Benzotriazole Reagents for the Syntheses of Fmoc-, Boc-, and Alloc-Protected Amino Acids

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Abstract: Stable Fmoc-, Boc-, and Alloc-benzotriazoles react with various amino acids including unprotected serine and glutamic acid, in the presence of triethylamine at 20 °C as reagents to introduce α-amino protecting groups to afford Fmoc-, Boc-, and Alloc-protected amino acids (77–94%) free of dipeptide and tripeptide impurities. Fmoc-, and Alloc-Gly-Gly-OH dipeptides were prepared in 90% yields by N-acylation of glycylglycine with Fmoc- and Alloc-benzotriazoles in the presence of triethylamine. Synthesized N-protected amino acids were greater than 99% pure, analyzed by HPLC.

Key words: amino acids, benzotriazole, protecting groups, acylation, HPLC

Protecting groups are of great importance in the synthesis of natural products,[2] carbohydrates,[3] and throughout synthetic organic chemistry.[4] As molecular targets have become more complex, the demand has increased for efficient cleavage techniques and orthogonal protection protocols[5] that offer a wide range of removal conditions.[4b,6]

Amino groups in peptide syntheses need protection. The 9-fluorenylmethoxycarbonyl (Fmoc)[7] and tertiary butyloxycarbonyl (Boc)[8] protection strategies are complementary in both solution and solid-phase peptide synthesis as the Fmoc protection can be removed using mild basic (nonhydrolytic) conditions and their cleavage monitored by UV,[4b] while Boc can be removed by acidolysis.[4b] Using the Fmoc protection, acid-labile groups can be used for protection of side chains and deprotection carried out under milder conditions compared to the Boc strategy.[9]

Allyloxycarbonyl (Alloc)[10] is a protecting group stable to both basic and acidic conditions. Alloc is a useful orthogonal protection strategy, in the syntheses of cyclic peptides,[11] in solid-phase peptide synthesis[12] and in the 'three-dimensional protection strategy'.[6b,13] Alloc has recently been applied as an α-amino protecting group for a peptide synthesis of the antitumor depsipeptide kahalalide F.[14] Its removal can be easily and selectively achieved by a palladium-catalyzed [usually tetrakis(triphenylphosphane) palladium $Pd(PPh_3)_4$] transfer of the allyl unit to various nucleophiles.[15]

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Numerous protection methodologies exist for the diverse types of amino protecting groups used for amino acids. Most of these methodologies are based on the reaction of the free amino acids, with either the haloformate (chloroformate)[15c,16] or the carbonate[17] of the protecting group under Schotten–Baumann conditions.[18] However, chloroformate esters such as Fmoc-Cl and Alloc-Cl suffer from (i) instability and (ii) the tendency to promote the formation of undesirable Fmoc/Alloc di- and tripeptides that can contaminate the Fmoc-/Alloc-amino acid.[12b,19]

The methodologies used to overcome this problem include the using of more shelf-stable carbonates such as pentafluorophenyl derivatives,[15c,20] Fmoc-pfp[21] (pfp = perfluorophenoxy), Fmoc-OBt[12c,d,19a] (Bt = benzotriazol-1-yl), 5-norbonene-2,3-dicarboximido-Fmoc derivative[22] and Fmoc-OSu (Su = succinimi-dyl).[19a,d,21,23] Hydroxysuccinimide derivatives (Su) such as Fmoc-OSu have been considered the reagents of choice for the introduction of the protecting moiety,[19a,b,d,23,24] but Fmoc/Alloc-succinimidyl carbonates undergo Lossen rearrangement in aqueous basic medium to give 0.1–0.4% of Fmoc-/Alloc-β-Ala-OH or even of Fmoc-/Alloc-β-Ala-Ala-OH in the preparation of Fmoc-/Alloc-α-Ala-OH.[25] Azide approaches could minimize formation of dipeptides,[7b,26] but their hazardous nature limits their use.

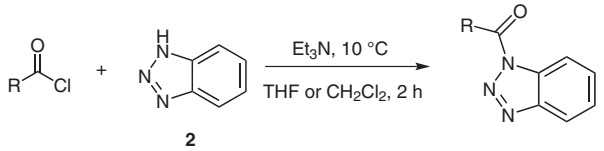
Recently, Fmoc-/Alloc-cyanopyridyloxime carbonates were used to prepare Fmoc-/Alloc-protected amino acids,[27] via a two-step procedure from Fmoc-/Alloc-chlorides and oximes or *N*-hydroxypicolinimidoyl cyanide; similar oximes were proposed to introduce the Boc protecting group.[28]

N-Acylbenzotriazoles, which can be synthesized easily without purification by column chromatography, are advantageous for N-, O-, C-, and S-acylation,[29] especially where the corresponding acid chlorides are unstable or difficult to prepare and/or store.[29] We now report that Fmoc-/Alloc- and Boc-benzotriazoles allow the syntheses of Fmoc-/Alloc- and Boc-protected amino acids at 20 °C without side products.

Benzotriazole reagents, *N*-(9-fluorenylmethoxycarbonyl)benzotriazole (Fmoc-Bt) (**3a**), and *N*-(allyloxycarbonyl)benzotriazole (**3b**) were prepared by reaction of chloroformate esters Fmoc-Cl (**1a**) and Alloc-Cl (**1b**) with benzotriazole (**2**) in the presence of triethylamine at 10 °C for two hours (Table 1). *N*-(*tert*-Butyloxycarbonyl)benzotriazole (Boc-Bt, **3c**) was prepared in 75% yield by the re-

action of Boc-anhydride with benzotriazole **2** in dioxane–NaOH (1 M, 4:6) according to the literature procedure.[30] Fmoc-, Boc-, and Alloc-benzotriazole reagents are stable crystalline compounds and can be stored in crystalline state at room temperature for at least five months.

Table 1 Preparation of Fmoc- and Alloc-Benzotriazole Reagents **3a**,**b**



2

1a, R = Fmoc
1b, R = Alloc

3a, R = Fmoc
3b, R = Alloc

Entry	R	Product **3**	Mp (°C)	Yield (%)
1	Fmoc	Fmoc-Bt **3a**	99–91	88
2	Alloc	Alloc-Bt **3b**	105–107[a]	92

[a] Lit.[31] oil.

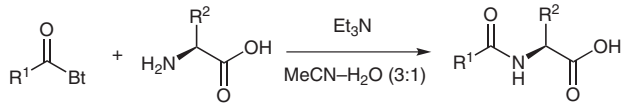
We selectively acylated the amino group of various amino acids **4** utilizing Fmoc-Bt **3a**, Alloc-Bt **3b**, and Boc-Bt **3c** by reactions of *N*-(Pg)-1*H*-benzotriazoles **3a–c** with amino acids **4** at 20 °C in the presence of two equivalents of triethylamine in MeCN–H_2O (3:1). Each gave exclusively the corresponding N-protected amino acids **5a–p** (Table 2) in 77–94% yields.

Fmoc-, Alloc-, and Boc-benzotriazole reagents were used for the synthesis of protected amino acids **5c**,**j**,**o** and **5f**,**l** of tryptophan and serine possessing free indole NH and hydroxyl groups, respectively, by selective N-acylation of amino group of the corresponding amino acids. Also, Fmoc-tyrosine (**5e**) and Fmoc-glutamic acid (**5g**) were prepared possessing free phenolic hydroxyl and carboxylic groups, respectively, by selective N-acylation using these Fmoc-, Alloc-, and Boc-benzotriazole reagents.

We obtained the N-protected glycylglycines [*N*-(Pg)-Gly-Gly-OH] **7a**,**b** in 90% yields by reaction of glycylglycine (**6**) with *N*-(Pg)-1*H*-benzotriazoles **3a**,**b** at 20 °C in the presence of two equivalents of triethylamine in MeCN–H_2O (3:1, Scheme 1).

The HPLC of Fmoc-glycine (**5a**) was recorded on a C-18 column, which showed >99% purity with no detectable formation of Fmoc-Gly-Gly-OH (**7a**, Table 3). HPLC analysis of Alloc-Gly-OH (**5m**) showed it to be a single compound with >99% purity with no detectable formation of Alloc-Gly-Gly-OH (**7b**, Table 3). The HPLC analysis of Boc-Gly-OH (**5h**) showed two main peaks, but was

Table 2 Preparation of Fmoc-, Boc-, and Alloc-Protected Amino Acids **3a**–**p**



4

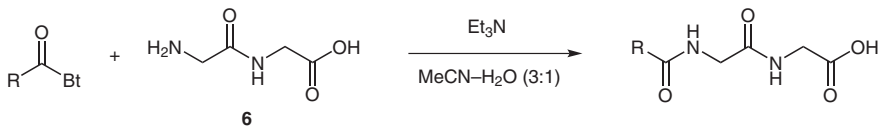
5a–p, 77–94%

3a, R^1 = Fmoc
3b, R^1 = Alloc
3c, R^1 = Boc

Entry	R^1CO-Bt **3**	Amino acid **4**	**5**	Yield (%)
1	Fmoc-CO-Bt **3a**	glycine	**5a**	94
2	Fmoc-CO-Bt **3a**	L-leucine	**5b**	88
3	Fmoc-CO-Bt **3a**	L-tryptophan	**5c**	86
4	Fmoc-CO-Bt **3a**	L-methionine	**5d**	84
5	Fmoc-CO-Bt **3a**	L-tyrosine	**5e**	85
6	Fmoc-CO-Bt **3a**	L-serine	**5f**	83
7	Fmoc-CO-Bt **3a**	L-glutamic acid	**5g**	83
8	Boc-CO-Bt **3c**	glycine	**5h**	90
9	Boc-CO-Bt **3c**	L-leucine	**5i**	77
10	Boc-CO-Bt **3c**	L-tryptophan	**5j**	85
11	Boc-CO-Bt **3c**	L-methionine	**5k**	84
12	Boc-CO-Bt **3c**	L-serine	**5l**	80
13	Alloc-CO-Bt **3b**	glycine	**5m**	80
14	Alloc-CO-Bt **3b**	L-leucine	**5n**	85
15	Alloc-CO-Bt **3b**	L-tryptophan	**5o**	86
16	Alloc-CO-Bt **3b**	L-methionine	**5p**	86

identical with the HPLC analysis of commercially available Boc-Gly-OH, which showed same peak pattern, because of the formation of rotamers,[31] as confirmed by ^{1}H NMR spectroscopy of Boc-Gly-OH (**5h**) at room temperature. However, ^{1}H NMR spectrum of **5h** at 65 °C showed single-isomer peaks by merging the rotamers' peaks. These results indicate that synthesized N-protected amino acids using our method are >99% purity with no detectable formation of N-protected dipeptide impurities.

In conclusion, Fmoc-, Boc-, and Alloc-benzotriazolides are selective amino protecting reagents for preparation of Fmoc-, Boc-, and Alloc-protected amino acids including the unprotected hydroxyl amino acids serine and tyrosine, under mild and efficient conditions with no detectable formation of side products.



6

3a, R = Fmoc
3b, R = Alloc

7a, R = Fmoc, 90%
7b, R = Alloc, 90%

Scheme 1 Preparation of Fmoc- and Alloc-protected glycylglycines **7a**,**b**

Table 3 The Purity of N-Protected Glycine

N-Pg-Gly-OH **5a**,**m**	Purity (%) of **5a**,**m**	*N*-Pg-Gly-Gly-OH **7** (%)
Fmoc-Gly-OH **5a**	>99	**7a**, no detectable formation
Alloc-Gly-OH **5m**	>99	**7b**, no detectable formation

Preparation of 1-[(9-Fluorenylmethyloxycarbonyl)-]benzotriazole [Fmoc-Bt] (3a)

(9*H*-Fluoren-9-yl)methyl chloroformate (**1a**, 1 g, 3.87 mmol), benzotriazole **2** (0.92 g, 7.74 mmol), and Et_3N (0.7 mL, 7 mmol) were stirred in CH_2Cl_2 (20 mL) for 2 h at 10 °C. The precipitate formed was filtered off, and the filtrate was evaporated under reduced pressure to give the crude product, which was washed with Et_2O and recrystallized from CH_2Cl_2–hexanes to afford Fmoc-Bt **3a** as white microcrystals; mp 90.0–91.0 °C, yield 88%. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.58 (s, 1 H), 5.10 (d, *J* = 5.1 Hz, 2 H), 7.23 (br s, 1 H), 7.29–7.38 (m, 2 H), 7.39–7.51 (m, 4 H), 7.81 (d, *J* = 7.2 Hz, 2 H), 7.91 (d, *J* = 7.2 Hz, 2 H), 8.09–8.18 (m, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 46.2, 69.5, 113.0, 119.9, 120.2, 125.0, 125.8, 127.3, 127.9, 130.1, 130.8, 140.9, 143.1, 145.0, 148.0. Anal. Calcd for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 73.84; H, 4.06; N, 12.29.

Allyl 1*H*-Benzo[*d*][1,2,3]triazole-1-carboxylate [Alloc-Bt] (3b)

To a solution of benzotriazole **2** (2 g, 7 mmol) and Et_3N (0.7 mL, 7 mmol) in THF (350 mL) was added with vigorous stirring allyl chloroformate **1b** (1.7 mL, 7 mmol) at 10 °C. After 2 h, the resulting precipitates were removed by filtration and washed with EtOAc (3 × 30 mL). The filtrate and washings were collected and the solvent evaporated to give a solid that was recrystallized from CH_2Cl_2–hexanes as white microcrystals; mp 105.0–107.0 °C (lit.[30c] oil), yield 92%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.11 (d, *J* = 6.0 Hz, 2 H), 5.45 (d, *J* = 10.5 Hz, 1 H), 5.58 (d, *J* = 17.1 Hz, 1 H), 6.04–6.30 (m, 1 H), 7.48 (t, *J* = 7.5 Hz, 1 H), 7.64 (t, *J* = 7.5 Hz, 1 H), 8.10 (t, *J* = 9.3 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 69.2, 113.4, 120.4, 120.9, 125.8, 130.2, 130.4, 131.7, 145.8, 148.7. Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.15; H, 4.38; N, 20.91.

General Procedure for Fmoc-, Boc-, and Alloc-Protected Amino Acids 5a–q and Fmoc- and Alloc-Protected Glycylglycines 7a,b

To a solution of amino acid **4** or glycylglycine **6** (1 mmol) and Et_3N (2 mmol) in MeCN–H_2O (3:1, 8 mL) was added the corresponding *N*-Pg-benzotriazole **3a–c** (1 mmol). The mixture was stirred at r.t. for 2 h. Solvent was removed under reduced pressure and EtOAc (10 mL) was added. The organic layer was washed with 2 M HCl and brine. Evaporation of the solvent followed by recrystalization (EtOAc–hexanes, 3:1) gave N-protected amino acids **5a–q** or N-protected dipeptides **7a**,**b**.

2-{([(9*H*-Fluoren-9-yl)methoxy]carbonyl)amino}-acetic Acid [Fmoc-L-Gly-OH] (5a)

White microcrystals, mp 166.0–167.0 °C (lit.[20b] mp 163.0–165.0 °C), yield 94%. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.72 (d, *J* = 6.0 Hz, 2 H), 4.25 (t, *J* = 7.2 Hz, 1 H), 4.34 (d, *J* = 6.9 Hz, 2 H), 7.34 (t, *J* = 7.5 Hz, 2 H), 7.43 (t, *J* = 7.5 Hz, 2 H), 7.68 (t, *J* = 6.0 Hz, 1 H), 7.74 (d, *J* = 7.2 Hz, 2 H), 7.90 (d, *J* = 7.5 Hz, 2 H), 12.68 (s, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 42.2, 46.7, 65.8, 120.1, 125.2, 127.1, 127.7, 140.8, 143.9, 156.5, 171.6.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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