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Selective amidation of unprotected amino-alcohols using Surfactant-in-Water Technology: A highly desirable alternative to reprotoxic polar aprotic solvents.

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Keywords: Amidation, Surfactant, TPGS-750-M

Abstract: A general selective and environmentally friendly method for the formation of amide bonds using a surfactant in water as medium is described. Use of readily available 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and Hydroxybenzotriazol (HOBt) as a coupling system, *N*-methylmorpholine (NMM), and TPGS-750-M represents mild conditions allowing for chemoselective amidation of unprotected amino-alcohols. Comparative results with classical polar aprotic solvents such as dimethylformamide or acetonitrile are presented.

Organic solvents represent the vast majority of mass consumption and waste generated by the chemical industry ;over 60% of the whole mass consumption in the pharmaceutical industry based on a recent benchmark.[1] In a recent survey on the use of organic solvents which were used in paper published in Organic Process Research and Development,[2] nearly 10% of all DMF, DMAc, DMSO or NMP consumption is used for amide bond-forming reactions. Moreover, it was identified in the Watson *et al*. report that 47% of amidations use DMF as the reaction medium.[3] The synthesis of amide bonds is also one of the most investigated reactions in medicinal chemistry and this functionality is present in most drug candidates.[4] It is, therefore, of importance to find a sustainable alternative to this extensive consumption of polar aprotic solvents and to offer a valuable option for amidation reactions that will greatly improve their environmental impact.[5]

Considerable attention has been directed towards the use of water as a medium in organic synthesis due to its readily availability, non-toxicity, and non-flammability.[6] The development of new aqueous-based processes, therefore, is of great interest in terms of safety and handling simplicity.

Organic reactions are oftentimes very sensitive to solvent effects and the major drawback of using water as medium for organic transformations is the lack of solubility of the reagents often observed, as well as suitable physical properties of the mixture for process development.[7] The addition of simple amphiphilic molecules such as surfactants can partially "solubilize" organic materials in an aqueous medium and therefore promote the reaction.[8] Surfactants have long been used in oil recovery[9] and as excipient in food[10] and pharmaceuticals[11] industries.

The group of Professor Lipshutz in California reported the used of the nonionic surfactant TPGS-750-M (Figure 1) in water applicable to a variety of transformations, most extensivety involving cross-coupling reactions.[12]

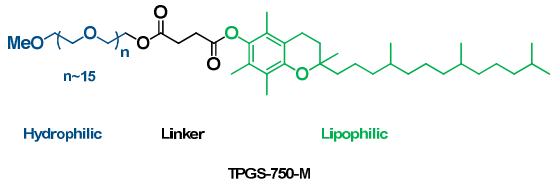
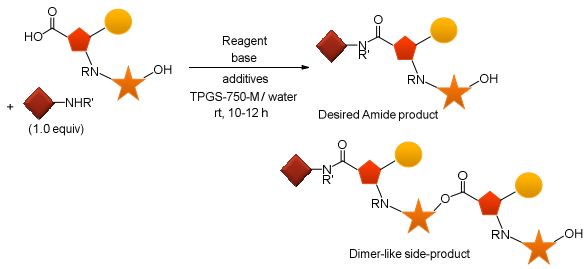


Figure 1: Structure of TPGS-750-M.

This series of reports was followed by a general protocol allowing for amidation reaction in water using TPGS-750-M as surfactant forming peptides and amides. In this report, the uronium salt (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)-dimethylamino-morpholinocarbenium hexafluorophosphate (COMU) was used as the coupling reagent of choice with yields up to 99% using a small excess of the carboxylic acid partner.[13]

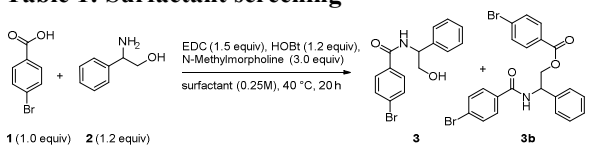
Recently, we reported a multistep synthesis of an Active Pharmaceutical Ingredient (API) in water containing surfactant as the only reaction medium for all the transformations, showing great improvement in term of yields, selectivity, environmental impact and cost.[11] Inspired by the remarkable selectivity obtained in our amidation step with an unprotected amino-alcohol using TPGS-750-M in water, which minimized the formation of the di-acylation side product by a factor 10 (Scheme 1), we decided to investigate the generality of such selective amidation reactions of unprotected amino alcohols. Herein we report a selective, general, and robust procedure for amide bond formation in water under mild conditions.



Scheme 1: Details on amidation reaction of an Active Pharmaceutical Ingredient (API) in water containing surfactant.

Optimization focused on the reaction between 4-bromo-benzoic acid and (*R*)-2-amino-2-phenylethanol, with coupling reagents EDC and HOBt. A preliminary screening of surfactants and bases was conducted to identify suitable reaction conditions that do not lead to formation of the undesired di-acylation by-product **3b** (Table 1 and 2). The conversion and the amount of **3b** were determined by LCMS-spectrometry.

Table 1: Surfactant screening



entry	surfactant (2wt% in water)	conv. of **1**[a] (%)	**3b**[b] (%)
1	TWEEN 80	95	3
2	Nok	93	6
3	SOLUTOL-HS	94	3
4	TPGS-1000	93 (87)	2 (1.5)
5	**TPGS-750-M**	**>99 (95)**	**2 (<0.5)**
6	none	96	17

[a]Determined by LCMS analysis. Isolated yield of **3** in parenthesis.[b] Determined by LCMS analysis. Amount of **3b** in the crude mixture; Amount of **3b** in the isolated product in parenthesis.

As described in Table 1, use of surfactant TPGS-750-M (2 wt % in water) and *N*-methylmorpholine as base at 40 °C led to the most desirable outcome; conversion was complete within 20 hours at room temperature and a minimum amount of the undesired di-acylation by-product **3b** was observed (Table 1, entry 5), reaching the limit of detection in the isolated product. It should be noted that running the reaction at lower temperature led to a slower rate and full conversion was usually not observed even after several days. High conversions were observed with most of the evaluated surfactants, however the level of by-product **3b** was higher, reaching 6% in the crude reaction mixture when Nok was used (entry 2). Surfactant containing unprotected alcohol in their structure such as Tween80, TPGS-1000 or Solutol (entries 1, 3 and 4) led to slightly lower isolated yield with an increased amount of by-product **3b**. The use of surfactant was clearly essential in this reaction. As exemplified in the control experiment (entry 6) using pure water. Here, 17% of the by-product **3b** was observed and the physical properties of the reaction mixture made it challenging to process. Indeed emulsion problems, as well as, oiling out was systematically observed in all the repeated runs resulting in poor reproducibility or limited generality.

Table 2: Base screening

entry	base[a] (pKa in Water)	equiv.	conv. of **1**[b] (%)	**3b**[c] (%)
1	Pyridine (5.2)	3.0	>99	15
2	K_2CO_3 (10.3)	3.0	61	10
3	Na_2CO_3 (10.3)	3.0	76	9
4	Cs_2CO_3 (10.3)	3.0	70	10
5	Li_2CO_3 (10.3)	3.0	66	10
6	K_3PO_4 (12.3)	3.0	18	nd
7	NaOH (15.7)	3.0	83	6
8	Et_3N (10.7)	3.0	56	4.5
9	DBU (12)	3.0	38	35
10	NMM (7.5)	2.0	>99	2.5
11	**NMM**	**3.0**	**>99**	**1**
12	NMM	5.0	88	2
13	NMM	10.0	79	2

[a]Reaction performed at 40°C for 20 h. [b]Determined by LCMS analysis.[c] Amount of **3b** in the crude mixture determined by LCMS analysis; nd= not determined.

The choice of base is known to play an important role on both the conversion and the chemoselectivity especially in peptide bonds formation.[14] Moderate to good conversion to the desired amide was observed with the use of inorganic base with a significant amount of the by-product **3b** (Table 2, entries 3-7). Organic bases such as Et_3N and DBU gave lower conversion (56% and 38% respectively, entries 8 and 9) whereas a weaker base such as NMM led to full conversion (entry 11). Increasing the amount of NMM in the mixture slowed down the conversion and increased the amount of by-product generated (entries 12 and 13). The purity profile was greatly impacted by the base used. It seems that strong base (pKa > 10) generates a substantial amount of the undesired di-acylation product **3b** potentially because of deprotonation of the free alcohol, leading to a more nucleophilic species. The low chemoselectivity observed when pyridine was used can be attributed to a change in mechanism, where a highly activated acyl-pyridinium intermediate is generated, leading to non-selective attack by the free alcohol (entry 1).

Based on this first round of optimization, we then probed the substrate scope. A variety of unprotected amino-alcohols was tested using 4-bromo-benzoic-acid as coupling partner (Figure **2**). Our optimized reaction conditions showed good tolerance to primary and secondary unprotected amino alcohols, as well as aromatic and aliphatic systems, resulting in good-to-excellent yields. Comparisons with commonly used solvents for amidation reactions such as acetonitrile and DMF were also performed. The use of TPGS-750-M in water as medium results in comparable isolated yields and purity as using dimethylformamide or acetonitrile. However, the environmental impact by using TPGS-750-M in water is greatly reduced since an aqueous workup followed by an extraction with an organic solvent is usually needed when DMF or CH_3CN are used as reaction solvent. Moreover, in most of the cases the product generated crystallizes out of the mixture when the reaction is performed in water, minimizing the number of operations which can be time consuming and costly when run on large scale.

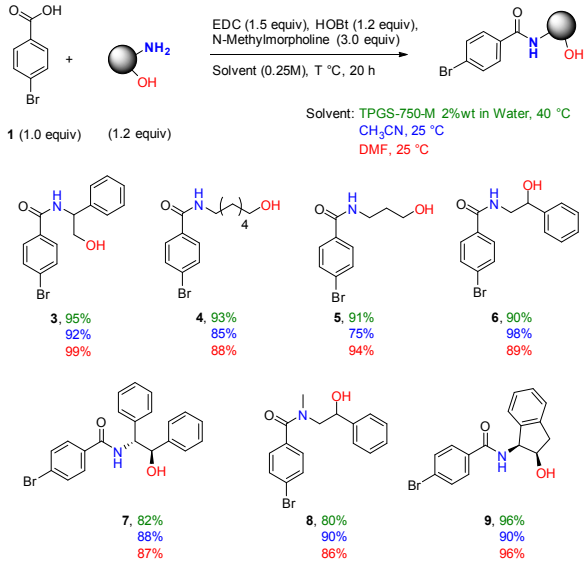
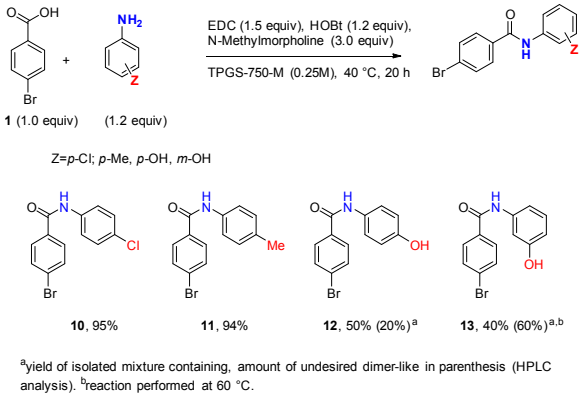


Figure 2: Amidation of various unprotected amino-alcohols using TPGS-750-M in water, acetonitrile or dimethylacetamide as solvent.

Aminophenols were also tested under the optimized reaction conditions (Figure 3), considering the importance of this backbone, as exemplified by paracetamol, to name just one. Surprisingly, full conversion cannot be achieved with both the *para*- or *meta*-aminophenol derivatives. High amounts of the corresponding di-acylation by product were also observed, reaching 60% in the case of *meta*-aminophenol **13**. To identify the reason for the lack of reactivity observed, we used aniline derivatives bearing either an electro-withdrawing or -donating group, such as *para*-chloroaniline or *para*-methylaniline. In both cases, the corresponding amides were obtained in very good yields, not showing any trace of di-acylation by-product. The lack of reactivity in the use of aminophenols can, therefore, be attributed to the presence of the phenolic alcohol. In the latter case, the use of acetonitrile or DMF did not deliver better results and a mixture of product and by-products were isolated.



[a]yield of isolated mixture containing, amount of undesired dimer-like in parenthesis (HPLC analysis). [b]reaction performed at 60 °C.

Figure 3: Amidation of substituted anilines using TPGS-750-M in water.

Finally, we conducted a competitive experiment between the aniline derivative **14** and *meta*-cresol **15**. The experiment showed that the rate of the amidation reaction is 2.5 times faster than esterification. This small difference is, therefore, not sufficient to achieve a chemoselective transformation and produce only the desired amide **17**, and thus requires additional points of control to have a chance to achieve high selectivity.

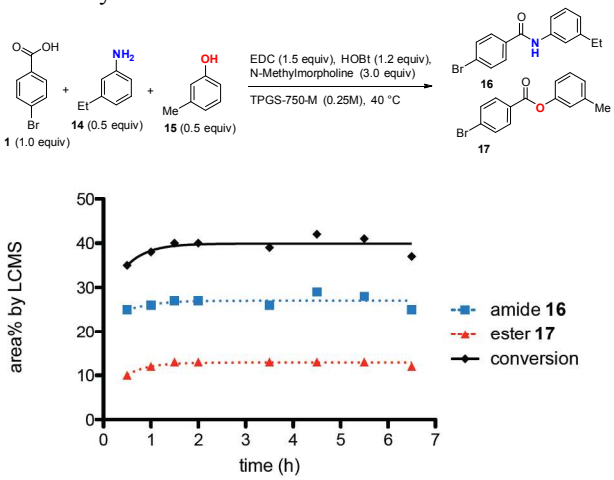


Figure 4: Competition experiment.

Various acids were screened using optimized reaction conditions, as illustrated in Figure 5. A broad scope of aromatic acids is tolerated, including furans (**18**), pyrazines (**19** and **23**), and substituted pyridines (**22** and **24**). Aliphatic acids are also well-tolerated (**20** and **23**). Steric hindrance at the *ortho* position of the

carboxylic acid moiety in **20** and **21** has an impact on the isolated yield when compared to use of the *para*-substituted derivative (**20** vs **4** and **21** vs **6**).

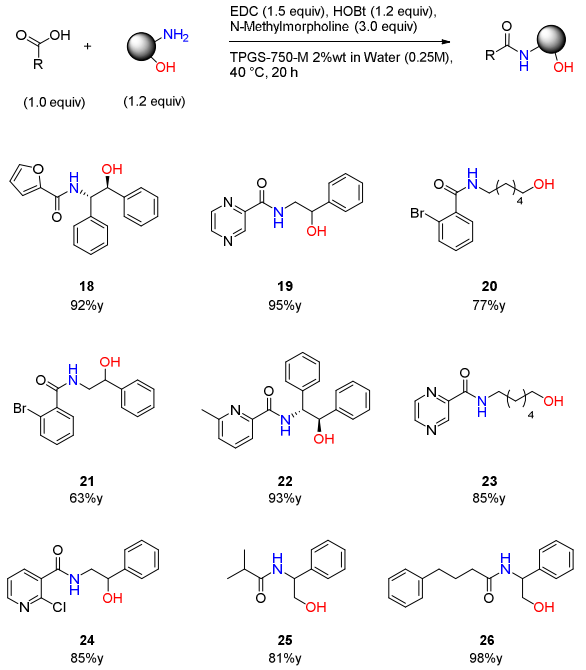


Figure 5: Scope of coupling products using different carboxylic acids and aminoalcohols.

In order to evaluate the suitability of this method for industrial applications, a scale up experiment was performed using 10 g of the starting carboxylic acid **1** and the aminoalcohol **2**. The reaction was performed under the optimized reaction conditions at 40 °C using 3 equivalents of NMM. The product was isolated directly as a solid by a simple filtration and washed with water. This very simple protocol reliably provides yields above 15 g of product (>95% yield) in ≥98.5% purity.

In summary, we describe a general method to selectively generate amide bonds in the presence of alcohols, utilizing TPGS-750-M in water as the medium. Under mild conditions, good-to-excellent yields and purities were obtained using standard and inexpensive EDC/HOBt together with NMM. Competitive reactions between *O*-acylation and *N*-acylation were seen when phenol derivatives were used. Further studies are currently ongoing to solve this issue, extend the scope of the reaction and also to reduce the reaction times. This protocol and the other recent ones we have elaborated by ourselves or in the course of our collaboration with Professor Lipshutz represent in our eyes a significant alternative to those described in reprotoxic polar aprotic solvents.[11b, 13, 15]

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ASSOCIATED CONTENT

Supporting Information: Experimental description, ^{1}H and ^{13}C NMR description for all intermediates and products. Synthesis and characterization data of by-products **3b** and 2-amino-2-phenylethyl-4-bromobenzoate. Structures of surfactant used in the study.
NMR spectra for compounds (PDF).

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Notes
The authors declare no competing financial interest.

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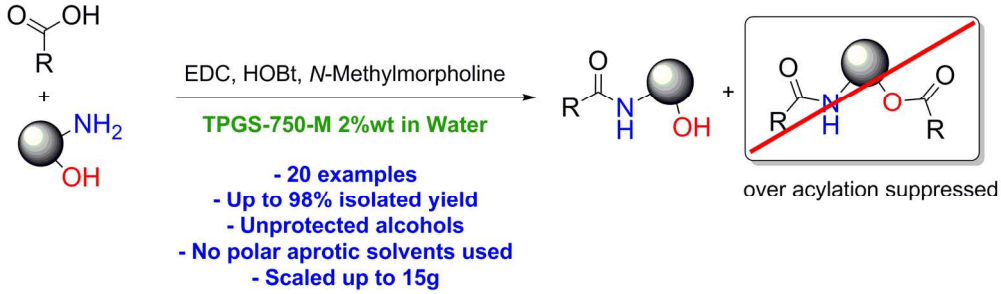

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