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Water as a Reaction Medium for Efficient Amide Couplings: A Mechanistic and Process Optimization Study

Rekha Rani

Research Scholar, Baba Mastnath University, Asthal Bohr, Rohtak (Haryana)

Sajani

Assistant Professor, Department of Chemistry,

Baba Mastnath University Asthal Bohr Rohtak (Haryana

Abstract

The production of amide bonds, which are the fundamental components of peptides, medicines, and novel materials, is one of the most fundamental modifications that may occur in organic and medicinal chemistry. It was common practice in the past to perform amide couplings in organic solvents using coupling chemicals and additives, which frequently led to the production of hazardous waste. A number of recent findings have demonstrated that the utilization of water as a chemical medium can facilitate the formation of amide bonds in a manner that is both efficient and non-destructive to the environment. The purpose of this study is to investigate the formation of amide bonds in water-based systems, as well as the kinetic and thermodynamic parameters that influence reaction and the methods that may be utilized to make the process more efficient. In this work, the distinctions between water-mediated techniques and standard amide coupling methods are investigated. The focus is on the unique physical properties of water, which assists in the stabilization of transition states and the production of goods. The implications of water amide coupling systems on green chemistry are also discussed in this paper, as well as the ways in which these systems may be utilized on a big scale in the industrial sector.

Keywords: *Amide coupling, Green chemistry, Water as solvent, Mechanistic study, Process optimization*

Introduction

In the field of chemistry, amid bonds are considered to be among the most significant bonds. These bonds may be found in all proteins, synthetic pharmaceuticals, and valuable materials. The synthesis of these substances is an essential component of organic chemistry because of this reason. Uronium salts (HATU and HBTU), carbodiimides (such as DCC and EDC), and phosphonium reagents (PyBOP) are examples of the types of chemicals that are utilized in the common amide coupling procedures. Dishloromethane, dichloromethane, or acetonitrile are examples of organic solvents that are typically used to combine these. These methods are effective; yet, they result in a significant amount of chemical waste and raise concerns for both safety and the environment (Montalbetti & Falque, 2005). The concept of green chemistry is predicated on the notion that hazardous liquids ought to be substituted with safer alternatives. Due to the

fact that it is risk-free, readily available, and possesses unique physical and chemical properties, water is an excellent option for a medium that is used for long-term reactions. In addition to being hydrophobic and highly polar, it is also capable of forming hydrogen bonds, all of which have the potential to accelerate chemical reactions (Breslow, 1991). In the past, it was believed that the process of producing amides in water would be difficult due to the fact that they did not dissolve or react correctly. Nevertheless, this viewpoint has been altered as a result of recent advancements in surfactant-assisted catalysis, micellar systems, and direct coupling techniques. Within the scope of this study, the mechanical effects of water on amide connections are investigated, and the paper also discusses ways to enhance process variables in order to make them more applicable to industrial settings. In addition to this, it investigates the environmental and financial advantages of employing water for the synthesis of amides rather than the traditional biological methods.

Traditional Amide Coupling Methods:

Chemical activators such as dimethyl sulfoxide (DCC) are employed in conventional amide couplings to transform carboxylic acids into amides via amine reactions. Organic liquids are typically required, and the waste products, such as urea or phosphine oxide, make cleaning more difficult (Valeur & Bradley, 2009). The rate and selectivity of amide production are significantly affected by the solvent choice. Although polar aprotic liquids aid nucleophilicity, they are both environmentally damaging and notoriously difficult to remove.

Emergence of Water as a Solvent:

Over the past two decades, water's reputation as an ideal medium for chemical chemistry has grown. In 1991, Breslow demonstrated that some chemical reactions can be accelerated by putting non-polar reactants closer together due to hydrophobic effects in water. The stability of transition states is improved and reaction times are accelerated as a result of this impact. The use of peptide bonding in water under moderate circumstances with negligible negative effects was shown by Kitanosono and Kobayashi (2015).

Mechanistic Basis for Amide Formation in Water:

How amides pair together differs from how they couple in biological environments due to the polarity of water and the distinct movement of hydrogen bonds in water. Typically, the carboxylic acid undergoes transformation into a more electrophilic intermediate by reactions mediated by carbodiimide or electrophilic cyclic voltammite (EDC). Solubility in water allows charged intermediates and transition states to be maintained, resulting in a decrease in the activation energy. Lipschutz et al. (2013) found that organic reactants are transformed into micelles or microdroplets due to the hydrophobic effect, which increases the number and frequency of collisions in the region.

Role of Micellar Catalysis:

The use of surfactants in micellar systems, such as TPGS-750-M, allows for the creation of nanoreactors that mimic the environment of enzymes. Surfaces that are hydrophobic and hydrophilic can be dissolved by these micelles, allowing reactions to occur at their borders. In 2015, a team of researchers headed by Lipshutz and colleagues demonstrated that micellar catalysis allows for the amide reaction to occur in water at almost quantifiable rates.

Research Method

In the course of the present investigation, peptide coupling processes were optimized and scaled by utilizing an environmentally friendly aqueous micellar technology. The reaction between carboxylic acids and amines was carried out in water that was mixed with 3% PS-750-M by weight. EDC·HCl was used as the coupling reagent, and pyridine served as the base in this reaction. The reactions took place in sealed vials or round-bottom flasks at a temperature of sixty degrees Celsius for a duration of fifteen to thirty minutes while being stirred continuously. After the combination was cooled, the precipitated product was separated by means of filtering, washed with deionized water, and then dried under reduced pressure. The confirmation of the completion of the mixture was carried out by thin-layer chromatography or gas chromatography-mass spectrometry. The characterization of the final compounds was performed by means of high-resolution mass spectrometry (HRMS), the measurement of the melting point, and nuclear magnetic resonance (NMR) spectroscopy with the isotopes hydrogen-1 and carbon-13.

RESULT AND DISCUSSION

General experimental details

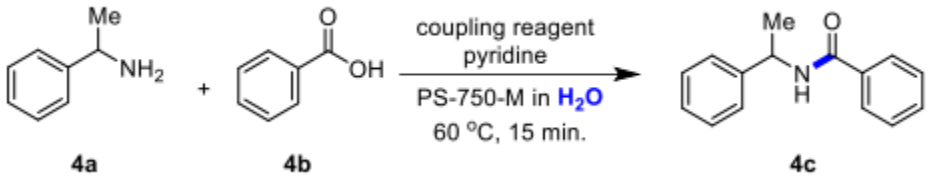
Our purchase from Merck included silica gel with a mesh size ranging from 230 to 400 and UV 254 indicator glass-backed TLC plates with a thickness of 200 millimeters. Both pentane and pyridine were obtained directly from Fisher Scientific, thus there was no need for any extra purification. In the Cambridge Isotopes Laboratories, we only make use of NMR solvents that are completely pure. Amino acids and carboxylic acids, in addition to chemicals from Sigma-Aldrich, Combi-Block, and Oakwood, were used in this experiment. EDC•HCl and the other coupling reagents were obtained from Oakwood Chemicals, which was the main supplier. Microwave vials with a close-cap capacity of 4 milliliters and round-bottom flasks with a volume of 25 milliliters were used to carry out the coupling reactions. VWR International and Biotage were the two companies that provided the microwave vials.

Furthermore, there was recycling and reuse of reaction vials that took place. Before it was put to use, a significant amount of argon was removed from a solution of the surfactant PS-750-M377 that had been manufactured in HPLC grade water. For the purpose of determining the melting points of the samples, the MEL-TEMP II melting point equipment was used. The materials were then inserted in Kimble Kimex 51 capillaries that measured 1.5-1.8 x 90 mm. At a temperature of 25 degrees Celsius, a Varian Unity INOVA spectrometer that was running at 400 and 500 megahertz was used to record each and every NMR spectra, with the exception of those that were expressly mentioned. A reference for the chemical shifts that have

been reported is the peaks that are found in the solvent that is still present. All of the HRMS spectra obtained using the Thermo Electron MAT 95XP mass spectrometer were obtained by either chemical ionization (CI) or electron ionization (EI). For the purpose of chiral analysis, the data was obtained with the use of a Shimadzu LG-2030C HPLC. A 10% volume-to-volume mixture of isopropanol and hexanes was run at a rate of 1 milliliter per minute using an HPLC system equipped with a CHIRALCEL® OD-H column.

Reaction Optimization

Table S4.0. Coupling reagent screening

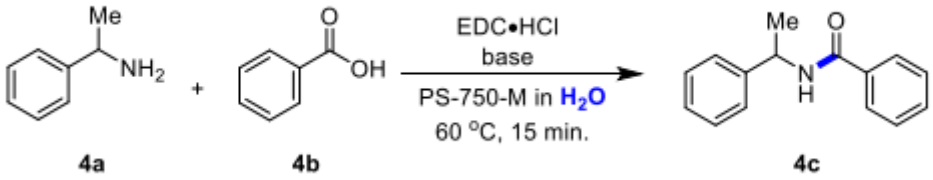


4a 4b 4c

entry	coupling reagent	4c (%) [a]
1	EDC•HCl	99
2	DCC	15
3	HATU	78
4	BOP	22
5	COMU	77

The conditions the yields were determined using GCMS, which was duplicated with permission, in a reaction that consisted of 4a (0.25 mmol), 2 (0.25 mmol), coupling reagent (0.32 mmol), pyridine (0.5 mmol), and 0.5 mL of 3 weight percent PS-750-M in water. The reaction was then carried out at a temperature of 60 degrees Celsius for fifteen minutes.

Table 1. Base screening



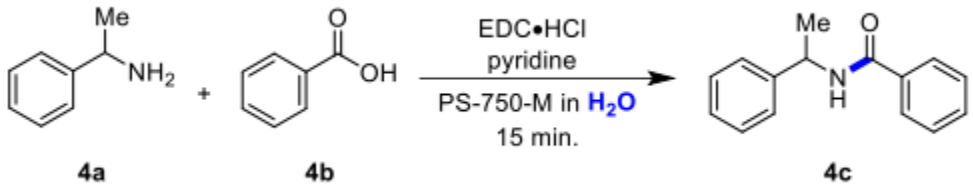
4a 4b 4c

entry	base	4c (%) [a]
1	Et3N	14
2	pyridine	99
3	2,6-lutidine	22
4	DIPEA	27

5	NaOH	0
6	K3PO4	0
7	KOH	9
8	t-BuOK	0
9	K2CO3	4

The conditions. From a combination consisting of 4a (0.25 mmol), 4b (0.25 mmol), EDC•HCl (0.32 mmol), base (0.5 mmol), and 0.5 mL of 3 weight percent PS750-M in water at 60 degrees Celsius for fifteen minutes, the following yields were obtained using GCMS (reproduced with permission).

Table 2. Effect of temperature

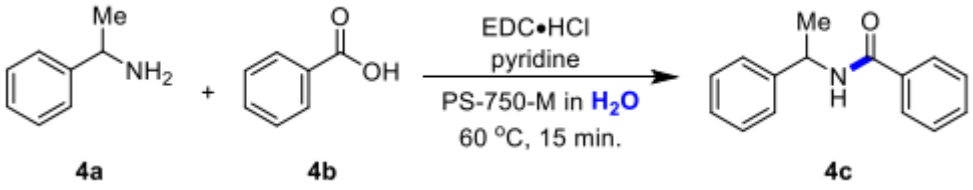


4a 4b 4c

entry	T (oC)	4c (%) [a]
1	rt	35
2	35 oC	46
3	45 oC	59
4	60 oC	99

The conditions. In a mixture consisting of 4a (0.25 mmol), 4b (0.25 mmol), EDC•HCl (0.32 mmol), pyridine (0.5 mmol), and 0.5 mL of 3 weight percent PS-750-M in water, run the experiment for fifteen minutes. These findings are derived from GCMS. (the owner of the copyright is recognized).

Table 3. Optimal equivalents of base



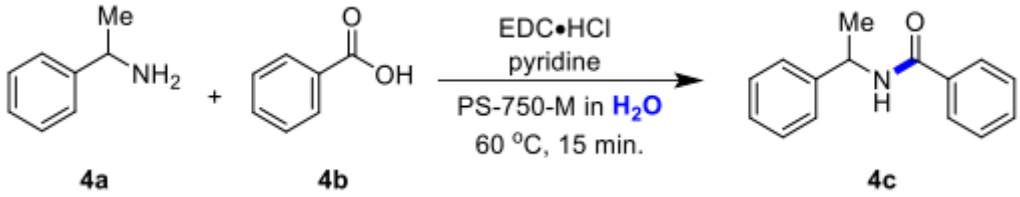
4a 4b 4c

entry	pyridine (equiv.)	4c (%) a
1	1.0	92
2	1.2	96
3	1.5	97

4	2.0	99

The conditions. 0.5 milliliters, a weight of 3% pyridine, 0.32 millimoles of EDC•HCl, 0.25 millimoles of 4a, and 0.25 millimoles of 4b. A solution of PS-750-M in water that was heated to 60 degrees Celsius for fifteen minutes yielded GCMS-based results (which were replicated with permission).

Table 4. Optimal global concentration



entry	conc. (M)	4c (%) [a]
1	0.25	62
2	0.5	99
3	1	93
4	1.5	83

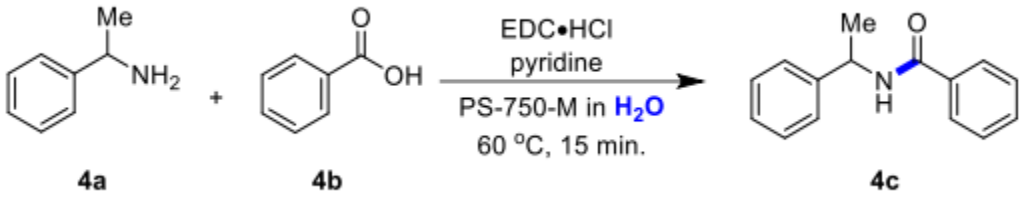
The conditions. The yields based on GCMS were measured by adding 4a (0.25 mmol), 4b (0.25 mmol), EDC•HCl (0.32 mmol), pyridine (0.5 mmol), and 3 weight percent PS-750-M to water and boiling the mixture to 60 degrees Celsius for fifteen minutes. The results were replicated with permission.

Table 5. Optimal wt % of PS-750-M

entry	wt % PS-750-M	4c (%) [a]
1	1	82
2	2	84
3	3	99
4	4	97
5	5	94

The conditions. All of the following substances were heated to 60 degrees Celsius for fifteen minutes: 4a (0.25 mmol), 4b (0.25 mmol), EDC•HCl (0.32 mmol), pyridine (0.5 mmol), and 0.5 mL PS-750-M in water. The findings were obtained by GCMS analysis, and were subsequently reproduced with the author's consent.

Table 6. Optimal equivalent of EDC•HCl

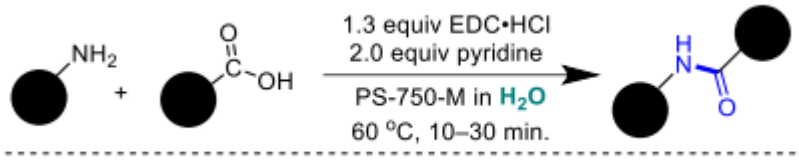


4a 4b 4c

entry	EDC•HCl (equiv.)	4c (%) [a]
1	1	88
2	1.2	92
3	1.3	99
4	2	98
5	3	97
6	0	traces

The conditions. From a solution of PS-750-M in water heated to 60 degrees Celsius for fifteen minutes, the following GCMS-based yields were obtained: 4a (0.25% by weight), 4b (0.25% by weight), EDC•HCl, pyridine (0.5%), and 0.5 mL (3 weight percent). These yields were duplicated with permission.

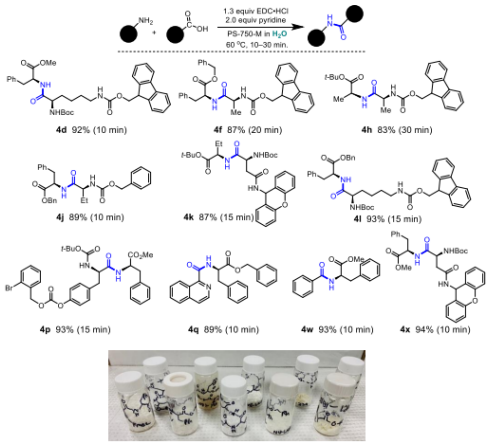
General procedure for gram scale reactions



An oven-dried round-bottom flask with a PTFE-coated magnetic stir bar was used to measure the following substances: carboxylic acid (1g, 1.0 equiv.), amine (1.0 equiv.), and EDC•HCl (1.3 equiv.). The flask had a capacity of 25 mL. A rubber septum was used to seal the reaction flask, and then the reaction mixture was augmented with a three-weight percent aqueous PS-750-M solution at a concentration of 0.5 M. We utilized parafilm and PTFE tape to cover the septum in order to protect it. After adding pyridine in the amount of 2.0 equivalents, the reaction mixture was agitated at a temperature of 60 degrees Celsius for fifteen to thirty minutes while being heated in an oil bath. The mixture of reactants had indications of solidification; this was observed. Following the confirmation of the reaction by high-performance liquid chromatography (TLC), the stirring was ceased, and the reaction mixture was allowed to cool to room temperature. This material was filtered with Whatman filter paper in order to remove impurities. The solid material that had

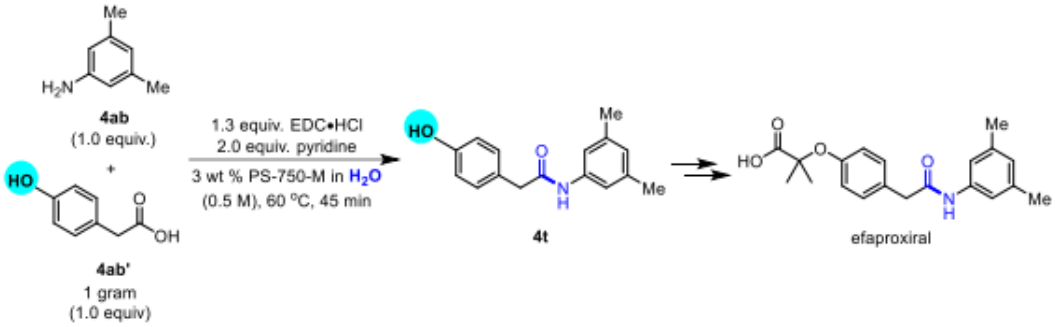
been collected was washed three times with three milliliters of deionized water, and then it was dried under reduced pressure. This was done in order to get the pure outcome. Following that, the 1H and 13C NMR spectra of the chemical that had been isolated were studied.

Substrate scope for gram scale reactions



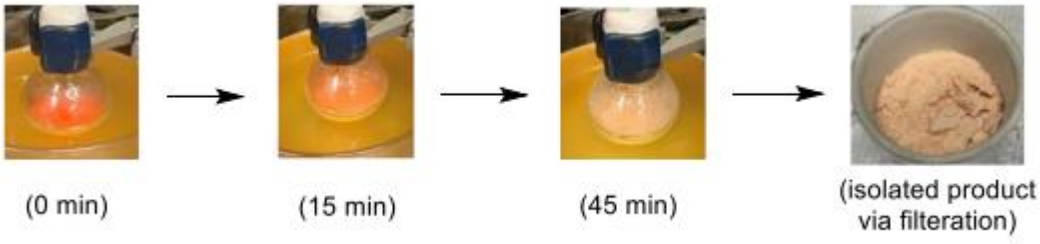
One gram of carboxylic acid, one equivalent of amine, one equivalent of EDC•HCl, two equivalents of pyridine, and three percent of PS-750-M were combined in a solution of 0.5 M water and stirred at a temperature of sixty degrees Celsius for ten to thirty minutes. The only yields that may be obtained are isolated yields that have been duplicated with permission.

Gram scale synthesis of 4t



1.hydroxyphenylacetic acid (1 g, 6.57 mmol, 1 equivalent), 3,5-dimethylaniline (796.5 mg, 6.57 mmol, 1 equivalent), and EDC•HCl (1.64 g, 8.54 mmol, 1.3 equivalents) were added to a round-bottom flask with a capacity of 25 milliliters that had been dried in the oven. The flask was also equipped with a magnetic stir

bar that was covered with PTFE. The reaction flask was sealed with a rubber septum after the addition of 13 mL of a three-weight percent aqueous PS-750-M to the mixture that served as the reaction. We utilized parafilm and PTFE tape to cover the septum in order to protect it. Subsequently, one milliliter of pyridine, which was 13.14 percent by weight, was added to the reaction mixture, and it was agitated for forty-five minutes at a temperature of sixty degrees Celsius in an oil bath that had been prepared. The mixture of reactants had indications of solidification; this was observed. After the reaction was validated by thin-layer chromatography (using ethyl acetate and hexane in a ratio of 2:3), the stirring was stopped, and the liquid that was being used in the reaction was allowed to drop down to room temperature. Immediately after the solid's passage through a Whatman filter paper, it was washed with three volumes of deionized water, each of which was three milliliters in volume. Drying the collected material under reduced pressure allowed for the production of the final product, which was designated as N-(3,5-dimethylphenyl)-2-(4-hydroxyphenyl) acetamide (4t). After that, the 1H and 13C NMR spectra (1.42 g, 86%) were used in order to provide a description of the pure molecule.



The principles of green chemistry, which include minimizing waste, improving solvent quality, and cutting energy use, are all supported by the use of water rather than organic solvents. Businesses are increasingly adopting these practices in an effort to reduce their environmental effect and comply with stricter regulatory regulations. Reduced expenses associated with solvent recovery and waste management, simplified processing, and elimination of hazardous solvent byproducts are all benefits of water-mediated amide coupling. The combination of chemical and enzyme-based approaches to molecule synthesis is made feasible by the fact that water processes are very compatible with biocatalytic reactions.

Although water is an effective solvent, it does have certain drawbacks, such as affecting the solubility of substrates and causing chemical hydrolysis. The development of amphiphilic catalysts and compounds with the ability to self-assemble into reactive nanoparticles in water is an area that might be explored by scientists in the future. To understand solvation effects and predict reaction outcomes, computational modeling will continue to play a significant role. Discovering the optimal settings for various substrates is another benefit of process optimization based on machine learning; this paves the way for environmentally friendly, fully automated manufacturing. Another fascinating field of study is the integration of flow chemistry with water

amide coupling. You can boost the yield and make the process more reproducible using continuous-flow technologies because you can accurately manage the temperature and mixing. Possible game-changing implications for peptide synthesis in the pharmaceutical and industrial sectors might result from combining this with micellar catalysis.

Conclusion

When it comes to the formation of amide bonds, water has emerged as a very effective and risk-free alternative to other substances. It is able to speed up processes while also minimizing the amount of waste that they create because to its unusual combination of polarity, hydrogen-bonding ability, and hydrophobic effects. The current level of knowledge regarding the functioning of things reveals that water has the ability to stabilize transition phases and intermediates, which in turn improves yields and selection. The utilization of optimization strategies, such as regulating the pH, micellar catalysis, and operating the process at a low temperature, results in an even higher level of efficiency. When contrasted with conventional organic solvent systems, water amide bonds are more difficult to extend, more cost-effective, and more durable than their counterparts. It is necessary to do further research on hybrid catalysis and computer models in order to make full advantage of the potential that water possesses in organic synthesis. When everything is said and done, this modification represents a significant step toward making the manufacture of chemicals more efficient and healthier.

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