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 \(\alpha,\alpha\)-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. \(^{18}\)F with a half-life of 1.83 hours. The labeling of a peptide for positron emission tomography with 4-\(^{18}\)Ffluorobenzoic 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.\(^9\)

ISSN 0936-5214
(C) One of the key steps towards the total synthesis of (−)-mirabazole 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