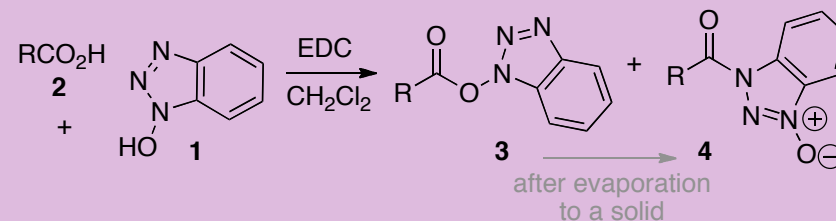


Hydrogen bonding peptides as asymmetric organocatalysts

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Hydroxybenzotriazole (HOBt **1**) is a common additive to the peptide synthesis reactions for our organocatalysts. The isolation of acylated HOBt derivatives unexpectedly produced two isomeric products (**3** and **4**), that differed in the regiochemistry of the acylation reaction.



The product ratios were determined to be a factor of steric bulk, solvent and a novel example of the Curtin-Hammett effect. Increased steric bulk on the acylating group disfavored the N-acyl form **4**. Kinetic analysis showed the immediate formation of the O-acyl form **3**, followed by an equilibration in solution to both isomers. The final product equilibrium product ratios were dependent on solvent, with more polar solvents favoring the O-acyl form **3**. This appear to be a result of the tautomeric ratio of HOBt forms **1** and **1'**, where the zwitterionic form is more favorable in more polar solvents.

An additional curiosity was observed with the complete isomerization to the N-acyl form **4** upon evaporation of the product mixture to a solid. This suggests that the N-acyl form **4** is the thermodynamic product, and formation of the O-acyl form **3** in solution is biased by the tautomeric equilibria of HOBt. Previously observed equilibrium product ratios were re-established by dissolving pure N-acyl isomer **4** in solvent and adding either nucleophilic or electrophilic reagents. This work was recently published in the *Journal of Organic Chemistry*.

