Phosphorus Pentoxide As An Effective Coupling Reagent for Synthesis of Amides

IITM Technology Available for Licensing

Problem Statement

- In the present era, the **biological process** of producing long peptides is known as protein biosynthesis & synthetic peptides are used either as drugs or in the diagnosis of disease.
- Based on the prior arts literature survey, it is noted that though the reagents provide excellent yields & low racemization for the coupling reaction, but they are relatively expensive & the guanidium by product has to be removed by column chromatography. Further it is noted in different scenario of Benzotraizol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate **(BOP)** reagents which liberate hexamethylphosphoramide (**HMPA**), which is highly **carcinogenic.**
- Hence, there is a **need** to develop **cheap, efficient, non-toxic & non-carcinogenic coupling reagents for peptide synthesis** & present invention has addressed the issues efficiently.

Technology Category/ Market

Technology: Phosphorus Pentoxide for Synthesis of Amides;
Industry: Industrial & Pharmaceutical.
Applications: Medicine, Pesticide, Petrochemical.
Market: The global **Phosphorus Pentoxide** market is projected to grow at a **CAGR** of **4.5%** during forecast period of **2023** to **2030.**

Intellectual Property

IITM IDF Ref. 1603; Patent No.339439

TRL (Technology Readiness Level)

TRL- 3, Proof of Concept & validated in Lab

Research Lab

Prof. Nandita Madhavan
Department of Chemistry,

Technology

- Present invention describes a **process for synthesizing amides in one-pot via in-situ formation of anhydride in presence of a coupling reagent.**
- The process comprising the steps of:

1. **preparing a solution of 1.2 equivalent part of acid in THF;**
   adding equivalents part of coupling reagent to the mixture
2. **allowing the resulting mixture to stir at room temperature for 30 min;**
   subsequently, adding 1 equivalent part of amine, equivalent part of base , & equivalent part of catalyst to the resultant mixture;
3. **allowing the mixture to stir until TLC indicates starting material is consumed,**
   removing the solvent in vacuo;
   quenching the remaining mixture with water;
4. **extracting the mixture with Ethyl cetate (EtOAc) and sequentially washing the mixture with saturated bicarbonate solution, 10% HCl solution and saturated Sodium Chloride (NaCl) solution**
5. **drying the organic layer formed over anhydrous Sodium sulfate (Na2SO4);**
   Filtering & Concentrating the filtrate in vacuo; &
   purifying and isolating the desired amide using column chromatography, wherein negligible by-product formation or minimal racemization occurs.

- Further, **one-pot in reaction** between the **carboxylic acid & amine** takes place in presence of **4 equivalent P_2O_5** & in presence of **3** equivalent part of diisopropylethylamine & **0.2** equivalent part of catalytic amounts of DMAP.

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Key Features / Value Proposition

❖ ***Technical Perspective:***

1. Present patent provides a **coupling agent**, wherein **phosphorous pentoxide** acts as a coupling agent for synthesis of amides from acids & amines, thereby resulting in **minimal racemization**.

❖ ***Industrial Perspective:***

1. Minimize the formation of **organic by product.**
2. Present Patent is utilizing **a coupling agent** of **phosphorous pentoxide** which is extremely **cheap, efficient, non-toxic & non- carcinogenic in nature,** when used as a coupling agent during amide synthesis.
3. **Cost-effective** process & the separation of the product are **very simple** makes it an **extremely attractive reagent for peptide synthesis.**
4. **Applicable in drugs or in the diagnosis of disease.**

Images

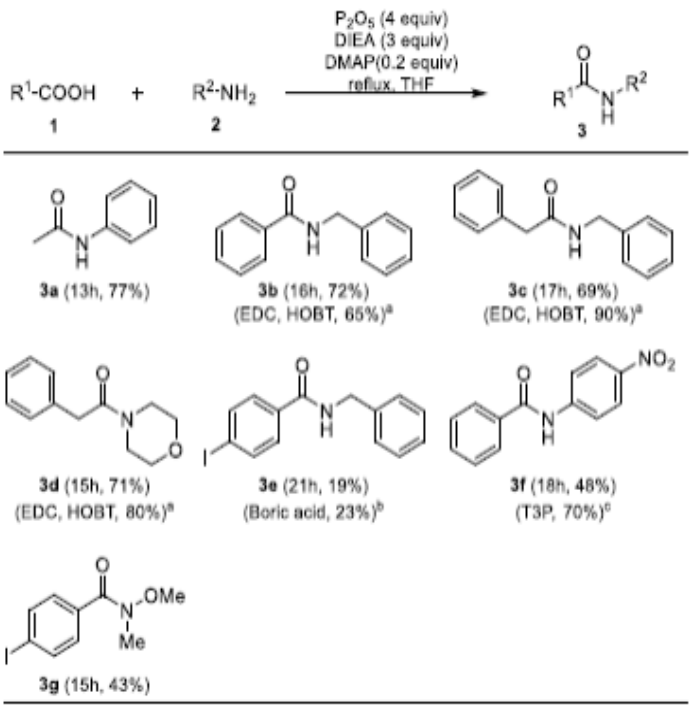

Fig 1: Illustrate schematic representation of amide bond formation using carboxylic acids and amines in presence of phosphorous pentoxide and substrate scope;

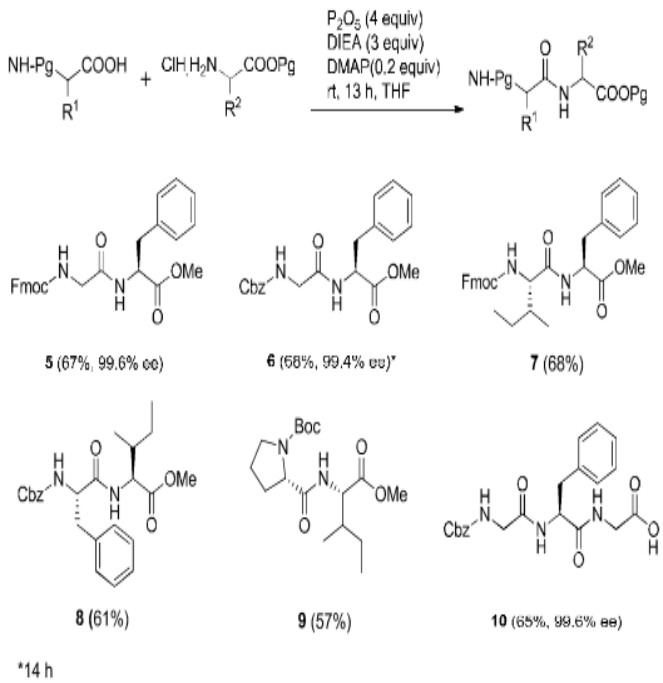

Fig 2: Illustrate synthesis of dipeptides and tripeptides using phosphorus pentoxide under optimal conditions;

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