SPOTLIGHT

SYNLETT

Spotlight 400

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

1-[[1-(Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholinomethylene]methane-aminium hexafluorophosphate

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Introduction

Peptide coupling reagents are rapidly evolving in the last years from the classical carbodiimide methods to a second generation onium salts based reactives, and nowadays the novel uronium-type reagents derived from Oxyma like 1-[[1-(Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholinomethylene]methane-aminium hexafluorophosphate (COMU) introduced by Albericio’s group. This third generation peptide coupling reagent is soluble and stable due to the presence of morpholin. By-products are water-soluble and easy to remove, making COMU an excellent choice as coupling reagent in solid- and liquid-phase peptide synthesis. In addition, COMU shows a less hazardous safety profile than benzotriazole-based reagents like HATU and HBTU, which exhibit unpredictable autocatalytic decomposition and therefore a higher risk of explosion, and cause allergic reactions. COMU gives better results than aza derivatives in the presence of only one equivalent of base, and no activation time is required reducing the common racemization problem. Further, the couplings can be monitored by advantageous visual or colorimetric reaction. Although commercially available, COMU can be prepared easily (Scheme 1).

Abstracts

Scheme 1 Synthesis of COMU

(A) By combining of microwave heating and solid-phase peptide synthesis, Yamada and Shimizu prepared cyclic RGD peptides using COMU as coupling agent in good yields. In the five coupling sequences COMU was as effective as HBTU at room temperature (73% and 69% yield, respectively). Although at 50 °C, the COMU-promoted coupling was faster and 84% yield instead of 39% using HBTU was obtained.
(B) A highly efficient COMU-mediated solid-phase methodology for the synthesis of para- and meta-arylopeptoids with free acids or free amides at the C-terminus was reported.\(^7\)

(D) Lu and Nan\(^2\) applied the methodology, previously described by Tyrrell\(^10\) and co-workers, of amino acids conversion into Weinreb amides to the synthesis of rubescencin S. This novel diterpenoid with cytotoxic activity against human leukemia cells was synthesized from oridonin employing COMU in the key step due to its zero tendency for racemization and bigger reactivity than other coupling agents like DCC or EDCl.

(F) COMU also has been reported to promote selective amidation in the presence of free hydroxyl groups. Blagg\(^12\) employed this reaction in the total synthesis of monoenomycin, a trinomycin A analogue with anticancer activity.

References