SYNLETT Spotlight 35

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

1-Hydroxy-7-azabenzotriazole (HOAt) and *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-yl-methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HATU)

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Introduction Peptide coupling methods based on aminium salts of 1-hydroxyazabenzotriazole (HOBt) and 1-hydroxy-7-azabenzotriazole (HOAt)¹ such as *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-yl-methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HATU)^{1,2} are currently being used more frequently than classical carbodiimide methods.³ Reactions with HOAt and HATU are generally faster and show less racemization than reactions with HOBt because of the anchimeric assistance of the 7-nitrogen atom in the active HOAt-ester intermediate.¹ They are especially useful for difficult couplings like those of *N*-methyl and α,α -disubstituted amino acids^{4,5,6} and for amide bond formation where time is a critical issue.⁷

Preparation Although commercially available, HOAt and HATU are expensive and hard to obtain in Europe because of shipping restrictions. They can be easily prepared according to the following scheme:^{1,8}

Abstracts

(A) Because amide bond formation is very fast in the presence of HATU, this reagent is ideally suited for reactions of molecules that contain instable isotopes, e. g. ¹⁸F with a half-life of 1.83 hours. The labeling of a peptide for positron emission tomography with 4-[¹⁸F]fluorobenzoic acid was accomplished by Bansal in almost quantitative yield within 3 min using HATU as an activating agent.⁷

(B) In the last step of the total synthesis of mauritine-A, HATU proved to be the reagent of choice to prevent racemization of the valine residue of the dipeptide during coupling to a secondary amine.⁹

(C) One of the key steps towards the total synthesis of (–)-mirabazone **C** is a successive coupling of the α,α -disubstituted amino acid 2-methylcysteine. Kiso showed in a model study with 2-aminoisobutyric acid (Aib), that the addition of HOAt to the coupling mixture could increase the yield of Fmoc-Aib-Aib-OMe from below 20% after 5 hours to more than 98% within 30 min.¹⁰

References and Notes

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