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Synthesis of Indole-3-Acetic Acid Derivatives and a Urea Carboxylic Acid Derivative by Propylphosphonic Anhydride (T3P)

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Synthesis of indole-3-acetic acid derivatives and a urea carboxylic acid derivative by propylphosphonic anhydride (T3P).

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Abstract

The purpose of medicinal chemistry is to efficiently create a variety of compounds with potential for pharmacological efficacy. To promote this diversity, indole-3-acetic acid, a common plant hormone, was used as the starting material for various reactions. The coupling reagent used for these reactions was propylphosphonic anhydride, or T3P, since it has demonstrated efficiency in selective amide formation under mild conditions and it is readily soluble. In the case of multiple viable reaction sites, the intended product will dimerize, as was the case in the synthesis of the compound labeled amide 2 when T3P coupled with both sites of piperazine. N-Hydroxysuccinimide, also referred to as HOSu and NHS, was used to decrease the reactivity of the carboxylic acid—T3P mixed anhydride, so it less readily formed the dimer. This increased the yield of the monomer. Pharmacological efficacy is more probable when synthesizing a chemotype with a known structure-activity relationship, or SAR. Urea carboxylic acid has been found to have antischistosomal activity. In an effort to synthesize a drug candidate with greater likelihood of pharmacological activity, a compound was synthesized from a urea carboxylic acid using T3P by the same method used to synthesize products from indole-3-acetic acid. Five compounds were synthesized using the T3P reagent in an attempt to expand the repository of potential drug candidates. The method for each compound was made largely similar, but it differed in the work-up and purification stages, as the acidity and polarity of the systems varied.

Synthesis

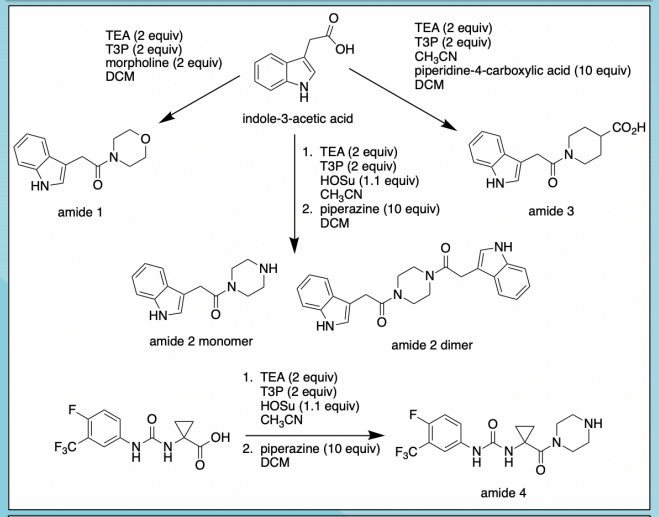


Figure 1. Synthesis of five amide compounds, including a dimer, by using the T3P reagent.

T3P Mechanism

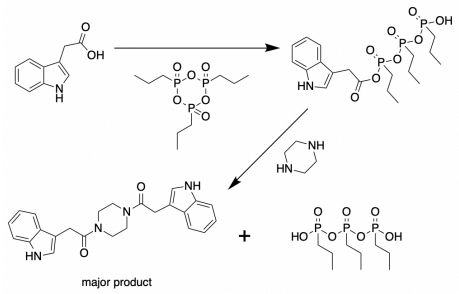


Figure 4. Reaction mechanism of T3P reagent with indole-3-acetic acid and piperazine.

NMR Data of Dimerized Product

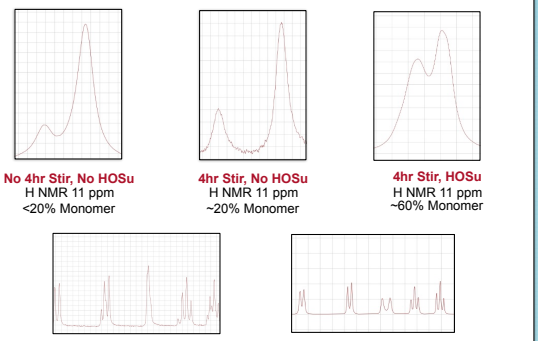


Figure 3. Proton NMR data from the crude product of the amide 2 reaction. The monomer is connoted by the peak on the left at about 11 ppm and one singlet at about 7.2 ppm, while the dimer is connoted by the peak on the right at about 11 ppm and two singlets at about 7.2 ppm.

HOSu Mechanism

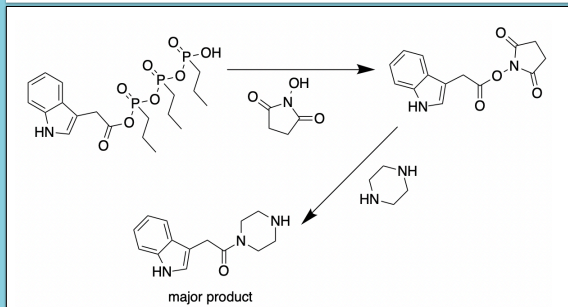
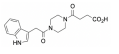
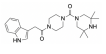


Figure 4. Reaction mechanism HOSu with indole-3-acetic acid—T3P mixed anhydride.

Conclusion and Future Directions

The T3P reagent successfully synthesized the five compounds labeled, and HOSu demonstrably improved the proportion of the monomer in the amide 2 crude product mixture.
More compounds could be made by the reagents listed, and the products of these reactions could also be used as starting materials for new products with different reagents to create more complexity and structural diversity. The product on the left could be synthesized from amide 2's monomer by using succinc anhydride. The product on the right could be synthesized from amide 2's monomer using isocyanate.

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