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-oxoethylidnaminoxy)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-oxoethylidnaminoxy)dimethylamino-morpholinomethylene)]methane-aminium hexafluorophosphate (COMU) introduced by Albercio’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**

(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-aryllopeptoids with free acids or free amides at the C-terminus was reported.  

(B) Tulla-Puche and Albericio performed the synthesis of N-Me-JB-01212, a highly methylated cyclopeptide with anticancer activity, using COMU as the key coupling agent. Among all coupling agents and additives, COMU and Oxyma allow to carry out the demanding reactions with a higher concentration, thus favoring high yields.

(C) A highly efficient COMU-mediated solid-phase methodology for the synthesis of para- and meta-aryllopeptoids with free acids or free amides at the C-terminus was reported.  

(C) Free amides at the C-terminus was reported.  

(D) Lu and Nan applied the methodology, previously described by Tyrrell and co-workers, of amino acids conversion into Weinreb amides. The 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 EDCI.

(D) Tulla-Puche and Albericio performed the synthesis of rubescensin S. This novel diterpenoid with anticancer activity 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 EDCI.

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

References