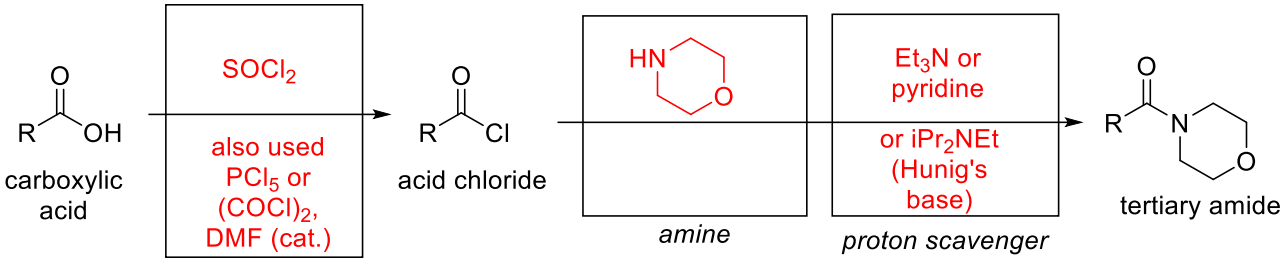
CHEM 515, Modern Medicinal Chemistry due: September 8, 2026

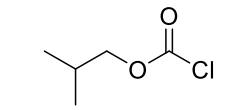
Problem Set #1: Amide bond synthesis in medicinal chemistry

Amide bond formation is one of the most common reactions used in drug synthesis. Answer the questions below which review a range of reagents and conditions that couple carboxylic acids with amines to make amides—a type of nucleophilic acyl substitution reaction. Note: You will have to investigate these reagents and processes. I suggest Googling key words for the more sophisticated reagents. Wikipedia has good information. More familiar processes in question #1 can be found in any organic chemistry textbook found in the library or on-line.

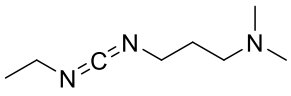
1. In introductory organic chemistry, the following sequence is typically taught and used to make amides from carboxylic acids. Provide the necessary reagents in the appropriate box. (5 pts.)



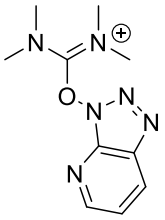
2. As I mentioned in class, fancy pants, sophisticated modern chemistry uses the same types of processes, but "dresses them up in drag". The reagents are often more expensive, but you usually gain efficiency (higher yields) and selectivity (fewer side reactions). The three reagents shown below all fit this category and are listed (L to R) in approximate chronological order of introduction into synthetic chemistry and, as such, demonstrate growing sophistication of an amide coupling reagent.



isobutyl chloroformate (iBCF)



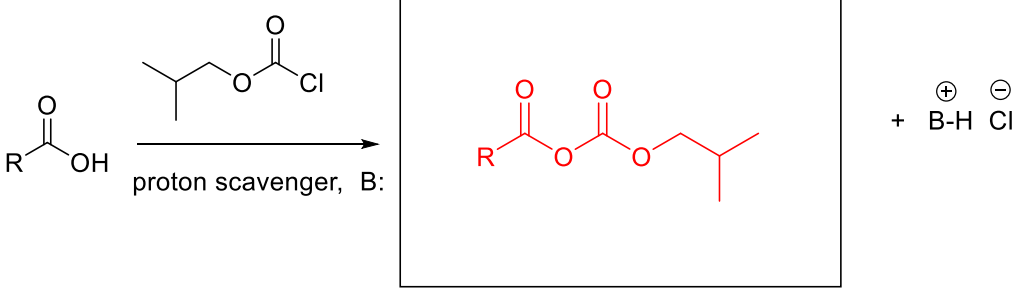
1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)



(1-[Bis(dimethylamino) methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU)

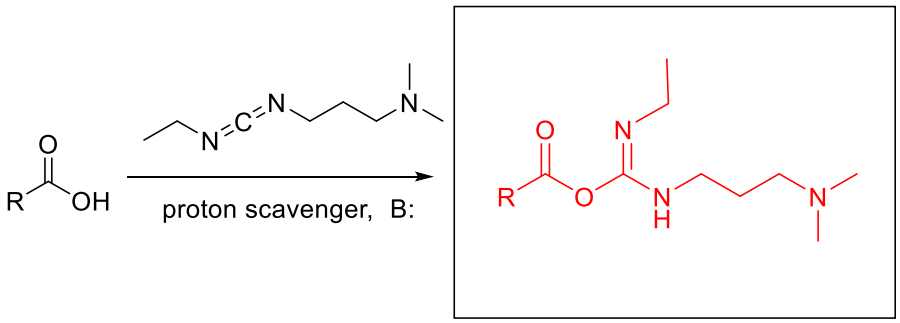
The first two reagents, iBCF and EDC, essentially form mixed acid anhydride intermediates (or something quite similar for EDC), which activate the carboxylic acid piece to an amine nucleophilic acyl substitution. The mixed anhydride acts as the acid chloride in the sequence above. Draw this mixed acid anhydride intermediate in the box to the right of each reaction. (4 pts.) Hint: These reactions can be understood as the carboxylic acid oxygen reacting with the most electrophilic carbon in the reagent, iBCF or EDC.

a)



mixed acid anhydride intermediate

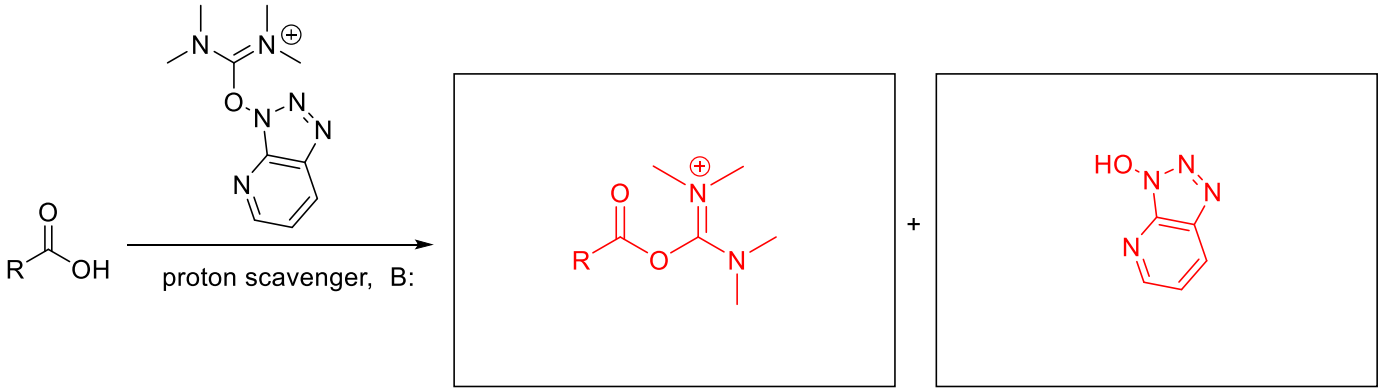
b)



mixed acid anhydride-like intermediate

HATU combines an acid anhydride formation reagent with an acylation catalyst 1-hydroxy-7-azabenzotriazole (HOAt). The acylation catalyst helps in the second step: the amine reaction with the mixed acid anhydride-like intermediate.

c) Draw the mixed acid anhydride formed when a carboxylic acid reacts with HATU. (3 pts.)



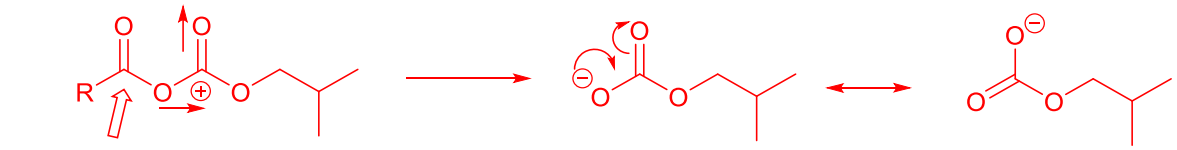
mixed acid anhydride-like intermediate 1-hydoxy-7-azabenzotriazole

3. Provide one reason (of two possible) why the original carboxylic acid is now more activated to a nucleophilic acyl substitution with an amine reagent as the mixed acid anhydride intermediates. You should consider the two principles that are typically discussed in introductory organic chemistry in evaluating acid derivative reactivity. (3 pts.)

All three now have a much better leaving group, i.e. a resonance-stabilized weak base, which is more inclined to leave than the -OH on the original carboxylic acid.

Also, the carbonyl of the acid anhydride intermediate is more electrophilic with an electron withdrawing group (due to electronegative atoms and bond polarization) than with the original -OH group.

One example for iBCF case:



electrophilic based on bond dipole moments from electronegative O.

resonance stabilized weak base