Water: An Underestimated Solvent for Amide Bond-Forming Reactions

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Abstract: Construction of the amide/peptide bond is one of the most encountered transformations in the pharmaceutical and chemical industries. Traditional protocols rely on the use of undesirable organic solvents, such as *N,N*-dimethylformamide (DMF), *N*-methyl pyrrolidone (NMP), or dichloromethane (CH_2Cl_2). These solvents adversely impact the environment, workers' safety, and health. This has led academia and industry to search and develop greener and more sustainable amide forming synthetic protocols to increase performance in terms of yield and selectivity, and avoid or reduce the dependency in these hazardous solvents. The following accountdiscusses the recent development of amide/peptide bond formation in water.

INTRODUCTION. Amide or peptide motifs are key structural features of many critical organic molecules. It can be found in many compounds, natural products, chemical entities from various industries such as for example agrochemicals, pharmaceuticals, materials, detergents, lubricants, polymers.[1-4] Their remarkable pharmacological properties make them play a pivotal role in drug discovery for example. More than 50 peptides canindeed be found on the market as the active pharmaceutical ingredients, *ca.* 170 in clinical trials, and more than 200 are under preclinical development stages (Figure 1).[5]

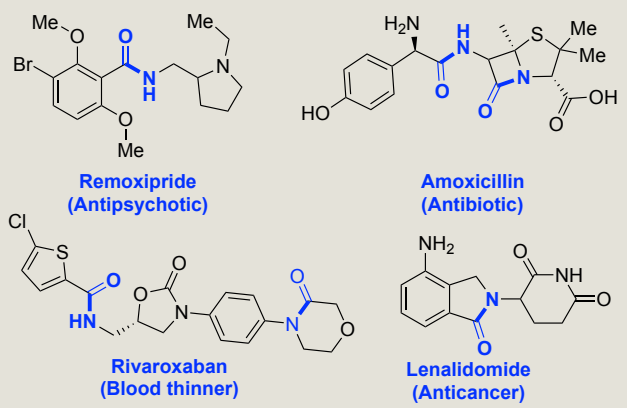
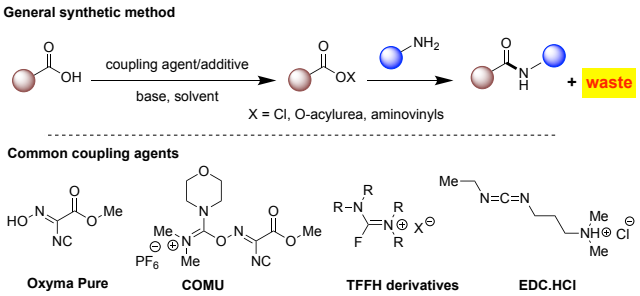


Figure 1. Selected drug molecules possessing amide functional groups.

Based on the above data, there is increasing demand for amides and peptides.[6-8] Their abundance requires more meaningful and excellent synthetic protocols, especially in context of their sustainability, scalability, and greenness. The standard methods for amide/peptide bond formation involve reacting an activated carboxylic acid with the relevant amine, in the presence of base and additive. (Scheme 1).[9,10]



Scheme 1. Classical synthetic method and common coupling agents for amide/peptide synthesis.

These classical approaches can have many limitations, such as limited selectivity and stability of defined stereoisomer especially, low efficiency or limited sustainability. A large fraction of such reactions is carried out in chlorinated solvents, e.g. CH_2Cl_2, or the reprotoxic polar aprotic solvents DMF, NMP, or DMAc.[11] There has been a huge push from the industrial community especially in the last decade to entirely avoid and replace such solvents and move towards sustainable alternatives.[12] Several initiatives and collective efforts such as those led by the American Chemical Society Green Chemistry Institute® Pharmaceutical Roundtable (ACS-GCIPR) for example triggered a variety of initiatives to accelerate the change towards better practices.[13] Key to success in improving sustainability is careful solvent selection.[14-16] *An sustainable solvent must be benign, readily available and ideally biorenewable, economically-attractive,, recyclable* (Figure 2).[17]

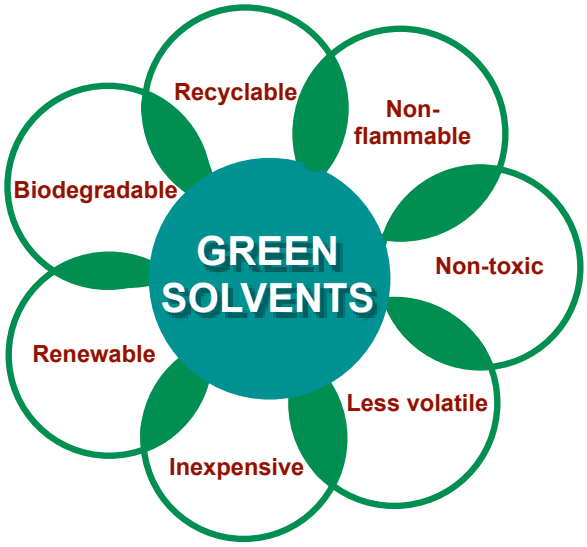


Figure 2. Green solvent's theme.

The ideal case from an environmental standpoint would dictate solvent-free reactions, as pointed outwith green chemistry principles, the best solvent is no solvent.[18,19] Protocols have been developed to conduct solvent-free synthesis of the amides/peptides, including ball-milling[20-22] and microwave-assisted couplings.[23, 24] These protocols are however still in their infancy, and are rarely solvent-free, requiring organic solvents during workup and purification of the final products. Besides, the reaction solvent is critical to optimize mass and heat transfer, enhancing reaction rates and selectivity.[17] Solvent selection should therefore be carefully made and ideally results in the use of safe and sustainable one(s). In recent years, several greener solvents as a sustainable alternative, such as water, biomass-derived solvents, and neoteric solvents, including ionic liquids (ILs) and deep eutectic solvents (DESs), have been used for peptide synthesis.[17] Several solvent guidelines and Pfizer's one especially recommendwater as an ideal choice over conventional organic solvents—it meets all the requirements, i.e., it is stable, non-toxic, inexpensive, recyclable, sustainable, and abundant.[25,26] However, a significant challenges when using water as the solvent for organic reactions are the poor aqueous-solubility of many organic substrates and the often unsuitable physical properties of the resulting mixture for process development, and the challenges with its disposal.[27] To overcome these challenges, recently, micelle-enabled organic transformations in water have come into prominence, and significant results have been achieved in the field of hydrophobic effects, whether via micellar catalysis [28-36] or polymer-induced catalysis.[53-54] In this account, we summarize the latest developments of amide/peptide synthesis in water as a green and sustainable reaction medium.

ALTERNATIVE SOLVENTS FOR AMIDE/PEPTIDE SYNTHESIS

Several greener solvents have been used in amide/peptide synthesis in recent years. 2-Methyltetrahydrofuran (2-MeTHF), derived from furfural or levulinic acid, has been exhaustively explored for amide couplings. [10] The results suggested that 2-MeTHF, along with EtOAc and dimethyl carbonate (DMC), can be considered as suitable alternative solvents. [37] Other neoteric solvents such as γ- valerolactone (GVL),[38] Propylene carbonate,[12] *N*-butyl pyrrolidinone (NBP).[39] biobased dihydrolevoglucosenone (Cyrene)[41,42] or *p*-cymene[43] have also been reported as a promising alternative solvent for amide bond synthesis.

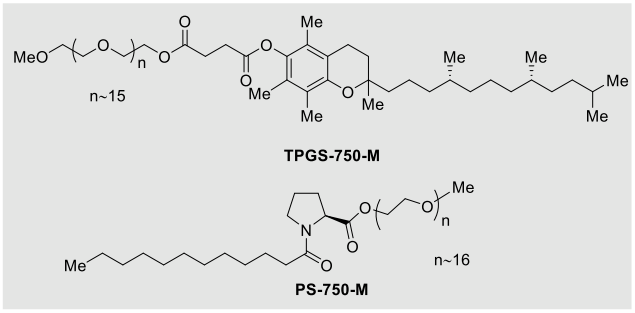
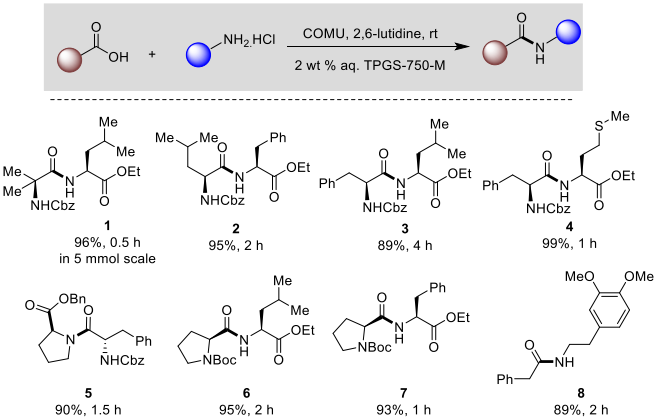


Figure 3. Structure of TPGS-750-M and PS-750-M.

To enable efficient chemistry in water, the Lipshutz and Handa groups have developed a strategy for more environmentally friendly, sustainable, and greener amide/peptide synthesis under aqueous micellar conditions.[44-47] In particular, these protocols enable clean chemistry with the use of 2 wt % TPGS-750-M, or 3 wt % PS-750-M as a nonionic surfactant (Figure 3). After dissolution in water and when used above their critical micellar concentration, the surfactants self-assemble into nanomicelles to create a solvating environment for the less hydrophilic molecules. It results into a net reduced need for organic solvents, as reported with Novartis.[48-50]

Table 1. Amide bond formation in water using TPGS-750-M[a]



[a]Data taken from reference 44.

In 2015, the Lipshutz group reported the formation of the amide/peptide bond using COMU as a coupling reagent under aqueous micellar conditions.[44] This method was demonstrated to apply to a wide range of substrates possessing different protected amino acids to achieve products in excellent yields (Table 1, **1**-**8**) in shorter reaction times (0.5─4 h) with negligible racemization. Although this method works well with primary aliphatic amine, it has limitations—aromatic amines as coupling partners failed. The authors have shown that the reaction medium can be easily recycled at least four times. This technology was used for the sequential deprotection/reprotection of amino groups in solution to access polypeptides (exemplified on a decapeptide).[45] Themethod requires organic solvents

during extraction and purification.

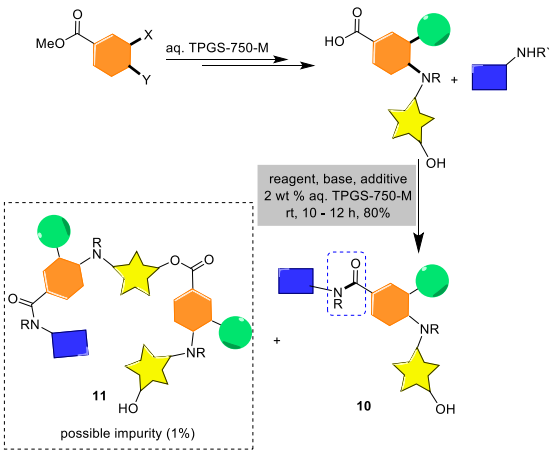
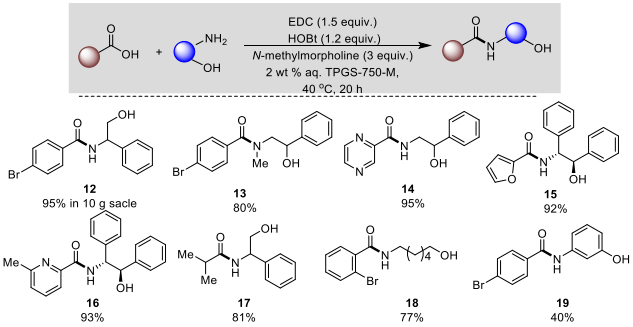


Figure 4. Synthesis of API in water. Reprinted (adapted) with permission from Gallou, F.; Guo, P.; Parmentier, M.; Zhou, J. A General and Practical Alternative to Polar Aprotic Solvents Exemplified on an Amide Bond Formation *Org. Proc. Res. Dev.* **2016**, *20*, 1388-1391. Copyright 2022 American Chemical Society (ref 48).

The surfactant has been widely used within the synthetic community. In particular, within an ongoing sustainability program in Novartis, we have shown successful multi-step kilogram scale preparation of active pharmaceutical ingredient (API) **10** in water (Figure 4).[49] The most problematic and challenging step was the formation of an amide bond in the presence of a free hydroxyl group. This was successfully solved by employing micellar technology which led to minimal formation of side product **11**, 1% in micellar medium *versus* 12 % in organic solvents. This technology involves aq. TPGS-750-M as the main reaction medium for the whole sequence. It allowed to utilize mild reaction conditions that resulted into significantimprovement of yields, selectivity, environmental impact, and cost.[49] Inspired by the selective amidation with an unprotected aminoalcohol using TPGS-750-M in water, we further exemplified the scope of the transformation. This method has good substrate scope in terms of coupling partners, such as aromatic carboxylic acids (Table 2, selected examples **12, 13, 18, 19**), aliphatic acid (**17**), heterocyclic acids (**14-16**) with both primary and secondary amines and amino alcohols.[50] However, this protocol has poor selectivity with the aromatic amino alcohols, most probably due to the presence of high reactive phenolic ─OH group (**19**). Recently, we have also demonstrated the amidation reaction of water sensitive acyl chloride with amines under micellar condition.[51]

Table 2. Selective amidation of unprotected amino alcohols in water using TPGS-750-M[b]

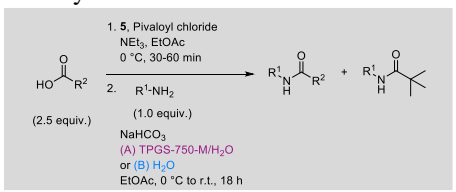


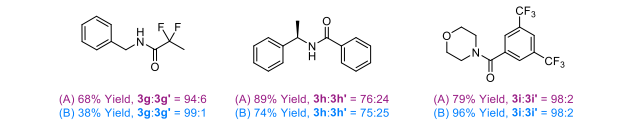
[b]Data taken from ref 50.

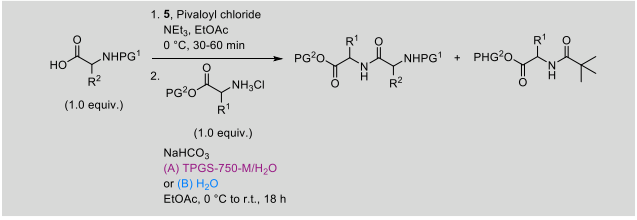
In aforementioned methodology, most of the products are crystalized out from the reaction mixture and purified thorough simple filtration and washing with water. However, these methods require pre-functionalized acid chlorides or explosive activators, such as HOAt or HOBt, a severe limitation for their application on scale.

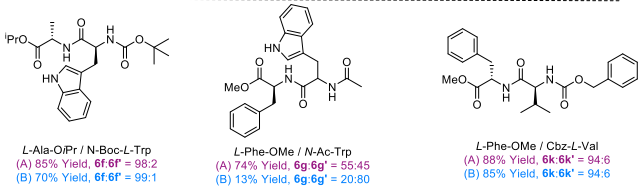
Very recently, scientists at Evonik reported the use of pivaloyl chloride as a cheap and readily available activating reagent.[52] They nicely studied amide and peptide couplings in water, with or without TPGS-750-M and EtOAc as a co-solvent to illustrate the specificity of each substrate. In most cases, TPGS-750-M did improve the yield, but not always substantially.

Table 3. Amide/peptide coupling in bulk water using pivaloate anhydride[c]







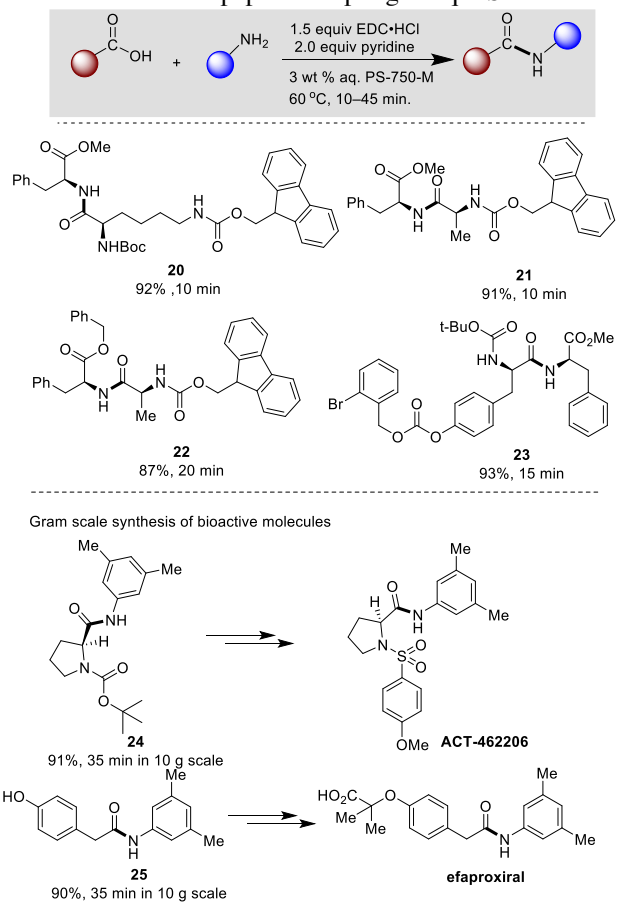


[c]Data taken from ref 52

To solve the longstanding issue of solvent usage and epimerization in amide coupling, Handa's group has developed a

custom-designed *L*-proline-based amphiphilic molecule PS-750-M, that structurally resembles dipolar aprotic organic solvents dimethylformadie (DMF), *N*-methyl-2-pyrrolidone (NMP), and dimethylacetamide (DMAc). It enables fast and efficient couplings without epimerization of sensitive products. Interestingly, 3 wt % aq. PS-750-M is highly capable of forming amide/peptide bond between carboxylic acids and amines using EDC as coupling reagent and pyridine as base under mild conditions.[46] Key features of this protocol are: (i) faster reaction rate, most of the reactions are completed within 15-30 min. (ii) no need of additive/HOBt activator; (iii) no need of extraction and purification steps (column chromatography and crystallization); (iv) totally organic solvent free; (vi) no epimerization; (vii) reproducible on multigram scale.[46]

Table 4. Fast amide/peptide coupling in aq. PS-750-M[d]



[d]Data taken from ref 46, 47

This protocol is applicable on a wide range of substrates with protected amino acids (Table 3, selected examples **20-24**) without epimerization. Notably, the aromatic amine can be successfully coupled with a free hydroxyl group containing carboxylic acid (**25**) with excellent yield and selectivity, making this protocol unique compared to the Lipshutz protocol. To showcase the potential of this technology, we have shown a multigram scale (10 g) reaction for the synthesis of intermediates of bioactive molecules, such as ACT-462206 and efaproxiral.[47] Previously, Lipshutz and co-workers reported that the synthesis of **24** was problematic under micellar conditions.[53] With PS-750-M technology, completion was observed in circa 30 minutes, and resulted in high yield and purity (Table 3).

We have recently explored the detailed mechanistic insights to answer a few fundamental questions. Of particular interest was the supramolecular arrangements of the various reaction components in the aqueous micellar medium and what factors influenced the reactivity?[47] Notably, EDC•HCl itself can act as an ionic amphiphilic molecule in water due to the presence of hydrophobic nonpolar carbon chain and hydrophilic ammonium chloride counterpart. Therefore, upon dissolution in aqueous PS-750-M, it can intercalate within the PS-750-M micelles, as confirmed by HRTEM analysis (Figure 6).[47]

This results into a high local concentration of EDC•HCl within the supramolecular arrangements and hence readily activation of the carboxylic acid, eventually enhancing the rate of reaction, and thus, avoiding epimerization. The urea byproduct formed in the reaction is quickly extruded from the micelles in virtue of the hydrophobic effect, contributing to the further enhancement of the reaction rate. Our study indicates that the amphiphilic nature of the reagent (EDC•HCl) is very much essential for fast amide coupling.

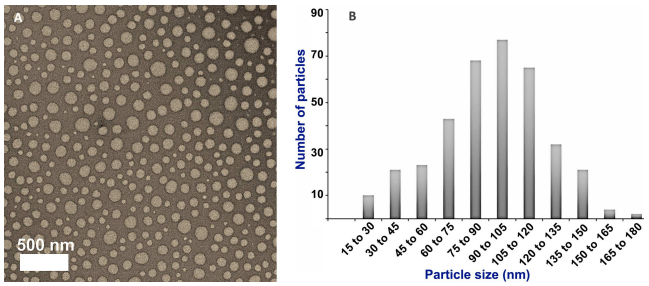
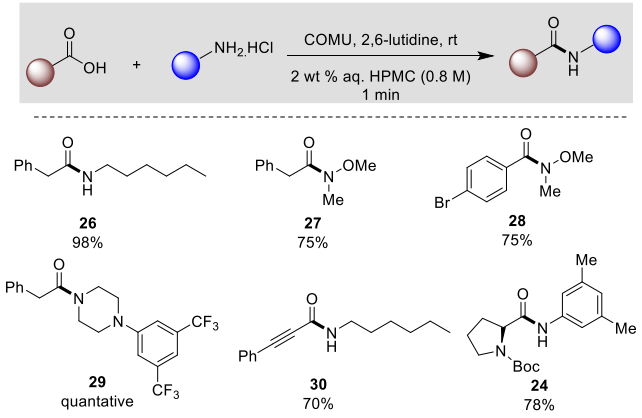


Figure 6. (A) HRTEM analysis of EDC•HCl in 3 wt % aqueous PS-750-M; (B) particle size distribution Reprinted (adapted) with permission from Sharma, S.; Kaur, G.; Handa, S. Insights into Fast Amide Couplings in Aqueous Nanomicelles. *Org. Process Res. Dev*. **2021**, *25*, 1960−1965. Copyright 2022 American Chemical Society. (ref. 47).

Due to the formation of hydrophobic pockets in water, hydroxypropyl methylcellulose (HPMC) can enable efficient amide chemistry in water.[54] Recently, in collaboration with AbbVie, the Handa group has reported ultra-fast amide couplings in water using HPMC as additive.[54,55]

Table 5. Aqueous HMPC enabled ultrafast amide coupling in water[e]

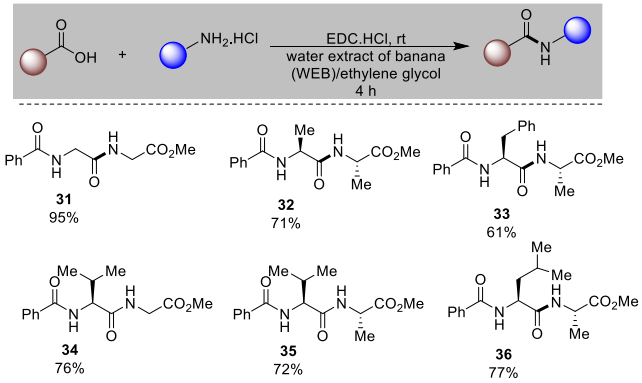


[e]Data taken from ref 53

This work demonstrated that the reactions were completed within one minute for most substrates (Table 4, selected examples **26-31**). Couplings of alkylamines with non-aromatic (**26, 27**, **29, 30, 31**) and aromatic (**28**) acids proceeded efficiently. Again, Lipshutz and co-workers mentioned that aromatic amines are incompatible under similar conditions when 2 wt % aq. TPGS-750-M was used. However, under aq. HPMC conditions, an aromatic amine worked well, forming desired amide (**24**) in 78% yield. Reactions were also performed on a 100-gram scale and a 4-step, 1-pot sequence.[53] Although the reaction is very fast, a saturated solution of aqueous Na_2SO_4 was required to crash out HPMC, and EtOAc was needed for product isolation. It must be emphasized here and for earlier situations that the organic solvents utilized could be more readily chosen from a shortlist of sustainable solvents, as the only need for solvents is to facilitate the work-up, not the reaction itself.

Recently, Sarma, et al. reported peptide synthesis in water extract of banana (WEB) using residual amount of ethylene glycol to act asa promoter (Table 5).[56]

Table 6: Peptide synthesis using WEB[f]



[f]Data taken from ref 55

This strategy resulted in superior results compated to the use of neat water. In addition, the basicity of WEB, due to the presence of carbonates of sodium and potassium in banana peels that act as bases, allowed for the avoidance of exogeneous base . Although, reaction medium can be recycled, these methods still require organic solvents to extract the final products.

SUMMARY AND PROSPECTIVE. In summary, a diverse toolbox of aqueous micellar and hydrophobic polymer (e.g., HPMC) technologies has been developed and demonstrated to offer a sustainable solution for fast and epimerization-free amide couplings. Upon implementing these protocols on industrial-scale reactions, a significant waste generation reduction is established. We hope that this brief account on the formation of amide bonds in using surfactant or polymer hydrophobic effects in water will inspire and further guide the chemistry community to develop better sustainable and greener procedures. Water as a reaction medium offers many advantages among all greener alternatives, as shown in the discussion. Within these efforts, we would also emphasize the care should be taken of the aqueous waste stream and its disposal.[57]

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Author Contributions

All authors contributed to the manuscript.

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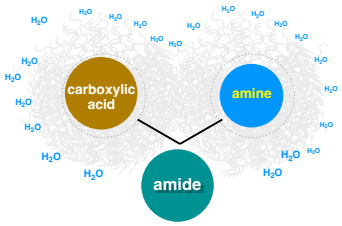
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