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Clean & Fast Amide Couplings in Water

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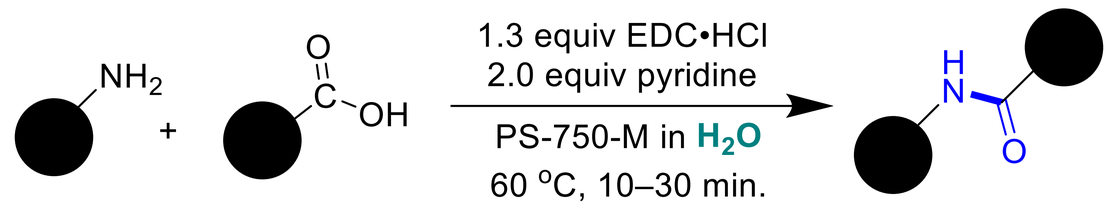
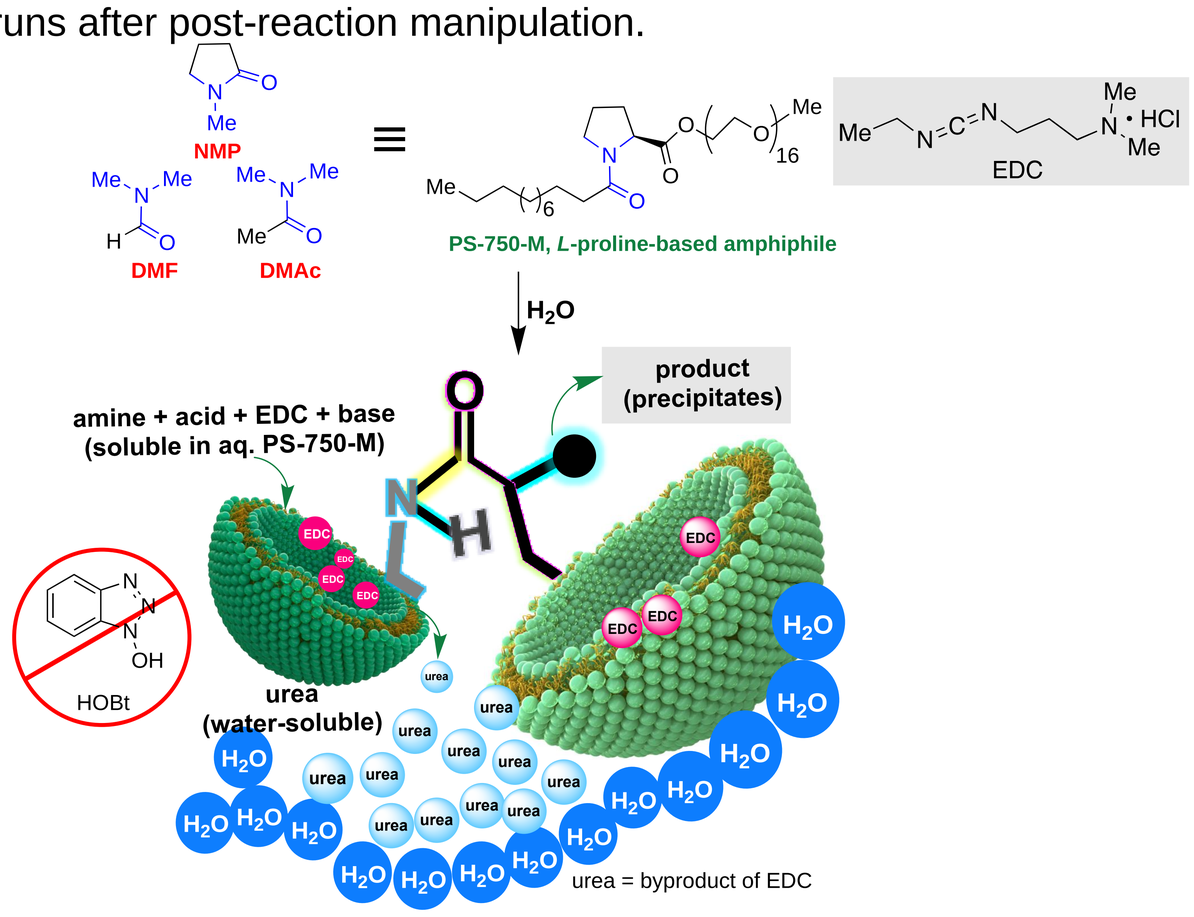
Introduction

Amide couplings are highly important to the pharmaceutical industry.[1] Presented is a methodology for amide couplings in water with a fast reaction rate using EDC as a coupling reagent and PS-750 M in water as a reaction medium. The reactions complete in 15-45 min, where the product precipitates out and can be isolated via simple filtration. It is an organic solvent-free and cost-effective approach towards amide bond forming reactions.[2]

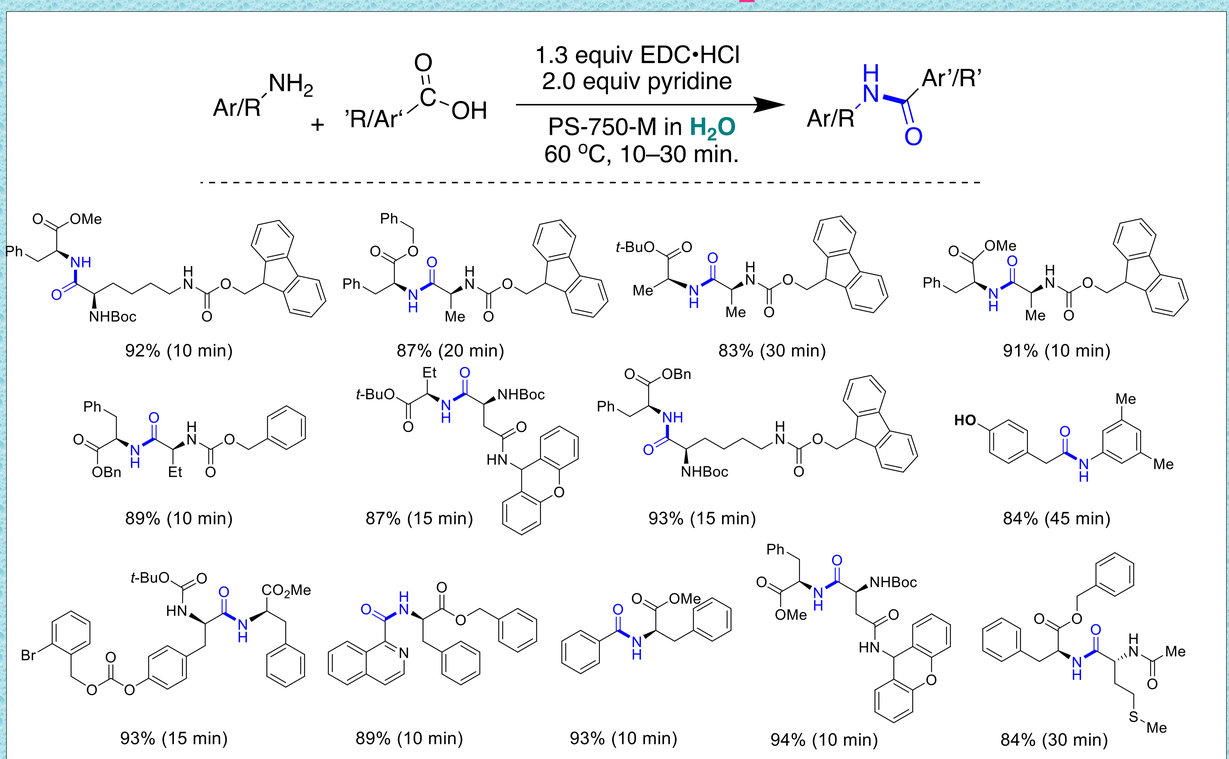


EDC-Mediated Amide Couplings in Water

EDC ((1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide) is a carbodiimide that is well known reagent for the amide coupling reactions between an amine and carboxylic acid in the presence of a base. It is the commonly used coupling agent in industries because it produces a water-soluble urea byproduct, which can be easily removed by an aqueous work-up. However, our methodology, the desired amide product precipitates out of the reaction mixture, and no additional work-up is required.[3] Using aqueous micelles of PS-750-M as a solvent dramatically increases the rate of reaction.[2] The filtrate recovered can be recycled to perform several coupling runs after post-reaction manipulation.

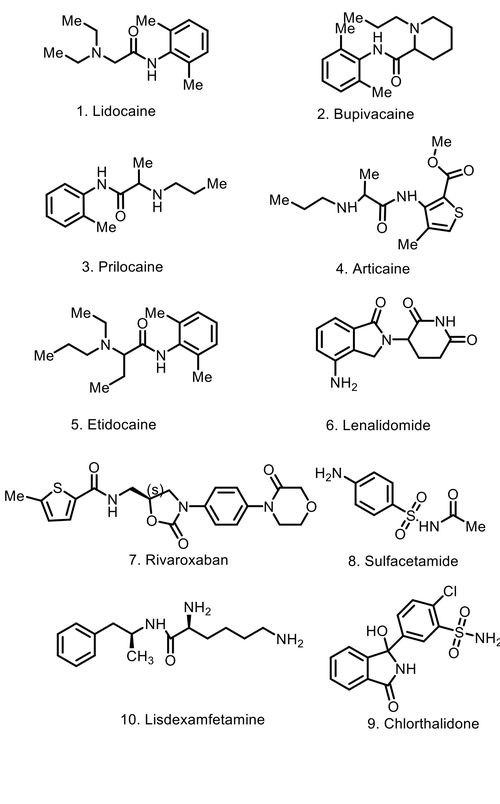


Substrate Scope



Conditions: Amine (0.25 mmol), carboxylic acid (.25 mmol), EDC•HCl (0.32 mmol), pyridine (0.5 mmol), 0.5 mL 3 wt % PS-750-M in H_2O, 60 °C, 10-45 min. The coupling reaction was performed on small scale as well as on gram scale to prove the scalability. HPLC studies concluded that there was no racemization occurring within mmol or gram scales.[2]

Examples of Drug Molecules



1. Lidocaine is used as a local anesthetic and has also proven useful as both diagnostic and therapeutic medicine.[4] The drug has found successful at easing pain and avoiding drug-drug interactions.[5]

2. Bupivacaine is also used an anesthetic that is commonly used in surgery. Epidural administration has proven to be an effective method for longer and less toxic pain relief in patients.[6] The drug has proven to reduce the need for addictive postoperative narcotics when intra-articular administration was used.[7]

3. Prilocaine is yet another anesthetic and has proven more useful than Lidocaine in shorter surgeries. Epidural administration is used for short term local anesthetic.[8] and as pain relief cream with various applications.[9]

4. Articaine is a local anesthetic used mostly in dental procedures. Articaine is non-toxic with a shorter half-life than other anesthetics.[10]

5. Etidocaine is longer acting local anesthetic, that is metabolized less quickly.[11] This drug has also proved to act faster than most other anesthetics.[12]

6. Lenalidomide is an immunomodulatory agent with anticancer properties. It is commonly used to treat multiple myeloma.[13] The drug has proven very successful in reversing the effects of myelodysplastic syndrome in the 5q31 deletion.[14]

7. Rivaroxaban is a direct factor Xa inhibitor that is used to prevent venous thromboembolism (VTE) in adult patients. The drug can be administered orally and seem to beneficial to patients regardless of age, gender or weight.[15]

8. Sulfacetamide is an antibacterial medicine. It is commonly administered with eye drop solutions as it boasts low toxicity.[16]

9. Chlorthalidone is a diuretic that is used to treat hypertension. Chlorthalidone can significantly lower risks for stroke, coronary artery disease and death.[17]

10. Lisdexamfetamine is used to treat attention deficit order. It is proven successful in both adolescence and adults.[18]

Conclusions

Our methodology could greatly benefit the pharmaceutical industry in manufacturing drugs. With short reaction time, mild reaction conditions, no use of an organic solvent in synthesis, as well as in isolation or purification, this technology will potentially save considerable production cost of useful drug molecules. Besides, it is a greener and sustainable way of amide bond formations. Other industries, such as agricultural chemistry, biochemistry, and polymer chemistry, could also benefit from our environmentally benign approach.

Acknowledgement

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