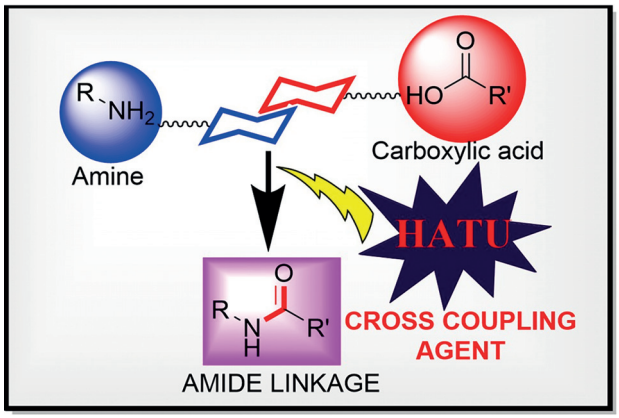
Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium (HATU): A Unique Cross-Coupling Reagent

Abhimannu Shome
Keshav Taruneshwar Jha
Pooja A. Chawla*

Department of Pharmaceutical Chemistry, ISF College of Pharmacy, Moga, Punjab, India
pvchawla@gmail.com



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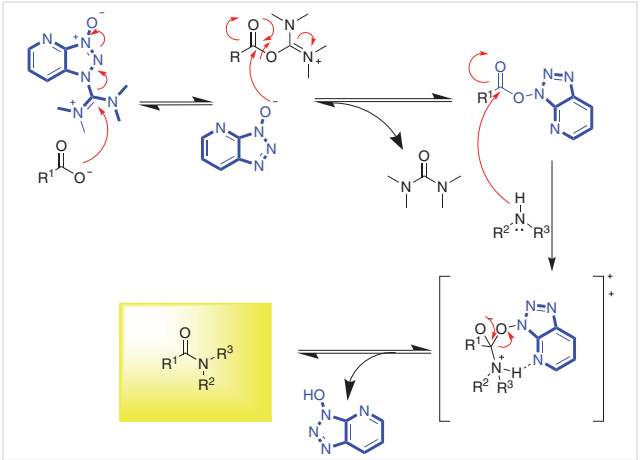
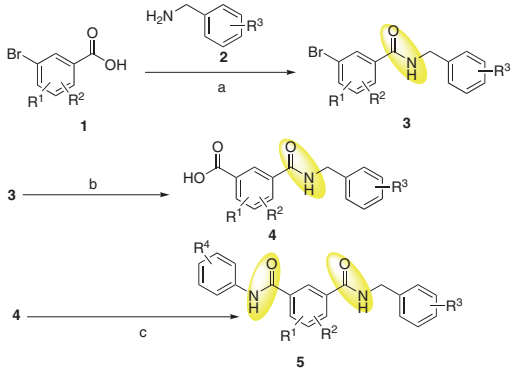
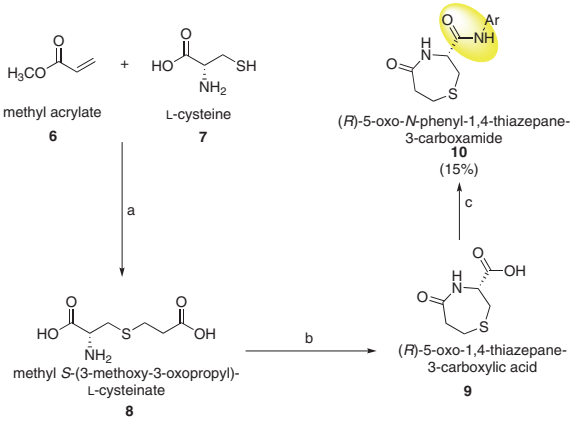
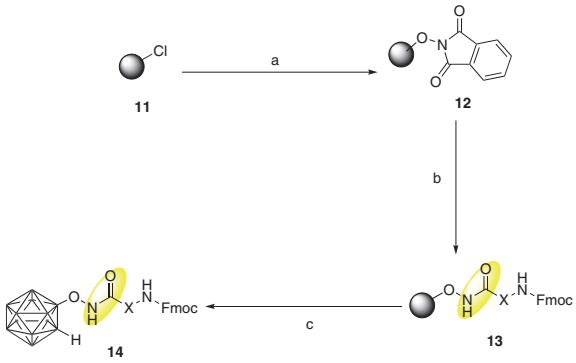
Keywords Cross-coupling, HATU, amide linkage, C-N coupling

Coupling reactions have piqued the curiosity of synthetic chemists since 1940. Since the mid-1990s to the present, coupling and cross-coupling reactions have been widely employed in the synthesis of monomers and polymers.[1] Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki were awarded the most prestigious Nobel prize in the preceding decade for inventing palladium-catalyzed cross-coupling processes, also known as the Suzuki coupling reaction. Yet, both metal-catalyzed and nonmetal-catalyzed processes are employed in both academia and industry.[2] There are several heterocyclic catalysts those are facilitate both coupling and cross-coupling reactions. Among them, hexafluorophosphate azabenzotriazole tetramethyl uronium (HATU), IUPAC name (*N*-{(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene}-*N*-methyl methanaminium hexafluorophosphate *N*-oxide) is used in both small molecule's synthesis or peptide synthesis.[3–6] Louis A. Carpino discovered a new ester derivative of 1-hydroxy-7-azabenzotriazole (HOAt) in 1993, which occurs in two states: uranium salt and iminium salt. HATU was a third-generation coupling reagent with the ability to decrease racemization. HATU causes amine acylation or the formation of an amide bond. In addition to nucleophiles, it is employed in peptide cyclization. HATU catalyzes the nucleophilic addition process. shown in Scheme 1. In terms of the coupling reaction, it refers to the coupling of the same fragment, whereas cross-coupling refers to the coupling of two separate fragments. The mechanism of HATU involves the activation of the carboxylic group through the formation of a carboxylate anion that attacks HATU to produce *O*-acyl(tetramethyl)isouronium salt, which then proceeds the addition of the nucleophile, i.e., amines.[7–10]



Scheme 1 Synthetic mechanism of cross-coupling mediated by HATU

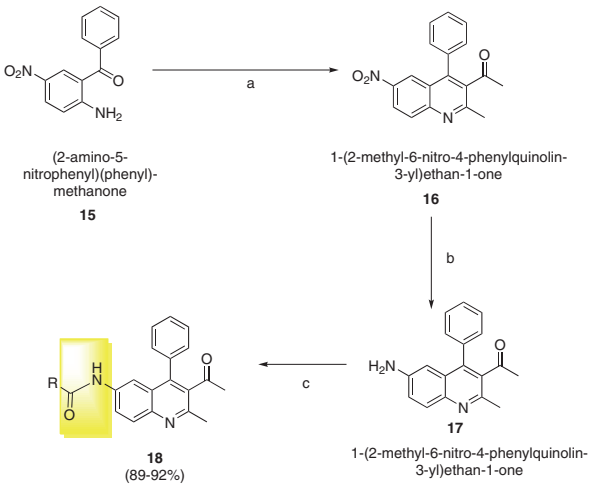
Table 1 Applications of ZNC

(A) At the end of 2022, Orsi *et al.* reported a synthetic route of 4-chloro-6-fluoro-sophthalamides. **Synthetic Procedure** The synthesis method began with HATU-mediated cross-coupling of **1** and **2**, yielding compound **3**, followed by C–N coupling to give **4** in the presence of diacetoxypalladium (5%), 1,1-bis(diphenylphosphino)ferrocene (DPPF), and triethylamine, yielding about **5**. The final stage employed comparable reagents and a cross-coupling procedure to produce the compound.[11]	 Reaction conditions: (a) HATU, DIPEA, DMF; (b) $Pd(OAc)_2$ (5 mol%), DPPF (20 mol%), Et_3N, 14.6 bar CO, MeOH; (c) HATU, DIPEA, DMF.
(B) In 2021, Kent and his colleagues created, synthesized, and physiologically optimized a series of substituted 1,4-thiazepane for mGlu4 PAMs with promising blood-brain barrier permeability in 2021.[12] **Synthetic Procedure** Under alcoholic conditions, methyl acrylate **6** reacts with L-cysteine (**7**) to produce methyl *S*-(3-methoxy-3-oxopropyl)-L-cysteinate (**8**, 88%). Furthermore, under ammonia and methanolic conditions, cyclization yielded (*R*)-5-oxo-1,4-thiazepane-3-carboxylic acid (**9**). Finally, the carboxylic group facilitates cross-coupling with aniline in the presence of HATU for hours in DMF as a solvent, providing (*R*)-5-oxo-*N*-phenyl-1,4-thiazepane-3-carboxamide (**10**, 15%).	 Reaction conditions: (a) NEt_3, EtOH, 5 min, rt, 88%; (b) 7 M NH_3/MeOH, 7 d, rt; (c) HATU, DIPEA, $ArNH_2$, DMF, rt, 12 h, 5–15%.
(C) Selg and colleagues investigated on a series of carborane-capped histone deacetylase. Histone deacetylase plays an important function in the reversible acetylation of the lysine amino group at the N-terminus of nonhistone proteins; these inhibitors are commonly utilized in cancer, anti-HIV, and other inflammatory disorders. **Synthetic Procedure** The solid-phase synthesis technique was constituted of a solid surface provided by resin; in this experiment, the 2-chlorotritylchloride resin **11** was used and bonded with *N*-hydroxy phthalimide **12** in the presence of hydrazine and methanol to modify the resin; phthaloyl residue cleavage occurs under alcoholic conditions. To obtain **13**, HATU enhanced coupling via amide linkage formation with Fmoc protection at the amine site. Further coupling with HATU and DIPEA in an aprotic environment yields compound **14**.[13]	 Reaction conditions: (a) PhthN-OH, NEt_3, DMF, 24 h, rt; (b) N_2H_4, H_2O, MeOH, 30 min, rt; Fmoc-linker-COOH, HATU, HOBt, H_2O, DIPEA, DMF, 18 h, rt; (c) 20% piperidine in DMF, rt; **3**, HATU, DIPEA, DMF, 18 h, rt, **4**, COMU, DIPEA, DMF, 18 h, rt; 5% TFA, DCM, 1 h, rt, 74–99%

(D) Kumar and colleagues developed, produced, and tested new amylase inhibitors for diabetes mellitus made of substituted arylamides. A library of *N*-(3-acetyl-2-methyl-4-phenylquinolin-6-yl) arylamides was synthesized via a coupling technique in the presence of HATU and DCC.

Synthetic Procedure

In the initial step, (2-amino-5-nitrophenyl)(phenyl)methanone (**15**) underwent cyclization in presence of *O*-Phosphoric acid, and ethanol to yield 1-(2-methyl-6-nitro-4-phenylquinolin-3-yl) ethan-1-one (**16**). Subsequently, a 20-minute grinding process with zinc dust and ammonium chloride was employed to transform the nitro group substitution into an amine group by reduction, resulting in the formation of 1-(6-amino-2-methyl-4-phenylquinolin-3-yl) ethan-1-one (**17**), which was then coupled with acid through a HATU-mediated coupling process. The amine was connected with the hydroxy portion of the substituted carboxylic acid through an amide linkage after 2 h of reflux, yielding **18** (89–92%).[14]

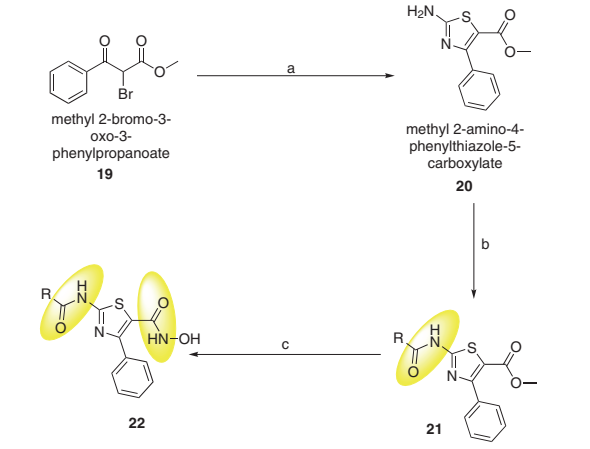


Reaction conditions: (a) pentane-2,4-dione, ethanol *O*-phosphoric acid, rt. 12 h; (b) Zn dust, NH_4Cl, grinding, 20 min; (c) substituted carboxylicacid, HATU, DMF, reflux, 2 h.

(E) Recently, Asfaha *et al.* designed and synthesized a series of thiazolyl-based hydroxamic acid for histone decarboxylase inhibitors.

Synthetic Procedure

The α-bromoester, starting material methyl 2-bromo-3-oxo-3-phenylpropanoate (**19**), was treated with thiourea in ethanol to produce methyl 2-amino-4-phenylthiazole-5-carboxylate (**20**). Furthermore, the amine substitution on the thiazole ring was coupled with substituted acid in the presence of HATU with DIPEA as a deprotonating reagent in DMF as a solvent to synthesize substituted 2-acetamido-4-phenyl-3-thiazolidine-5-carboxylate **21**, followed by amide formation on the steric site in the presence of HATU and DIPEA in KOH, mediated basic medium with hydroxylamine hydrochloride in DMF obtained the final compound, substituted 2-amido-*N*-hydroxy-4-phenyl-3-thiazolidine-5-carboxamide (**22**).[15]



Reaction conditions: (a) 1.00 eq thiourea, EtOH, reflux, 6 h; (b) 1.00 eq HATU, 1.00 eq RCOOH, 2.00 eq DIPEA, DMF, 60 °C; (c) 30.0 eq KOH 1.00 eq HATU, 3.20 eq DIPEA, 1.20 eq $NH_2OH{\cdot}HCl$, THF, reflux, 12 h, DMF, 60 °C, 6 h.

We have examined recent uses of HATU as a coupling reagent in the synthesis of small molecules and peptides through amide linkage (Table 1). Additionally, we observed the significant role of DIPEA (*N*,*N*-diisopropylethylamine) as a deprotonating agent in HATU-mediated coupling reactions. These applications have clearly demonstrated the potential of HATU in organic synthesis. Furthermore, the introduction of DMAP as a catalyst in the reaction has proven instrumental in enhancing the coupling process. DMAP aids in the deprotonation of the amine, increasing its nucleophilicity and facilitating its attack on the activated ester. Moreover, DMAP contributes to the removal of the byproduct, dimethylamine (DMA), by forming a stable complex with it, effectively preventing unwanted side reactions.

Conflict of Interest

The authors declare no conflict of interest.

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