2-Azaaryl-1-methylpyridinium Halides: Aqueous-Soluble Activating Reagents for Efficient Amide Coupling in Water

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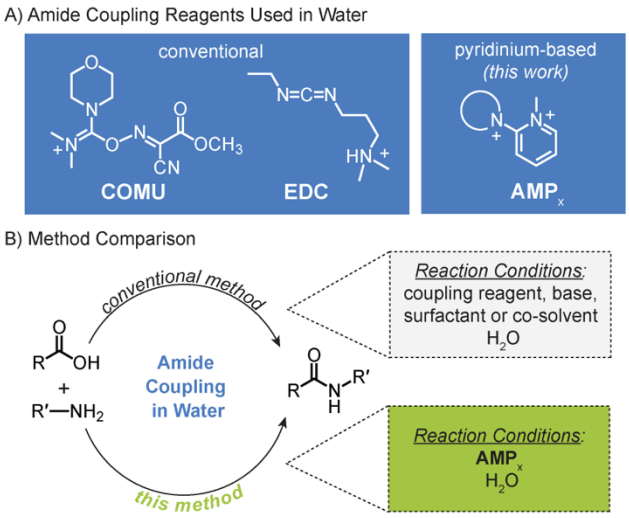
ABSTRACT: In this work, a class of 2-azaaryl-1-methylpyridinium (**AMP**$_x$) reagents capable of promoting amidation processes in 100% water is reported. The process mass intensity of the **AMP**$_x$-promoted reactions is similar to or lower than that of reactions using conventional coupling reagents, which suggests that the former has potential as a green amide synthesis method. It was found that the *N*-methylimidazole-based **AMP**$_{im1}$ could be used to couple a wide range of carboxylic acids with primary amines, including natural amino acids to form peptide bonds. Tandem oxidation-amidation and reduction-amidation reactions in the presence of **AMP**$_{im1}$ were achieved with up to moderate efficiency. It is proposed that the azaarene in **AMP**$_x$ plays multiple roles in the amide bond forming process, including as a leaving group, activator, and base.

INTRODUCTION

Amide bonds are covalent C(=O)–N linkages prevalent in a wide range of natural (e.g., proteins, alkaloids, cofactors, etc.) and synthetic compounds and polymers (e.g., agrochemicals, household chemicals, food additives, and pharmaceuticals).[1-3] Approximately 25% of drugs on the market have at least one amide bond, and over 80 therapeutic peptides have been approved for clinical use.[4]

The most common method to form amide bonds is to treat carboxylic acids with an activator, followed by the addition of an amine coupling partner.[3] Nearly 80% of amidations employ dichloromethane or dimethylformamide as the reaction medium,[5] which are hazardous to human health and the environment. Although water is a green solvent because it is non-toxic, non-flammable, and widely available, it is often used in combination with superstoichiometric amounts of base, surfactants, or organic co-solvents to achieve high amide coupling efficiency (Scheme 1).[1,2] Unfortunately, the need for these additives reduces the atom economy of the process and potentially generates more undesirable side products. In 2018, due to the critical importance of amide-containing compounds in the chemical industry, the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable listed direct amide bond formation as one of the top 10 key green chemistry areas to pursue.[6]

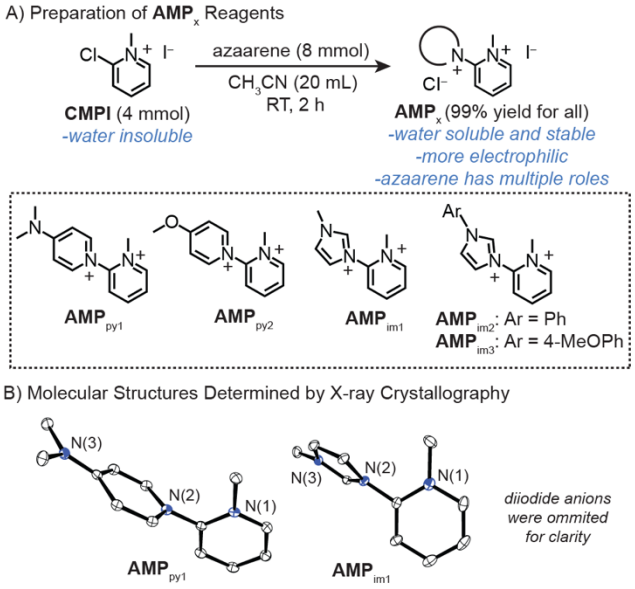
During the course of our investigations on C-N bond forming reactions, we discovered a novel class of amide coupling reagents derived from 2-chloro-1-methylpyridinium iodide (CMPI, also known as Mukaiyama reagent).[7] Although CMPI itself is commonly used in amide synthesis, it is insoluble in water and its chloride atom is susceptible to nucleophilic displacement by the iodide counterion, which renders the reagent less active.[8,9] We found that when CMPI was combined with an appropriate azaarene in acetonitrile, a precipitate comprising 2-azaaryl-1-methylpyridinium chloride iodide (**AMP**$_x$, where x is the abbreviation for the azaaryl group) had formed. The dicationic species is capable of promoting amide coupling in 100% water. In comparison to other amide coupling reagents used in aqueous mixtures, such as ((1-[(1-cyano-2-ethoxy-2-oxoethylideneaminooxy)-dimethylaminomorpholinomethylene)]methanaminium hexafluorophosphate) (COMU)[10] or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)[11] (Scheme 1), **AMP**$_x$ possesses comparable sustainability ratings but is less expensive based on current market prices. Herein, we report on the reactivity of the **AMP**$_x$ activators and their potential applications in small molecule amide synthesis and tandem reactions. We also carried out NMR spectroscopic studies to study the **AMP**$_x$ activation process.



Scheme 1. A) Representative examples of amide coupling reagents used in water and the pyridinium-based reagents reported in this work. B) Comparison of amide coupling methods in water.

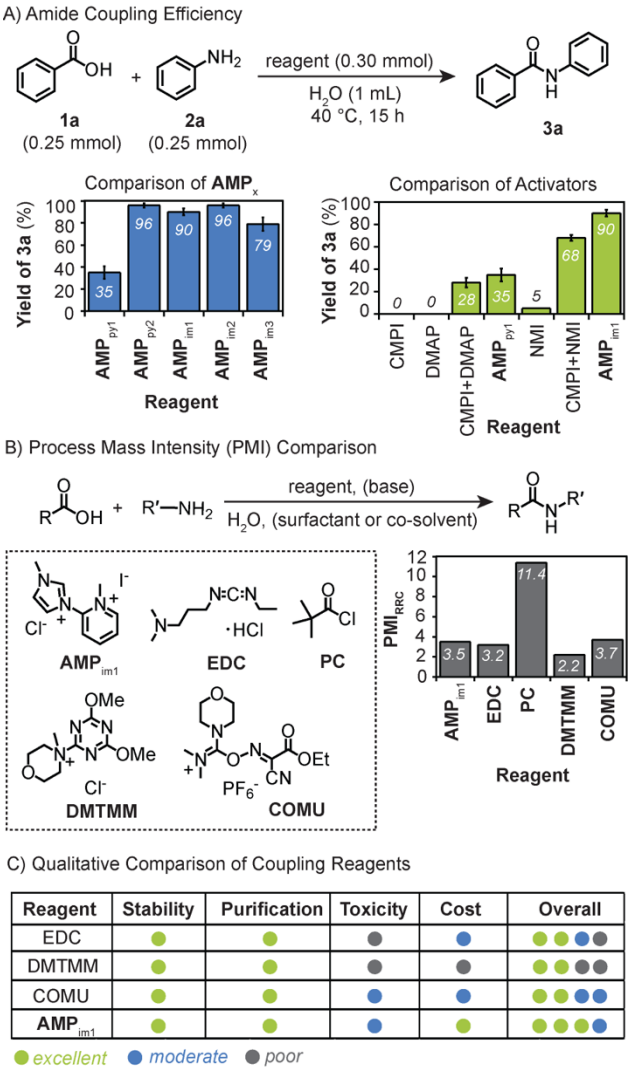
RESULTS AND DISCUSSION

In our efforts to develop green amide coupling methods, we focused on the pyridinium-based activators due to their air and moisture tolerance and ease of handling.[7] We observed that when 4-(dimethylamino)pyridine (DMAP) was combined with CMPI in CH_3CN at RT, large amounts of a pale-yellow solid precipitated over the course of 2 h (Scheme 2A). NMR spectroscopic characterization of this material revealed the presence of a new species with two methyl and six aromatic resonances (Figure S22). We hypothesized that this product formed from nucleophilic attack of DMAP at the 2-position of CMPI, affording 2-(4-dimethylamino-1-pyridyl)pyridinium chloride iodide (**AMP**$_{py1}$). To avoid having mixed halides for crystal growth, we treated **AMP**$_{py1}$ with silver iodide to obtain the corresponding diiodide salt. Slow evaporation of a methanol solution of this salt gave single crystals suitable for X-ray structural analysis. The structure of **AMP**$_{py1}$ showed that the nitrogen donor of DMAP is attached to the *ortho* position of the 1-methylpyridinium ring (Scheme 2B, Table S8). Two non-coordinating iodide anions were identified, suggesting that the pyridinium species is dicationic. Mass spectrometric analysis of **AMP**$_{py1}$ shows a fragment peak for $[DMAP+H]^+$, further supporting the presence of the azaarene in the structure (Figure S17). **AMP**$_{py1}$ was also found to be stable in water after 3 d (Figure S2).



Scheme 2. A) General reaction conditions for the preparation of **AMP**$_x$ reagents; B) The molecular structures of **AMP**$_{py1}$ and **AMP**$_{im1}$ obtained from single crystal X-ray crystallography. The displacement ellipsoids are drawn at the 50% probability level. The process mass intensity values for the synthesis of **AMP**$_x$ are provided in Table S6.

We found that other **AMP**$_x$ variants could be prepared by combining CMPI with 4-methoxypyridine, *N*-methylimidazole (NMI), *N*-phenylimidazole, or *N*-(4-methoxyphenyl)imidazole to give **AMP**$_{py2}$, **AMP**$_{im1}$, **AMP**$_{im2}$, and **AMP**$_{im3}$, respectively (Scheme 2A). These salts were isolated with high purity by filtration and obtained in quantitative yields. The **AMP**$_x$ reagents were fully characterized by NMR spectroscopy and mass spectrometry. The 1-methyl-2-(3-methyl-1-imidazolyl)pyridinium structure of **AMP**$_{im1}$ was further confirmed by X-ray crystallography (Scheme 2B, Table S8). Surprisingly, no reactions occurred between CMPI and the heterocycles pyridine, 1-methyl-1,2,3-triazole, 1-methyl-1,2,4-triazole, 1-methylimidazole-4,5-dicarbonitrile, benzoxazole, or benzothiazole in acetonitrile (Table S1). This lack of reactivity may be due to the weaker nucleophilicity of these nitrogen donors in comparison to those in the **AMP**$_x$ reagents that were successfully synthesized.[12]



Reagent	Stability	Purification	Toxicity	Cost	Overall
EDC	●	●	●	●	● ● ● ●
DMTMM	●	●	●	●	● ● ● ●
COMU	●	●	●	●	● ● ● ●
AMP$_{im1}$	●	●	●	●	● ● ● ●

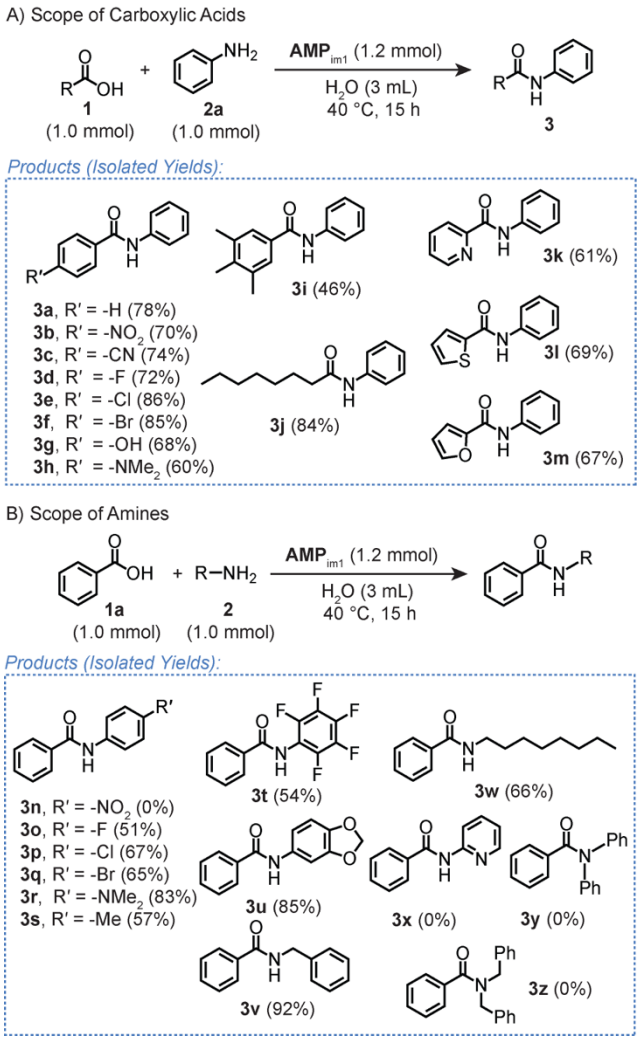
Scheme 3. A) Comparison of various activators in the amide coupling reactions between **1a** and **2a**. The yields were determined by GC-MS using an internal standard. B) Comparison of the process mass intensity (PMI_{RRC}) of amidation reactions using different coupling reagents. See Scheme S2 for details of each reaction. C) Qualitative comparison of the different coupling reagents based on several green chemistry metrics.

Next, the **AMP**$_x$ salts were tested as activators for amide coupling between carboxylic acids and amines in water. For these studies, benzoic acid (**1a**), aniline (**2a**), and **AMP**$_x$ were dissolved in 100% H_2O and stirred for 15 h at 40 °C under air (Scheme 3A). All of the reactions produced an off-white solid, which was determined to be the desired amide product **3a**. Gas chromatography-mass spectrometry (GC-MS) analysis of the reaction mixtures showed that **AMP**$_{py1}$ gave low yield (35%),

AMP$_{im3}$ gave moderate yield (79%), and **AMP**$_{py2}$, **AMP**$_{im1}$, and **AMP**$_{im2}$ gave excellent yields (90-96%). This reactivity trend may be due to differences in the electrophilicity and water solubility of the amide coupling reagents. Pyridinium rings with less electron-donating azaarenes will be more susceptible to nucleophilic attack because they have greater partial positive charge character. Based on the estimated pK_a values of the protonated azaarenes in water, 4-methoxypyridine in **AMP**$_{py2}$ (4-methoxypyridinium pK_a = ~6.6[13]), *N*-methylimidazole in **AMP**$_{im1}$ (*N*-methylimidazolium pK_a = ~7.1[14]), and *N*-phenylimidazole in **AMP**$_{im2}$ (*N*-phenylimidazolium pK_a = ~5.4[15]) are less basic than DMAP in **AMP**$_{py1}$ (4-dimethylaminopyridinium pK_a = ~9.6[13]), which suggests that the former are weaker donors than the latter. Furthermore, **AMP**$_{im3}$ has lower water solubility than the other pyridinium reagents so it is not ideal for use in aqueous reactions. Amid coupling using **AMP**$_{im1}$ could be shortened to 8 h if the temperature was increased to 60 °C (Table S4, entry 4).

To compare the amide coupling efficiency of **AMP**$_x$ versus that of its precursors, we carried out the following experiments (Scheme 3A, right plot). When **1a** and **2a** were mixed with either CMPI or DMAP in H_2O and stirred at 40 °C for 15 h, no products were observed. Addition of both CMPI and DMAP (1:1) to a solution containing **1a** and **2a** provided about 28% yield of **3a**. In comparison, use of **AMP**$_{py1}$ as the activator gave the desired amide in 35% yield. In another study, we found that NMI itself was a poor coupling reagent, giving only about 5% of **3a**. However, reactions using either NMI/CMPI (1:1) or **AMP**$_{im1}$ afforded **3a** in 68 and 90% yield, respectively. When the reactions were scaled up by about 40× (i.e., using 10 mmol rather than 0.25 mmol of **1a**+**2a**), the differences in the amide coupling efficiency between NMI/CMPI and **AMP**$_{im1}$ were even more dramatic (Table S4). For example, using 1.2 equiv. of NMI/CMPI (1:1) relative to substates afforded about 11% yield of **3a** (entry 1), which was significantly lower than that obtained using **AMP**$_{im1}$ (78%, entry 3). Addition of 2.4 equiv. of NMI and 1.2 equiv. of CMPI to **1a**+**2a** provided ~47% yield of the amide product (entry 2). These results showed that in all cases combining the precursors azaarene and CMPI in situ was less effective than using the pre-synthesized **AMP**$_x$ reagents. A possible reason for this difference is that aqueous solutions containing CMPI are heterogenous (Figures S1 and S13) so there may be mass transport limitations. Thus, our water-soluble **AMP**$_x$ activators are advantageous over CMPI because they are more likely to be compatible with applications requiring homogeneous solutions (e.g., in aqueous continuous flow reactions)[16] and can be used on large scales. They can also be stored in the dark on the benchtop for several months without any loss in activity.

To assess the chemical sustainability of our amide coupling method, we calculated the process mass intensity (PMI$_{RRC}$) of reactions using different **AMP**$_x$ reagents.[17,18] The PMI$_{RRC}$ is defined as the total mass of all reactants, reagents, and catalysts used in a process divided by the mass of the product, which means that reactions with lower PMI$_{RRC}$ values are more atom economical than those with higher values. According to Table S5, the **AMP**$_x$-promoted reactions have PMI$_{RRC}$ values ranging from about 3-10. The PMI$_{RRC}$ of the **AMP**$_{im1}$ reaction is 3.5, which is similar to those using EDC (3.2)[19], (4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM, 2.2),[20] and COMU (3.7)[21] but lower than that using pivaloyl chloride (PV, 11.4)[22] (Scheme 3B). Considering that the **AMP**$_x$ coupling reactions require only a single reagent, it is simpler to set up compared to those requiring multiple reagents. To fully assess sustainability (Scheme 3C), it is useful to compare the toxicology data for all the chemicals needed to produce the coupling reagents as well as their byproducts (however, comprehensive toxicology data are not always available). For **AMP**$_{im1}$, none of its components (e.g., CMPI,[23] 1-methylimdazole,[24] and *N*-Methyl-2-pyridone[25]) are listed as particularly hazardous substances. The coupling reagent EDC[26] was found to be extremely toxic to aquatic life and DMTMM[27] can cause serious skin and eye damage. In terms of cost, the precursors for **AMP**$_x$ (i.e., CMPI + azaarene) are significantly less expensive than COMU, EDC, and DMTMM based on current market prices (Table S7).

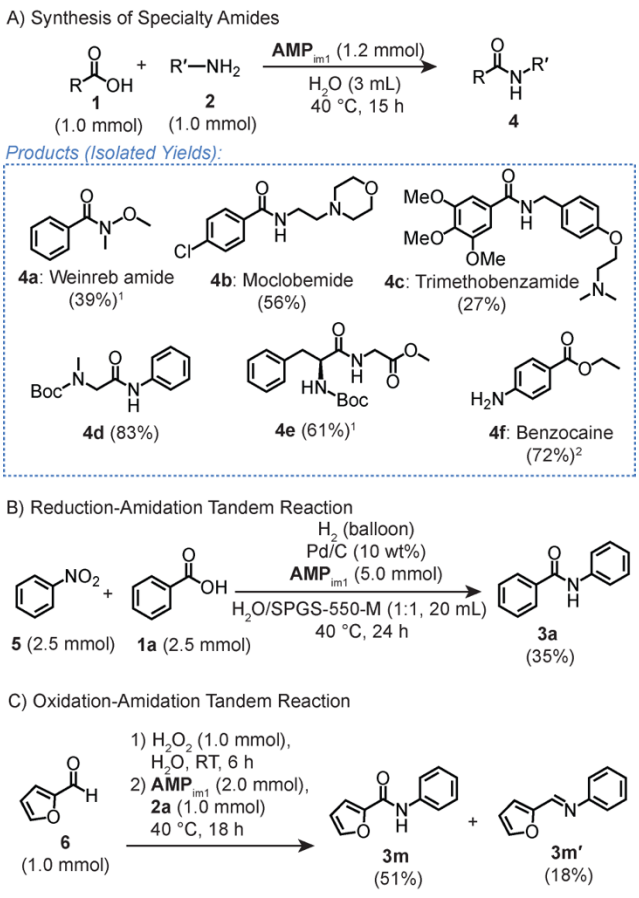


Scheme 4. Carboxylic acid (A) and amine (B) substrate scope studies using the **AMP**$_{im1}$ reagent in water at 40 °C for 15 h. All yields given are isolated yields.

After evaluating the different **AMP**$_x$ activators, we next proceeded to investigate the substrate scope. All subsequent studies were performed using **AMP**$_{im1}$ due to its favorable reactivity, ease of preparation, and low cost. Using our standard reaction conditions in water, we found that a variety of carboxylic acids could be coupled to **2a** to form the corresponding amide (Scheme 4A). Reactions employing benzoic acids with electron-withdrawing groups at the *para* position gave slightly higher yields (~70-86% of **3b**-**3f**) than those with electron-

donating groups (68% of **3g** and 60% of **3h**). Compound **1i** with 3,4,5-trimethyl substitution, which has poor solubility in water, was converted to **3i** in 46% yield. Further improvement in yield was achieved (80%) when SPGS-550-M was added as a surfactant at 60 °C. Carboxylic acids featuring pyridyl, thiofuranyl, or furanyl rings furnished the corresponding **3k**, **3l**, and **3m** products in ~60-70% yields. Finally, octanoic acid and aniline were successfully transformed to **3j** with high efficiency (84% yield).

To determine the amine scope, we performed reactions using **1a** with different primary and secondary *N*-donors in the presence of **AMP**$_{im1}$ (Scheme 4B). Our results showed that electron rich amines, such as **2r**, **2u**, and **2v**, gave excellent yields of the corresponding amide (>80%). However, electron-poor amines, such as halide-substituted aniline (**2o**-**2q**) and pentafluoroaniline (**2t**), afforded only moderate yields (~50-70%) of the desired products. We found that 4-nitroanline (**2n**) was not soluble in water and could not be coupled to **1a**. The aliphatic amine **2w** was successfully converted to **3w** in 66% yield. Lastly, 2-aminopyridine (**2x**), which is a weak nucleophile due to resonance effects,[28] and secondary amines (**2y** and **2z**) did not react with **1a** in the presence of **AMP**$_{im1}$. For unreactive substrates, we added SPGS-550-M to the aqueous mixtures and stirred at 60 °C. Under these conditions, we were able to obtain appreciation yields of **3y** (31%) and **3z** (47%), indicating that it is possible to couple secondary amines.

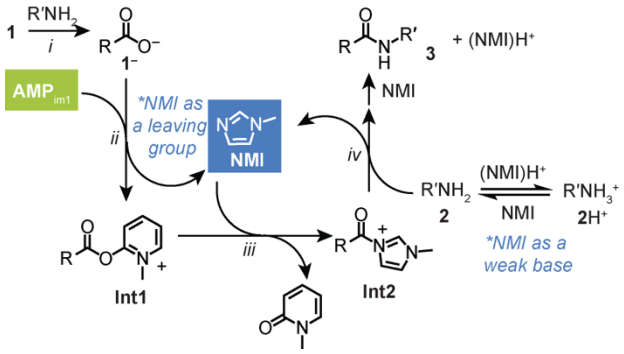


Scheme 5. A) Using **AMP**$_{im1}$ to synthesize specialty amides. [1]Na_2CO_3 (1.0 equiv.) was added to deprotonate the ammonium salt. [2]Ethanol was used as the solvent instead of water. B) Tandem reduction-amidation reaction to prepare **3a**. C) Tandem oxidation-amidation reaction to prepare **3m**. All yields given are isolated yields.

The synthetic versatility of our **AMP**$_x$ coupling method was further demonstrated by showing that it can provide access to functionally important small molecules (Scheme 5A). Starting from **1a** and *N*,*O*-dimethylhydroxyamine in water, we successfully obtained the Weinreb amide (**4a**, 39% yield), which is a reagent commonly employed in ketone synthesis.[29,30] We were able to prepare the clinically approved drugs Moclobemide (**4b**)[31,32] and Trimethobenzamide (**4c**)[33,34] in moderate (56%) and modest (27%) yields, respectively. We found that **AMP**$_{im1}$ can promote peptide bond formation very efficiently,[35,36] as exemplified by the synthesis of *tert*-butoxycarbonyl (Boc)-protected glycine (**4d**, 83% yield) and phenylalanine-glycine conjugates (**4e**, 61%). Epimerization of **4e** was not observed but additional studies are needed to determine whether it could occur in other amino acid substrates.[37] We were able to prepare the well-known anesthetic benzocaine (72% yield)[38] from 4-aminobenzoic acid using **AMP**$_{im1}$ in ethanol as solvent instead of water and no amines. This result suggests that the **AMP**$_x$ reagents could be used for ester synthesis but studies of C–O bond forming reactions were not pursued in this work.

Another potential application of the **AMP**$_x$ reagents is in tandem synthesis.[39,40] Because some amines are prone to air-oxidation, we wondered if they could be generated in situ and then coupled with carboxylic acids using **AMP**$_{im1}$ in one-pot. To test this possibility, we combined nitrobenzene **5**, **1a**, **AMP**$_{im1}$, and Pd/C under 1 atm of H_2 using a balloon (Scheme 5B). Because the Pd/C catalyst forms aggregates in water, we also used a SPGS-550-M surfactant to improve its aqueous dispersion. After stirring at 40 °C for 24 h, the reaction mixture was worked up and the amide product **3a** was isolated in 35% yield. Reactions at elevated H_2 pressure did not give any products, which may be due to reductive degradation of **AMP**$_{im1}$ (Table S2, entry 3). Varying other reaction conditions, such as using methanol instead of water (entry 2) or other surfactants (entry 6), did not increase the yield of **3a**. Performing the reaction in two-steps, by combining **1a, 5**, and **AMP**$_{im1}$ first, followed by treatment with H_2/Pd/C, afforded 48% isolated yield of **3a** (entry 7).

Because **AMP**$_{im1}$ is somewhat stable under mild reducing conditions, we next evaluated whether it could be used under oxidizing conditions. For this experiment, we selected furfural (**6**) as the starting material because it could be obtained from natural sources.[41,42] We reasoned that oxidation of **6** would produce a carboxylic acid that could be subsequently coupled to an amine. After screening different oxidants (Table S3), H_2O_2 was determined to be the most efficient. In our optimized reaction (Scheme 5C), **6** was first treated with H_2O_2 and then stirred for 6 h. Solid **AMP**$_{im1}$ and **2a** were then added and the resulting mixture was stirred for another 18 h. After workup, a mixture of **3m** (51%) and **3m′** (18%) was obtained. Compound **3m′** most likely formed from imine condensation between **2a** and **6**, which suggest that the oxidation of **6** was not complete in the first step. Because **AMP**$_{im1}$ degrades in the presence of H_2O_2, this oxidation-amidation process must be carried out in two-steps. Although the reduction-amidation and oxidation-amidation reactions described above gave only modest to moderate yields, they demonstrate that **AMP**$_x$ may be suitable for future tandem reaction studies in water.



Scheme 6. Proposed mechanism for the activation of carboxylic acids by **AMP**$_{im1}$ and subsequent reactions to produce amides.

The role of **AMP**$_{im1}$ in the amide coupling process was probed using NMR spectroscopy. When **AMP**$_{im1}$ was added to a D_2O solution of **1a**, no changes in the NMR spectra were observed (Figure S5), suggesting that the carboxylic acid is not a strong enough nucleophile to attack the pyridinium ring of **AMP**$_{im1}$. In contrast, when sodium benzoate (**1a**$^-$) was treated with **AMP**$_{im1}$, new NMR resonances appeared (Figure S9). For example, three different C=O peaks at 167.4, 162.4, and 162.0 ppm were detected. The peak at 162.0 ppm was attributed to the presence of *N*-methylpyridone because its chemical shift matched that of an authentic sample. However, additional studies are needed to make further NMR assignments. We hypothesize that in the presence of **2**, compound **1** converts to **1**$^-$ (step *i,* Scheme 6). The carboxylate reacts with **AMP**$_{im1}$ to afford **Int1** (step *ii*), which is an intermediate that can be formed independently from the reaction of carboxylic acid, base, and CMPI.[7,43] **Int1** is then proposed to undergo substitution by NMI to generate an *N*-acylimidazolium species (**Int2**) (step *iii*),[44,45] which can be subsequently attacked by R′NH$_2$ to give **3** after deprotonation (step *iv*). Based on our observation that increasing the amount of NMI present increases the reaction yield (Figure S4 and Table S4), we propose that the azaarene converts the R′NH$_3^+$ generated in the first step back to R′NH$_2$, which is needed in step *iv* to form the amide. Thus, as shown in Scheme 6, NMI serves as a leaving group, an activator, and a base.

CONCLUSIONS

In summary, we have developed a new class of water-soluble pyridinium-based amide coupling reagents. The **AMP**$_x$ activators are chemically stable in water and showed higher amidation activity in comparison to that of the parent CMPI. In general, **AMP**$_x$-promoted reactions do not require external bases or surfactants and can be used to couple a wide range of carboxylic acid and amine substrates, including amino acids to form peptide bonds. The process mass intensity of **AMP**$_x$-based reactions are similar to or lower than those reported for other aqueous amide coupling reactions, indicating that our method has favorable sustainability ratings. Furthermore, we have demonstrated that **AMP**$_x$ can be used in tandem one-pot reactions, such as oxidation-amidation or reduction-amidation. The yields of such processes could likely be improved by further reaction optimization or engineering. Because the **AMP**$_x$ reagents are easy to prepare, air and moisture stable, and can be used on large scale in 100% water, we anticipate that they will have practical applications in the construction of many amide-containing small molecules and polymers.

KEYWORDS

Amide coupling, carboxylic acid activators, aqueous chemistry, peptides, Mukaiyama reagent

ASSOCIATED CONTENT

This material is available free of charge via the Internet at http://pubs.acs.org.

Experimental procedures, characterization data, NMR spectra, mass spectrometric data, and X-ray crystallographic data.

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Notes

The authors declare no competing financial interest.

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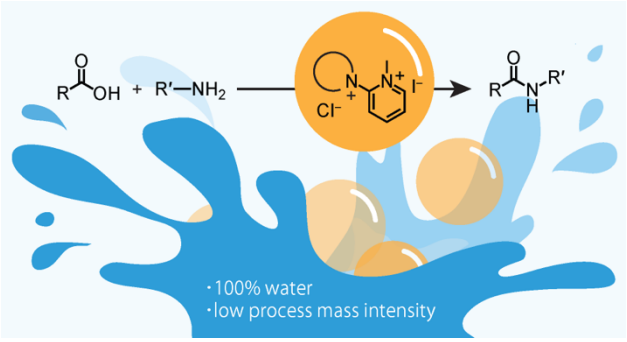

Synopsis

A family of easy-to-synthesize reagents that promotes amide bond formation in water is developed.
