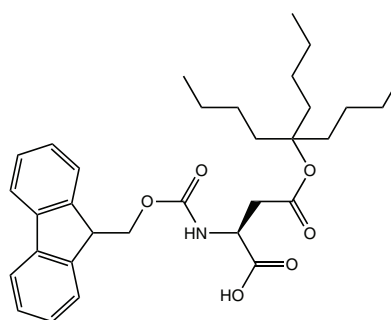
Novabiochem®
Over 30 Years of Innovation



New Products for Fmoc SPPS

NEW • Fmoc-Asp(OBno)-OH

A generic approach to minimizing aspartimide formation in Fmoc SPPS



Features & Benefits

- Highly effective at minimizing aspartimide formation in sensitive sequences, even with Asp-Gly containing peptides
- Combination with Oxyrna Pure reduces aspartimide formation to negligible levels

Aspartimide formation is a serious problem in Fmoc SPPS, especially for the synthesis of long peptides because of the repeated exposure of the growing peptide chain to piperidine leads to accumulation of aspartimide related by-products (Figure 1) [1]. It is particularly insidious as the β -aspartyl peptides and epimerized α -aspartyl peptide generated by this side reaction have the same retention time as the target peptide and have the same mass as the target, making the presence of these side products hard to detect. Therefore, the implementation of synthetic strategies that minimize aspartimide formation are a prerequisite to obtaining homogenous aspartyl-containing peptides in good yield.

The use of novel building block, Fmoc-Asp(OBno)-OH [2], for introduction of Asp in Fmoc SPPS provides a generic and simple approach to ameliorating this side reaction. Fmoc-Asp(OBno)-OH is a hindered variant of Fmoc-Asp(OtBu)-OH in which the steric bulk of the t-butyl group is increased by linear homologation, shielding the aspartyl β -carbonyl group and thereby reducing the formation of aspartimide derived by-products. In tests using the challenging Asp-Gly containing aspartimide model, scorpion toxin II, H-Val-Lys-Asp-Gly-Tyr-Ile-OH, the use of Fmoc-Asp(OBno)-OH instead of Fmoc-Asp(OtBu)-OH was found to dramatically reduce the extent of aspartimide formation per piperidine treatment from approximately 2.23% to only 0.14% [3]. The latter value is within the purity limits of commercially available Fmoc-amino acids. For a peptide containing 40 amino acids with C-terminal Asp-Gly, this improvement translates to an increase in yield for the product from 41% to 95%.

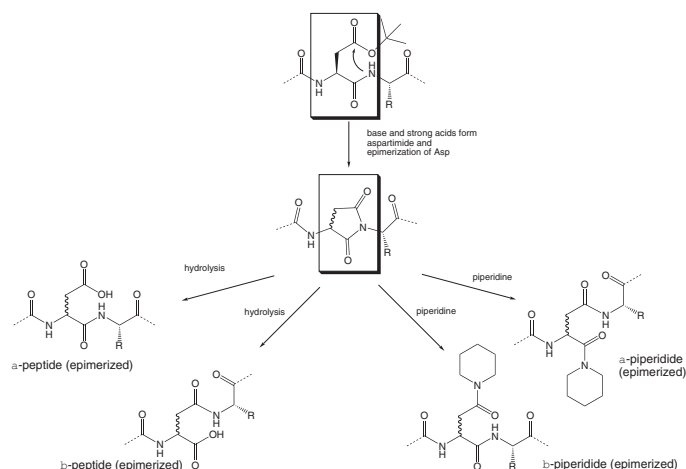


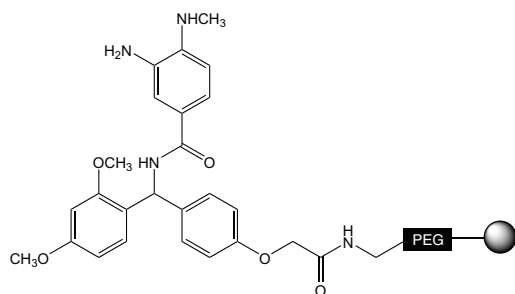
Fig. 1: Aspartimide formation, showing potential by-products.

Aspartimide formation can be reduced to almost negligible levels when Fmoc-Asp(OBno)-OH is used in conjunction with 0.1 M Oxyma Pure in 20 % piperidine in DMF [4] for Fmoc removal; with the scorpion toxin II Asp-Gly model peptide, only 0.04% aspartimide formation/cycle was observed under these conditions [3].

Cat.No.	Product	Contents
852418	Fmoc-Asp(OBno)-OH	1 g
NEW		5 g
852401	Fmoc-Asp(OEpe)-OH	1 g
		5 g

NEW • Resin for synthesis of peptide thioesters

MeDbz NovaSyn® TGR resin



Features & Benefits

- Improved version of Dbz resin for synthesis of peptide thioesters
- Compatible with base-mediated coupling methods without risk of branching

Since its introduction the 3,4-diaminobenzoic acid (Dbz) linker [5] has proven to be a valuable tool for the synthesis of peptide thioesters (Figure 2) [6]. However, lack of regioselectivity between the two anilino groups can lead to formation of branched peptides, particularly when the peptide contains glycine residues [7]. Recently, Dawson and co-workers have introduced a second generation linker, in which the *p*-anilino group is N-methylated [8]. This modification eliminates double acylation (Figure 3), even under basic conditions, to afford a robust approach to the synthesis of peptide thioesters by Fmoc SPPS.

Novabiochem offers the MeDbz linker attached to NovaSyn TGR resin. This product is used exactly in the same manner as Dbz resins described on page 5.4 of the 2014/15 Novabiochem catalog; however, no special conditions are required for loading of the first amino acid. Peptide chain extension is performed on the 4-anilino group, followed by formation of an imidazolidinone (MeNbz) with *p*-nitrophenyl chloroformate, and cleavage from the resin with TFA. The peptide-MeNbz is used directly in chemical ligation reactions to generate *in situ* the desired peptide thioester (Figure 2).

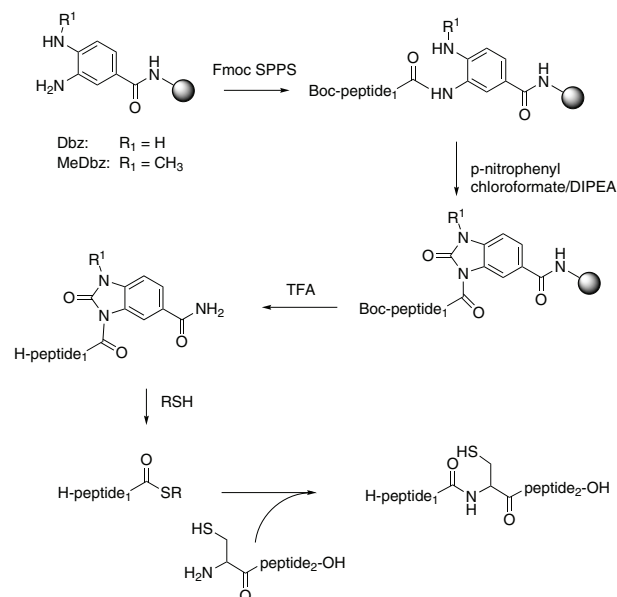


Fig. 2: Synthesis of peptide thioesters using (Me)Dbz resins.

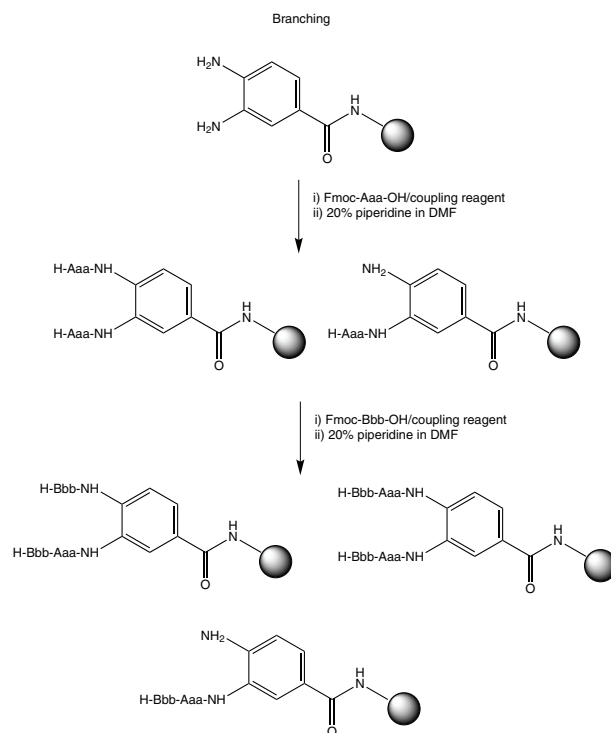
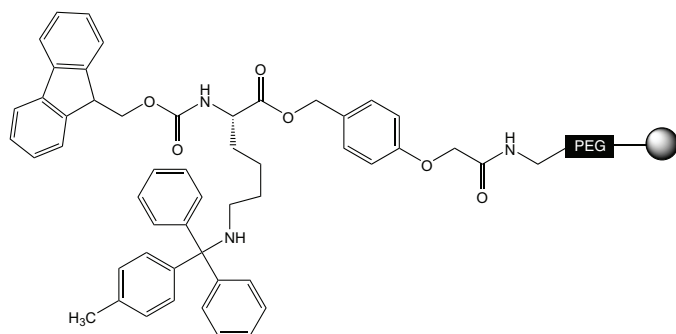


Fig. 3: Branching on Dbz Rink Amide resin.

Cat.No.	Product	Contents
855157	MeDbz NovaSyn® TGR resin	1 g
NEW		5 g
852131	Dawson Dbz Rink AM resin (100 - 200 mesh)	1 g
		5 g
852142	Dawson Dbz NovaSyn® TGR resin	1 g
		5 g

NEW • Resin for side-chain modified peptides

Fmoc-Lys(Mtt)-Wang resin LL (100-200 mesh)



Features & Benefits

- Mtt group removed with 1% TFA in DCM, without affecting standard protecting groups
- Enables on-resin modification of C-terminal lysine side-chain ϵ -amino group

Novabiochem's Fmoc-Lys(Mtt)-Wang resin LL is an excellent tool for the synthesis of biotin-, fluorophore- and other C-terminally labeled peptides. The Mtt group can be removed on the solid phase with 1% TFA in DCM, without affecting the standard t-butyl-based protection. The unmasked amino group can then be acylated with biotin, fluorophores and any moieties bearing a carboxylic acid functionality. TFA cleavage releases a peptide tagged on the ϵ -amino group of the C-terminal lysine.

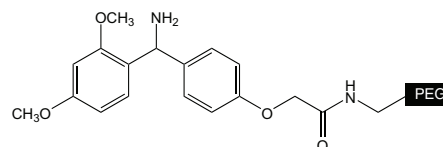
The resin is prepared from low loading Wang resin and complements our existing high-load Fmoc-Lys(Mtt)-Wang resin; the reduced substitution makes it more suited to the synthesis of longer and aggregated peptides.

Cat.No.	Product	Contents
856221	Fmoc-Lys(Mtt)-Wang resin LL	1 g
NEW		5 g
Other orthogonally protected pre-loaded resins		
852062	Fmoc-Asp(Wang resin)-OAll	1 g
		5 g
852024	Fmoc-Glu(Wang resin)-OAll	1 g
		5 g
852022	Fmoc-Glu(Wang resin)-ODmab	1 g
		5 g
852186	Fmoc-Lys(ivDde)-Wang resin	1 g

		5 g
852021	Fmoc-Lys(Alloc)-OH	5 g
		25 g
852094	Fmoc-Lys(Mtt)-Wang resin	1 g
		5 g
852121	Fmoc-Asp(Wang resin LL)-OAll	1 g
		5 g
		25 g
852123	Fmoc-Asp(Wang resin LL)-ODmab	5 g
		25 g
852109	Fmoc-Glu(OtBu)-Wang resin LL	1 g
		5 g
852122	Fmoc-Glu(Wang resin LL)-OAll	1 g
		5 g
852122	Fmoc-Glu(Wang resin LL)-ODmab	1 g
		5 g

NEW • High recovery NovaPEG resin

NovaPEG Rink Amide resin HRY



Features & Benefits

- Version of NovaPEG Rink Amide resin with improved product recovery

NovaPEG resins are excellent supports for the synthesis of difficult and/or long peptides. However, their use is often associated with low recovery of the desired peptide. Novabiochem's NovaPEG Rink Amide resin HRY is made from a special formulation of NovaPEG resin which has been designed to cause less peptide sequestration. The resin is furnished with the Rink amide linker, making it the perfect tool for the synthesis of aggregated and difficult to prepare peptide amides.

Cat.No.	Product	Contents
855158	NovaPEG Rink Amide resin HRY	1 g
NEW		5 g
855047	NovaPEG Rink Amide resin	1 g
		5 g
		25 g
855125	NovaPEG Rink Amide resin LL	1 g
		5 g

References

1. E. Nicolás, et al. (1989) *Tetrahedron Lett.*, **30**, 497; R. Dölling, et al. (1994) *J. Chem. Soc., Chem. Commun.*, 853; Y. Yang, et al. (1994) *Tetrahedron Lett.*, **35**, 9689; J. Lauer, et al. (1994) *Let. Pept. Sci.*, **1**, 197; I. Schön, et al. (1991) *J. Chem. Soc., Chem. Commun.*, 3213.
2. R. Behrendt, et al. (2015) *J. Pept. Sci.*, **21**, 680.
3. R. Behrendt, et al. (2015) *J. Pept. Sci.*, submitted for publication
4. R. Subirós-Funosas, et al. (2012) *Biopolymers*, **98**, 89.
5. J. B. Blanco-Canosa & P. E. Dawson (2008) *Angew. Chem. Int. Ed.*, **47**, 6851.
6. Z. Harpaz, et al. (2010) *ChemBioChem*, **11**, 1232; B. L. Pentelute, et al. (2010) *ACS Chem. Biol.*, **5**, 359; c) T. K. Tiefenbrunn, et al. (2010) *Pept. Sci.*, **94**, 405.
7. P. D. White & R. Behrendt (2010) *J. Pept. Sci.*, **16** Suppl. 1, 71 – 72.; S. K. Mahto, et al. (2011) *ChemBioChem*, **12**, 2488.
8. J. B. Blanco-Canosa, et al. (2015) *J. Am. Chem. Soc.*, **137**, 7197.

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