

# Benzotriazole: A Versatile Synthetic Auxiliary



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## Introduction

Benzotriazole (BtH) is particularly versatile synthetic auxiliary because of its attractive properties. Benzotriazole can be easily inserted into molecules and equally can also act as a good leaving group. This molecule is a weak acid (pKa 8.2) as well as weak base (pKa < 0) and because of this acid-base property of benzotriazole. This molecule also shows not only electron donating but also electron attracting ability, which leads to various synthetic applications. In 1980, benzotriazole was first reported as synthetic auxiliary in organic chemistry [1]. Since then benzotriazole is used in the construction of various monocyclic and bicyclic heterocyclic compounds which are difficult to prepare by other methods [2-5].

## Benzotriazole in heterocyclic synthesis

Heterocycles are important class of compounds. Benzotriazole extensively used for the synthesis of various heterocycles. 1-Aza-1,3-bis(triphenyl phosphoranylidene)propane synthesized from N-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)-1,1,1-triphenyl-1,5-phosphanimine and methylene triphenyl phosphorane in presence

of n-butyllithium, used as potential building block for the synthesis of heterocycles like 3H-benzo[c] azepine and 2,3-disubstituted pyrroles [6].

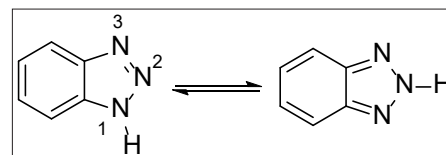


Figure 1.

2-Substituted benzothiazoles are well known for their biological properties with numerous accounts listing their synthesis [7]. Recently, benzotriazole technology was used in water as a one-pot approach to synthesize 2-peptidyl benzothiazole in excellent yield without any detectable racemization [8]. The effectiveness of this approach relies in the fact that it neither required any additional reagents nor catalyst for completion (Figure 1-3).

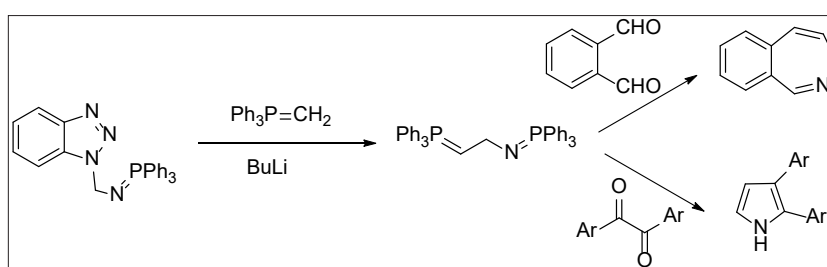


Figure 2.

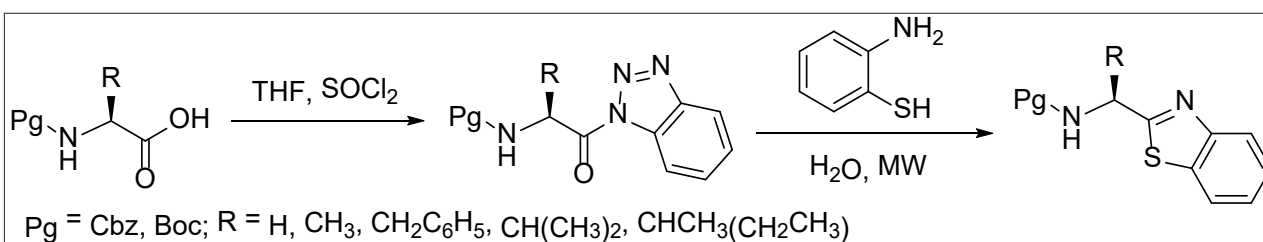


Figure 3.

## Benzotriazole in Acylation, Aroylation and Substitution Reactions

Benzotriazole and its derivatives plays important role in various reactions like acylation, aroylation and substitution reactions [2,9]. Substitution of hydroxyl group with chloride group of the sterically and electronically hindered alcohol of carbohydrates involves harsh reaction conditions and expensive reagents. Furthermore, the formation of halides from nucleofugal groups leads in the formation of unsaturated products and also chances of losing chirality due to harsh reaction condition. Saxena et. al. reported benzotriazole sulfonate (prepared in-situ from benzotriazole and thionylchloride) as potential reagent for the one pot conversion for the sterically and electronically hindered alcohol of carbohydrates into their corresponding chloride derivatives in excellent yield [9].

## Benzotriazole in Phosphorous Chemistry

Organophosphorus compounds are important class of compounds. Dialkyl- and diaryl halo phosphates are generally used as building block for the synthesis of organophosphorous compounds. However these building blocks suffer from lack of stability, particularly to hydrolysis and also required toxic reagents to synthesize them. Katritzky group synthesized and demonstrated the use of 1Hbenzo[d][1,2,3]triazol-1-yl-1-phosphonates as a

potential phosphorylation Reagents, which is quite stable than chloro derivatives [10].

## Benzotriazole in Peptide Synthesis

N-acylbenzotriazoles are superior acylating agent with various advantages over traditional acid chlorides. N-acylbenzotriazoles are quite stable and utilized in peptide chemistry and showed better applications in compared to other peptide coupling reagents. Unprotected amino acids couple with N-protected aminoacylbenzotriazoles in aqueous acetonitrile to deliver enantiopure dipeptides in good yield. For the synthesis of tripeptide, the carboxylic group of dipeptide is activated by benzotriazole in presence of thionylchloride followed by treatment with unprotected amino acids resulted in desired tripeptide in excellent yields. Hence, benzotriazole assisted chemistry was successfully utilized to synthesize up heptapeptides in solution phase without any detectable loss of absolute configuration [11-13].

## Benzotriazole in Peptidomimetic Synthesis

Peptidomimetics are special class of compounds which are mimic to natural peptides but resistant to enzymatic hydrolysis. Several peptidomimetics like aminoxopeptides, depsipeptides, azapeptides, oxyazapeptides and hydrazine peptides were synthesized [14-18].

## Benzotriazole in cyclic peptide synthesis

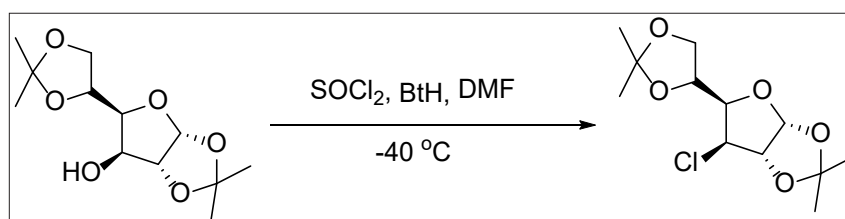


Figure 4.

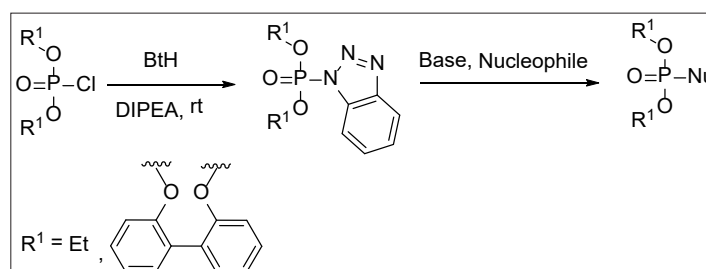


Figure 5.

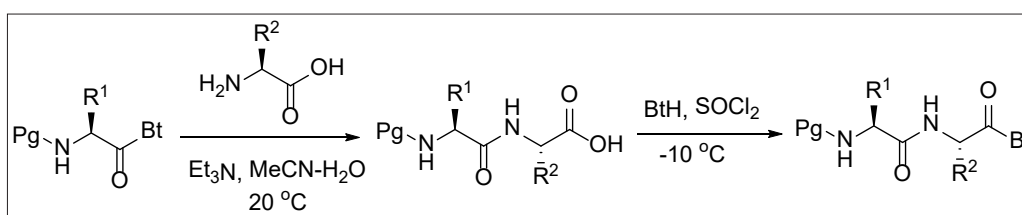


Figure 6.

Cyclic peptides are unique class of compounds. The synthesis of cyclic peptides is often challenging. Benzotriazole methodology was extended to use in the synthesis of various cyclic peptides via dimerization macrocyclization approach [19] Figure [4-6].

N-Cbz-dipeptidoyl benzotriazolides are forced to dimerization/cyclization to form both C2 symmetrical and unsymmetrical cyclic

tetrapeptides by utilizing a Pd-assisted tandem deprotection/cyclization reaction. However synthesis of these types of cyclic peptides is not efficiently prepared by other reported methods [20].

## Conclusion

Benzotriazole offers wide range of application as a potential synthetic auxiliary for various synthetic applications Figure 7 & 8.

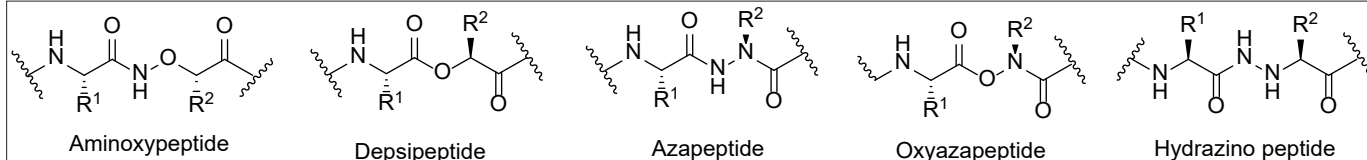


Figure 7.

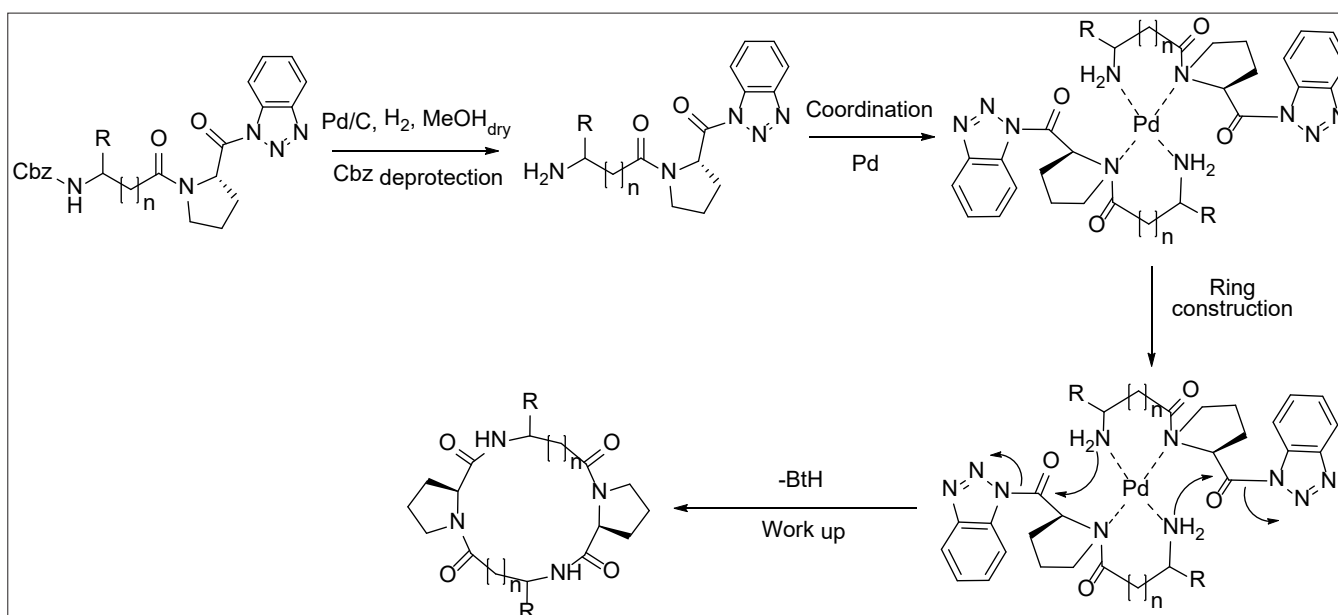


Figure 8.

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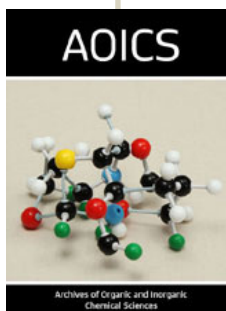
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