SYNLETT
Spotlight 314

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

2-(1*H*-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium Hexafluorophosphate (HBTU)

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Introduction

The title compound (HBTU, **1**) is a useful condensing agent, which has become in the past decade one of the most popular coupling reagents for in situ activation of peptide synthesis both in solid phase and in solution.[1–5] The same benzotriazolyl derivative has also been successfully employed for esterifications, as for example in solid-phase nucleotide synthesis.[6,7] In addition to its high reactivity, HBTU has also been shown to fulfill the very important requirement of minimizing racemization at adjacent sites. Sometimes, hydroxybenzotriazole (HOBt) is used together with HBTU as racemization suppressor. Thus, HBTU effectively performs condensation with high yields and minimal racemization, in simple experimental conditions and within short reaction times.

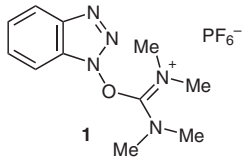
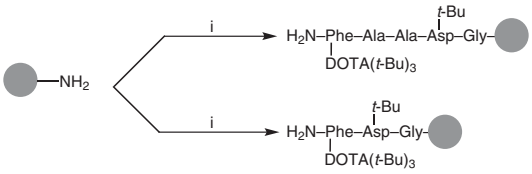


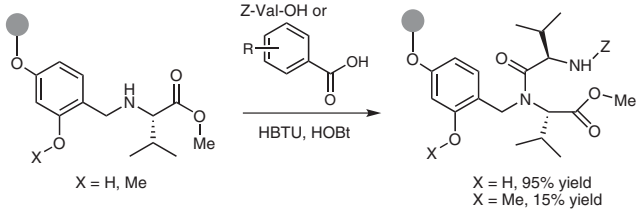
Figure 1

Applications of HBTU:

(A) *Solid-Phase Peptide Synthesis*:
The attachment of amino acid residues to Rink amide resin to initiate the polypeptide synthesis using Fmoc amino acids, and the HBTU/HOBt/*N*,*N*-diisopropylethylamine (DIPEA) protocol has been reported by A. D. Sherry and co-workers.[8]



(B) *Solid-Phase Synthesis of Hindered Amides*:
In the solid-phase synthesis of sterically hindered amides simple acylation conditions (HBTU/HOBt/*N*-methylmorpholine) were found to be efficient to provide near quantitative reaction of test acids with support-bound hindered amines.[9]



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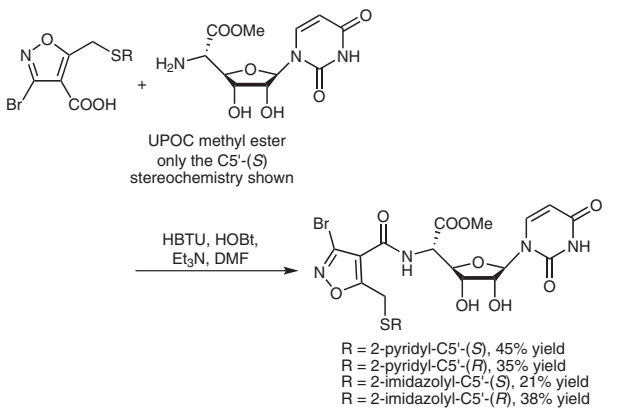
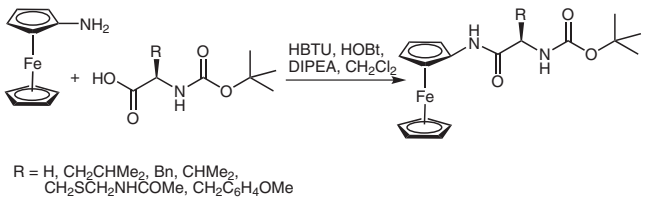
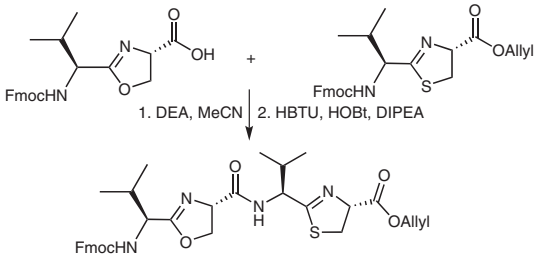
(C) *Stereoselective Synthesis*:
The stereoselective syntheses of both the natural [C5′-(*S*)] and unnatural [C5′-(*R*)] diastereoisomers of uracil polyoxin C (UPOC) methyl esters is reported by Plant, Thompson, and Willams. A variety of substrate mimics designed as inhibitors of chitin synthase have been prepared by conjugation of the methyl ester of UPOC with activated isoxazolecarboxylic acids. The amide bond formation was accomplished via coupling of the amino functionality of UPOC methyl ester with a free isoxazole acid using HBTU.[10]



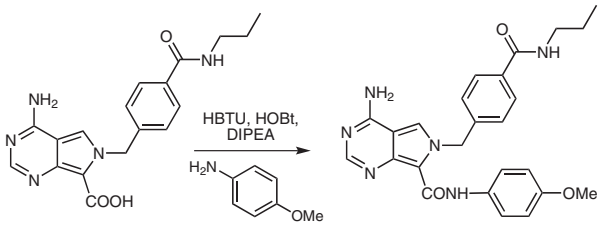
(D) *Organometallic Chemistry*:
Aminoferrocene (H_2NFc), has been condensed with the C-terminus of six amino acids using the HBTU/HOBt coupling protocol in good yields by Metzler-Nolte and co-workers showing the synthetic utility of HBTU in organometallic chemistry.[11]



(E) *Synthesis of Natural Products*:
A total synthesis of bistratamides has been reported by Kelly and co-workers. Most of the amide bonds required alongway are generated by means of the HBTU/HOBt/DIPEA protocol.[12]



(F) *Synthesis of Biologically Active Compounds*:
In the synthesis of the potential HSP90 inhibitors 4-amino-6-benzyl-6*H*-pyrrolo[3,4-*d*]pyrimidine and 7-amino-2-benzyl-2*H*-pyrazolo[4,3-*d*]pyrimidine derivatives from starting dezapurine, Corelli and colleagues have employed the HBTU/HOBt/DIPEA conditions for the synthesis of amide analogues.[13]



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