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# A simple and versatile method to synthesize N-acyl-benzotriazoles

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Keywords :

N-Acyl-benzotriazoles

T3P

Carboxylic acids

## ABSTRACT

An efficient method for the synthesis of N-acyl-benzotriazoles from a wide variety of protected amino acids, as well as from compounds frequently used in drug discovery such as biotin and N-Fmoc polyethylene glycol, has been developed. The reaction of carboxylic acid derivatives with benzotriazole in the presence of T3P yielded the corresponding N-acyl-benzotriazoles, which were obtained in high purity following a simple work-up procedure, in most cases via precipitation of the desired product in water.

## Introduction

N-Acyl-benzotriazoles, which were introduced in the 2000's as acylating agents, show advantages in a number of organic transformations. They react with different types of amines [1,2] to produce amides, which have been used in stepwise and fragment peptide synthesis to give peptides [3,4] and peptide conjugates [5]. Fluorescent coumarin-labelled aryl-, aminoxy acid-, aminoxy hybrid peptides, peptides and depsipeptides [6–8], as well as dye-labelled nucleosides have also been obtained via benzotriazole activation [9]. A series of compounds with different functionalities, including esters, thioesters, thioacids, ureas and carbamates, have been prepared from N-protected  $\alpha$ -aminoacyl-benzotriazoles [10–12]. This methodology has also been reported for the synthesis of diverse N-heterocyclic compounds under Friedel-Crafts conditions in the presence of  $AlCl_3$  [13], or N-acyl-3-amino-1,2-pyrazoles via the reaction with NAOA hydroxy-carboxyamidines [14]. N-Protected  $\alpha$ -aminoacyl-benzotriazoles were also used to efficiently access  $\alpha$ -diazo- $\beta$ -keto esters, phosphonates and sulfones via acylation of the corresponding diazomethyl anions [15], as well as to acylate oximes [16]. Recently, a two-step approach was proposed to efficiently produce  $\alpha$ -aminoacyl-amino-substituted heterocycles by applying the microwave-to-flow paradigm [17]. Interestingly, the benzotriazole ring cleavage of N-acyl-benzotriazole derivatives in the presence of  $Bu_3SnH$  under free radical conditions resulted in the production of the corresponding N-phenylamides [18]. In solid phase peptide synthesis (SPPS), the resin-bound benzotriazole entity was proposed for on-resin modification of the C-terminus of peptides. Treatment of the resin-bound Bt with nucleophiles allowed long peptides, cyclic peptides, as well as peptide-decorated polymers to be obtained on a solid support [19].

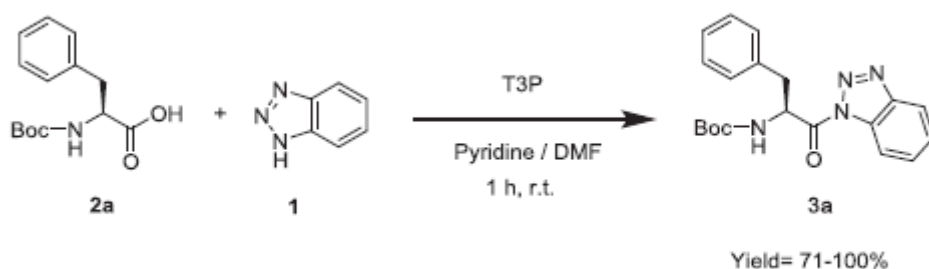
Despite their usefulness in a broad range of chemical reactions, only a limited number of methods to synthesize N-benzotriazoles have been developed. Among the initial methods allowing the preparation of N-acyl-benzotriazoles from carboxylic acids, the use of N-(1-methanesulfonyl)benzotriazole, which needs to be prepared by the treatment of benzotriazole with methanesulfonyl chloride in the presence of pyridine, should be noted [1]. Another method utilises thionyl chloride in the presence of benzotriazole [20]. However, one of the major disadvantages of this methodology is the production of HCl, which is not compatible with acid labile protecting groups. In recent years, the synthesis of N-acyl-benzotriazoles was proposed through the activation of carboxylic acids with 2,4,6-trichloro-1,3,5-triazine in the presence of triethylamine [21], and in aqueous media in the presence of sodium bicarbonate [22], as well as via the activation of carboxylic acids with either tosyl chloride or Ph<sub>3</sub>P/I<sub>2</sub> [23]. Herein, we propose a simple and efficient method for the synthesis of N-acyl-benzotriazole derivatives, starting from carboxylic acids, in the presence of benzotriazole and N-propanephosphonic acid anhydride (T3P).

## Results and discussion

In order to develop this method, we prepared different activated N-acyl-benzotriazole amino acid derivatives, which are useful for peptide synthesis. This procedure was determined to be compatible with the protecting groups commonly used in peptide synthesis including acid sensitive ones.

However, during the last decade it was mainly used for the large-scale synthesis of amides, due to its attractiveness on an industrial scale. Indeed, T3P has low toxicity (LD<sub>50</sub> > 2000 mg/kg), long shelf-life stability, easy handling (commercially available as a 50% solution in organic solvents such as EtOAc, DMF, or MeCN), and its water-soluble by-products are readily extracted into aqueous waste streams [24–26].

Advantages of this reagent also include its moderate cost, and the reduced environmental impact in generating non-toxic phosphonate waste streams. A preliminary experiment showed that T3P allowed the conversion of Boc-(L)Phe-OH **2a** into Boc-(L)Phe-Bt **3a** in the presence of benzotriazole **1** and pyridine, in good yield and high purity (Scheme 1).



**Scheme 1.** Synthesis of Boc-(L)Phe-Bt **3a**.

To optimize the formation of N-acyl-benzotriazole derivatives, several reaction conditions were explored (Table 1). We have chosen to work exclusively with T3P/DMF because this solvent allows us to have no problem of solubility during the reaction and its solubility in water allows the easy treatment of reactions. Dunetz and co-workers showed that pyridine was one of the best bases for low-epimerization amide bond formation in combination with T3P [25]. Therefore, using Boc-(L)Phe-OH as the model carboxylic acid in the presence of

pyridine, we optimized the experimental reaction conditions to obtain Boc-(L)Phe-Bt **3a** by varying the equivalents of T3P, benzotriazole **1** and pyridine (Table 1).

**Table 1**  
Synthesis of Boc-(L)Phe-Bt **3a** from Boc-(L)Phe-OH.<sup>a</sup>

Entry	T3P (eq.)	BtH (eq.)	Pyridine (eq.)	Conversion <sup>b</sup>
1	1.2	1.2	2	71%
2	1.5	1.2	2	82%
3	2	1.2	2	83%
4	2	2	2	82%
5	2	1.2	3	100%
6	1.5	1.2	3	100%

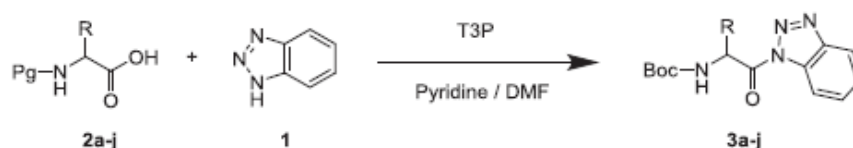
<sup>a</sup> Reagents and conditions: Boc-(L)Phe-OH (0.5 mmol), DMF (0.5 mL), r.t., 1 h.

<sup>b</sup> Based on HPLC.

The optimal experimental conditions were pyridine (3 eq.) and T3P (1.5 eq. 50% in DMF) with stirring at room temperature for 1 h. After the complete conversion of Boc-(L)Phe-OH was observed, the addition of water to the reaction mixture produced a precipitate of pure Boc-(L)Phe-Bt **3a** (84% yield) (Table 1). As an example to verify whether epimerization occurred during the formation of N-acyl-benzotriazole compounds, we synthesized Boc-(L)Phe-Bt and Boc-(D)Phe-Bt. Both compounds were reacted with (R)-(+)-4-methoxy-*a*-methylbenzylamine to produce the corresponding amides. The HPLC profile of both diastereomeric amides were analysed by HPLC; no epimerization was observed (ESI).

Using these experimental conditions, we then studied the scope and limitations of this method. For this purpose, we investigated the conversion of several N-protected amino acids into their respective benzotriazole derivatives. N-Z, N-Boc and N-Fmoc amino acids, some of them bearing Alloc, *t*-Bu, Boc, Trt and Pbf side-chain protecting groups [27], were efficiently transformed into their respective benzotriazole derivatives in good yields (Table 2).

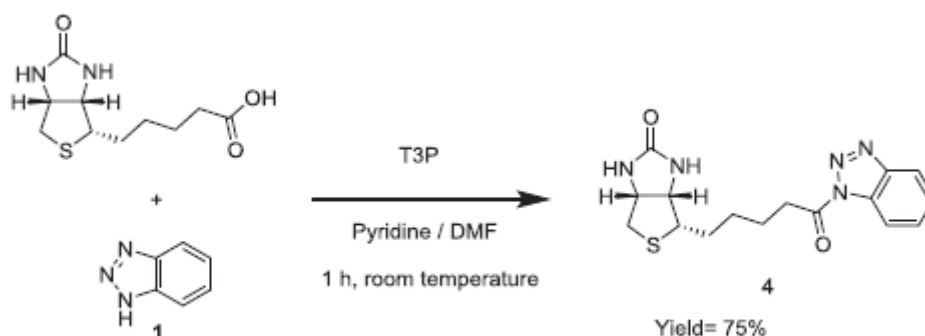
**Table 2**  
Synthesis of N-acyl-benzotriazole amino acid derivatives.<sup>a</sup>



Entry	Amino acid	Bt-Amino acid	Yield (%)
1	Boc-(L)Phe-OH <b>2a</b>	Boc-(L)-Phe-Bt <b>3a</b>	84
2	Fmoc-(L)Phe-OH <b>2b</b>	Fmoc-(L)Phe-Bt <b>3b</b>	88
3	Z-(L)Phe-OH <b>2c</b>	Z-(L)Phe-Bt <b>3c</b>	92
4	Boc-Gly-OH <b>2d</b>	Boc-Gly-Bt <b>3d</b>	94
5	Fmoc-(L)Pro-OH <b>2e</b>	Fmoc-(L)Pro-Bt <b>3e</b>	92
6	Fmoc-(L)Trp(Boc)-OH <b>2f</b>	Fmoc-(L)Trp(Boc)-Bt <b>3f</b>	98
7	Fmoc-(L)Ser( <i>t</i> -Bu)-OH <b>2g</b>	Fmoc-(L)Ser( <i>t</i> -Bu)-Bt <b>3g</b>	88
8	Fmoc-(L)Gln(Trt)-OH <b>2h</b>	Fmoc-(L)Gln(Trt)-Bt <b>3h</b>	82
9	Fmoc-(L)Arg(Pbf)-OH <b>2i</b>	Fmoc-(L)Arg(Pbf)-Bt <b>3i</b>	92
10	Fmoc-(L)Lys(Alloc)-OH <b>2j</b>	Fmoc-(L)Lys(Alloc)-Bt <b>3j</b>	89

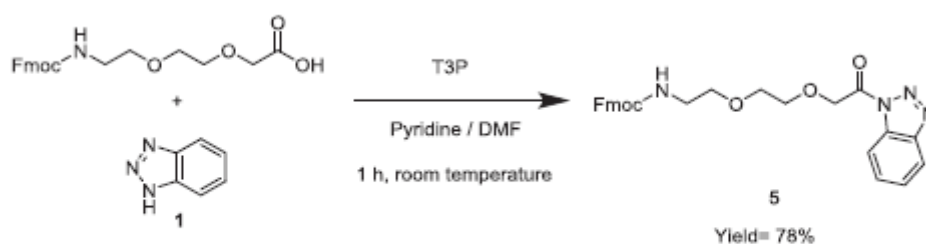
<sup>a</sup> Reagents and conditions: amino acids (0.5 mmol), benzotriazole (0.6 mmol), T3P (0.75 mmol), pyridine (1.5 mmol) DMF (1 mol/L), r.t., 1 h.

This reaction could also be adapted to other carboxylic acid containing compounds. One frequently used molecule in chemical biology is biotin [28]. Using the T3P methodology, we synthesized pre-activated Biotin-Bt **4** in 75% yield, which was easily precipitated in acetonitrile after reaction completion (Scheme 2).



**Scheme 2.** Synthesis of biotin-Bt **4**.

To complete this study, we prepared a N-Fmoc polyethylene glycol (PEG) derivative, Fmoc-O<sub>2</sub>Oc-Bt **5**. Many PEG chains have been incorporated into biomolecules to enhance their water solubility, their bioavailability and/or for linking two entities in the new drug discovery Proteolysis Targeting Chimera (Protac) strategy [29,30]. Using the T3P methodology, Fmoc-O<sub>2</sub>Oc-Bt **5** was obtained in 78% yield after recrystallization from toluene (Scheme 3).



**Scheme 3.** Synthesis of Fmoc-O<sub>2</sub>Oc-Bt **5**.

## Conclusion

In summary, T3P has been demonstrated to be an efficient reagent for the one-pot synthesis of Bt amino acid derivatives from N-protected amino acids. The method is compatible with various side-chain protecting groups, including the highly sensitive trityl group, and can be used to avoid tedious purification and the use of more toxic reagents. In addition, T3P was used for the synthesis of biotin and N-Fmoc polyethylene glycol derivatives.

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