

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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Julián Bergueiro Álvarez received his BSc in Chemistry in 2007 and his MSc in Organic Chemistry in 2009, both from the Universidad de Santiago de Compostela (USC). Presently he is a PhD student at the USC under the supervision of Professor Susana López. His research interests mainly focus on the synthesis of biologically active polyenes and polyenynes by using metal-catalyzed cross-coupling reactions, and on bioorganic studies of retinoids. Nowadays his work is focused on poly(phenylacetylene)s chemistry.

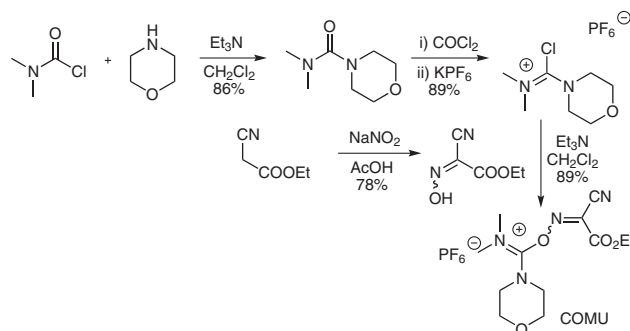
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Introduction

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

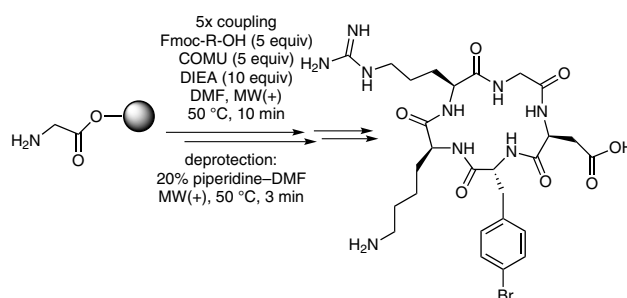
time is required reducing the common racemization problem. Further, the couplings can be monitored by advantageous visual or colorimetric reaction. Although commercially available, COMU can be prepared easily (Scheme 1).^{2a,4}



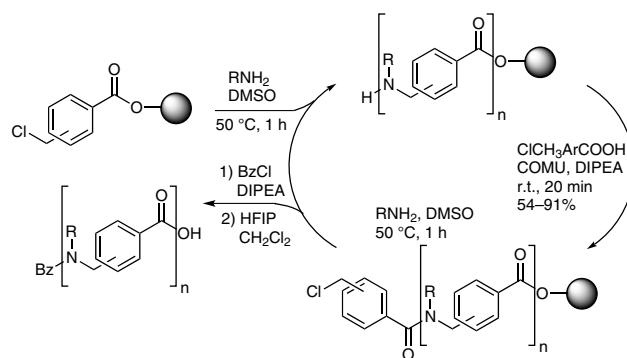
Scheme 1 Synthesis of COMU

Abstracts

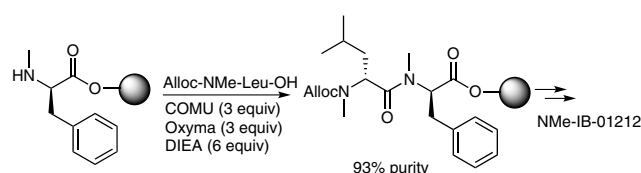
(A) By combining of microwave heating and solid-phase peptide synthesis,⁵ Yamada and Shimizu⁶ prepared cyclic RGD peptides using COMU as coupling agent in good yields. In the five coupling sequences COMU was as effective as HBTU at room temperature (73% and 69% yield, respectively). Although at 50 °C, the COMU-promoted coupling was faster and 84% yield instead of 39% using HBTU was obtained.



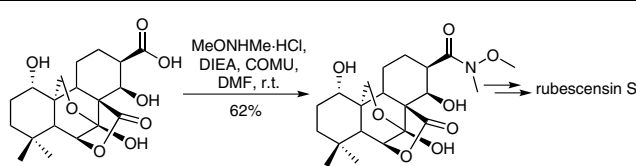
(B) A highly efficient COMU-mediated solid-phase methodology for the synthesis of *para*- and *meta*-arylopeptoids with free acids or free amides at the C-terminus was reported.⁷



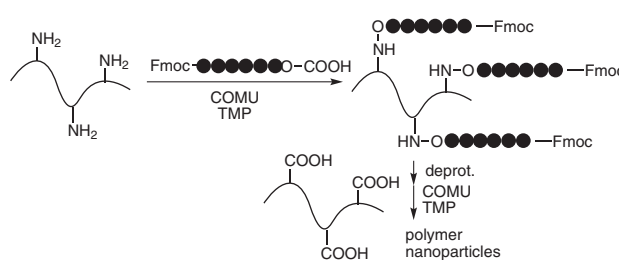
(C) Tulla-Puche and Albericio performed the synthesis of *N*-Me-IB-01212, a highly methylated cyclopeptide with anticancer activity, using COMU as the key coupling agent. Among all coupling agents and additives, COMU and Oxyma allow to carry out the demanding reactions with a higher concentration, thus favoring high yields.⁸



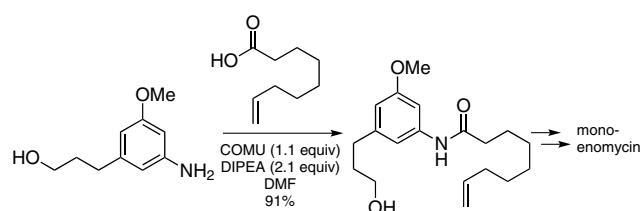
(D) Lu and Nan⁹ applied the methodology, previously described by Tyrrell¹⁰ and co-workers, of amino acids conversion into Weinreb amides to the synthesis of rubescensin S. This novel diterpenoid with cytotoxic activity against human leukemia cells was synthesized from oridonin employing COMU in the key step due to its zero tendency for racemization and bigger reactivity than other coupling agents like DCC or EDCI.



(E) Landfester and co-workers used COMU and TMP in the coupling of a labeled Fmoc N-protected FRET pair and an amino-functionalized polystyrene. Deprotected, hydrophobic peptide cross-linked polystyrene nanoparticles were synthesized by coupling in inverse miniemulsions, showing COMU's versatility.¹¹



(F) COMU also has been reported to promote selective amidation in the presence of free hydroxyl groups. Blagg¹² employed this reaction in the total synthesis of monoenomycin, a trinomycin A analogue with anticancer activity.



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