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-oxoethylidenaminoxy)dimethylaminomorpholinomethylene]]methaneaminium 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 reagents,¹ and nowadays the novel uronium-type reagents derived from Oxyma like 1-[[1-(Cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylaminomorpholinomethylene]]methaneaminium hexafluorophosphate (COMU) introduced by Albericio's group.² This third generation peptide coupling reagent is soluble and stable due to the presence of morpholin.^{2b} By-products are water-soluble and easy to remove, making COMU an excellent choice as coupling reagent in solid- and liquid-phase peptide synthesis.³ 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).^{2a,4}

Scheme 1 Synthesis of COMU

Abstracts

(A) By combining of microwave heating and solid-phase peptide synthesis,⁵ Yamada and Shimizu⁶ 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.