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)

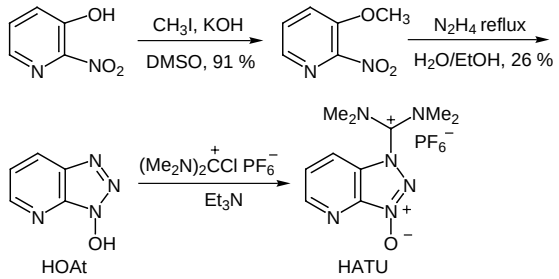
Compiled by Alexander Kienhöfer

Alexander Kienhöfer studied chemistry at the Universität Konstanz where he received his Diplom in 1999. After the Vordiplom he spent one year abroad at the University of Northern Arizona (NAU) in Flagstaff. Currently he is working on his Ph. D. thesis under the supervision of Prof. D. Hilvert at the Eidgenössische Technische Hochschule Zürich.

Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule Zürich, ETH-Hönggerberg, CH-8093 Zürich, Switzerland
E-mail: Kienhoefer@org.chem.ethz.ch

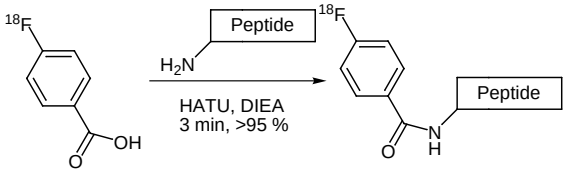
Introduction Peptide coupling methods based on aminium salts of 1-hydroxyazabenzotriazole (HOBt) and 1-hydroxy-7-azabenzotriazole (HOAt)[1] such as *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-b]pyridin-1-yl-methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HATU)[1,2] are currently being 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]

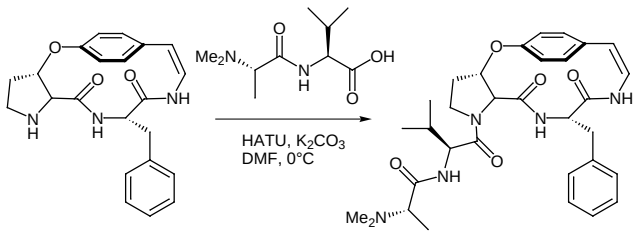


Abstracts

(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. ^{18}F with a half-life of 1.83 hours. The labeling of a peptide for positron emission tomography with 4-[^{18}F]fluorobenzoic acid was accomplished by Bansal in almost quantitative yield within 3 min using HATU as an activating agent.[7]



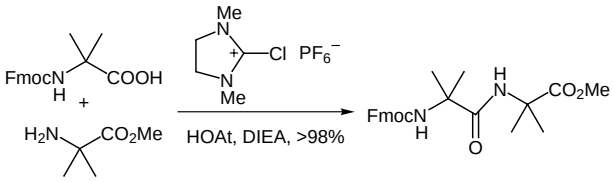
(B) In the last step of the total synthesis of mauritine-A, HATU proved to be the reagent of choice to prevent racemization of the valine residue of the dipeptide during coupling to a secondary amine.[9]



Synlett 2001, No. 11, 26 10 2001. Article Identifier:
1437-2096,E;2001,0,11,1811,1812,ftx,en;V04001ST.pdf.

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

(1) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397.
(2) Albericio, F.; Bofill, J. M. *Tetrahedron Lett.* **1999**, *40*, 2641.
(3) Albericio, F.; Bofill, J. M.; El-Faham, A.; Kates, S. A. *J. Org. Chem.* **1998**, *63*, 9678.
(4) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243.
(5) Li, P.; Xu, J. *Chin. J. Chem.* **2000**, *18*, 456.
(6) Bozs, Z.; Tth, G.; Murphy, R. F.; Lovas, S. *Lett. Pept. Sci.* **2000**, *7*, 157.
(7) Sutcliffe-Goulden, J. L.; O'Doherty, M. J.; Bansal, S. S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1501.
(8) Williamson, D. A.; Bowler, B. E. *Tetrahedron* **1996**, *52*, 12357.
(9) Laïb, T.; Bois-Choussy, M.; Zhu, J. *Tetrahedron Lett.* **2000**, *41*, 7645.
(10) Akaji, K.; Kuriyama, N.; Kiso, Y. *J. Org. Chem.* **1996**, *61*, 3350.