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Unprecedented “In Water” Imidazole Carbonylation: Paradigm Shift for Preparation of Urea and Carbamate

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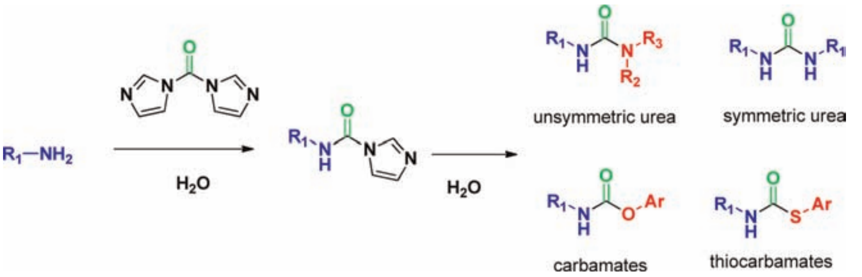
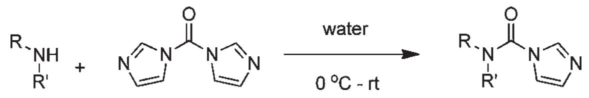
ABSTRACT



The first “In Water” imidazolecarbonylation of amine is described. A one pot reaction of carbonylimidazolide in water with a nucleophile provides an efficient and general method for the preparation of urea, carbamates and thiocarbamates. Use of an anhydrous solvent and an inert atmosphere could be avoided. Product precipitate out from the reaction mixture and can be obtained in high purity by filtration, resulting in a simple and scalable method.

Water is the most economic and eco-friendly solvent available in nature. However, it is not a popular choice of solvent for chemists,[1] as most organic substances have poor solubility and many of the reagents are unstable in water. Recently the concepts of “On Water”[2] and “In water”[3] synthesis have achieved a great deal of attention for their high efficiency and ease of process. Herein we report a general and versatile method for preparing urea, carbamates, and thiocarbamates in an aqueous media.

Scheme 1. “In Water” Reaction of Amine and CDI



Urea and carbamate are important functional groups found in pharmaceutical candidates,[4] agrochemicals, and material science.[5] Although a number of methodologies, such as oxidative carbonylation of amines[6] and dialkyl

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(1) For general review, see: (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Springer: New York, 1997. (b) *Clean Solvents: alternative Media for Chemical Reactions and Processing*; Abraham, M. A., Moens, L., Eds.; ACS Symposium Series 819; American Chemical Society: Washington, DC, 2002. (c) *Organic Reactions in Water*; Lindstroem, U. M., Ed.; Blackwell: Oxford, U.K., 2007.

(2) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275.

(3) (a) Shapiro, N.; Vigalok, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2849. (b) Chankeshwara, S. V.; Chakraborti, A. K. *Org. Lett.* **2006**, *8*, 3259.

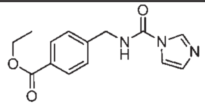
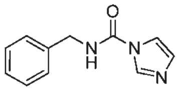
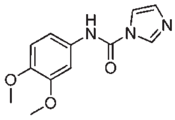
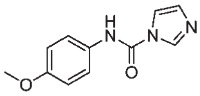
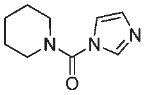
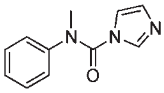
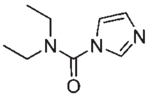
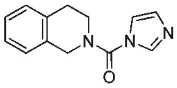
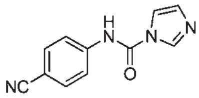
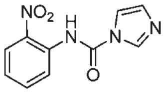
(4) (a) Gallou, I. *Org. Prep. Proc. Int.* **2007**, *39*, 355. (b) McMorris, T. C.; Chimmani, R.; Alisala, K.; Staake, M. D.; Banda, G.; Kelner, M. J. *J. Med. Chem.* **2010**, *53*, 1109. (c) Maier, T.; Beckers, T.; Baer, T.; Vennemann, M.; Gekler, V.; Zimmermann, A.; Gimmnich, P.; Padiya, K.; Joshi, H.; Joshi, U.; Makhija, M.; Harel, D. U.S. Patent 20110021494. (d) Feng, Y.; Lograsso, P.; Schroeter, T.; Yin, Y. U.S. Patent 200899642.

(5) (a) Kim, J.; Riju, D.; Rudolf., Z. *J. Colloid Interface Sci.* **2011**, *359*, 428.

(6) Diaz, D. J.; Darko, A. K.; White, L. M. *Eur. J. Org. Chem.* **2007**, 4453.

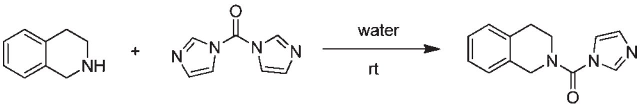
10.1021/ol301009d

Table 1. Reaction of Amine with CDI in Water[a]

entry	product		yield (%)[b]
1		**1a**	90
2		**1b**	81
3		**1c**	85
4		**1d**	90
5		**1e**	86
6		**1f**	88[c]
7		**1g**	61[c]
8		**1h**	96[c]
9		**1i**	no reaction[d]
10		**1j**	no reaction[d]

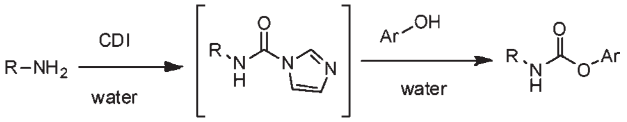
[a] To the solution of amine (10 mmol) in water at 0 °C was added 1,1′-carbonyldiimidazole (12 mmol) in solid form. The reaction mixture was stirred at 0 °C and monitored by TLC. [b] Isolated yield. [c] Reactions carried out at rt gave similar results. [d] Starting amine recovered unchanged.

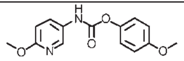
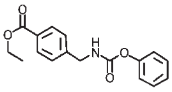
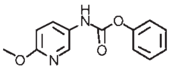
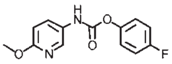
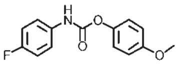
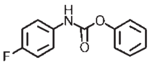
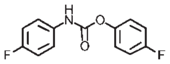
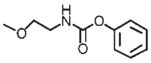
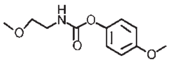
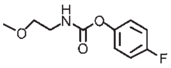
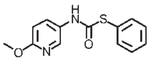
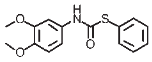
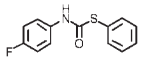
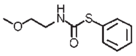
Table 2. Effect of Solvent on Preparation of Carbonylimidazolide of Tetrahydroquinoline



entry	solvent	time	yield (%)
1	water	10 min	94
2	MeOH	7 h	30
3	*tert*-butanol	75 min	90
4	DMSO	80 min	53
5	DMF	40 min	78
6	dioxane	16 h	50
7	THF	90 min	33
8	CH_3CN	90 min	79
9	CH_2Cl_2	65 min	50
10	toluene	16 h	55

Table 3. Preparation of Carbamate by in Situ Generation of Carbonylimidazole in Water[a]



entry	product		yield (%)[b]
1		3a	75
2		3b	75
3		3c	70
4		3d	70
5		3e	75
6		3g	78
7		3h	80
8		3i	98
9		3j	73
10		3k	87
11		4a	77[c]
12		4b	75[c]
13		4c	54[c]
14		4d	72[c]

[a] CDI (12 mmol) was added to the solution of amine (10 mmol) in water at 0 °C and monitored by TLC. The reaction mixture was then warmed up to room temperature. Phenol or thiophenol (12 mmol) was added. The reaction mixture was stirred at room temperature and was monitored by TLC. [b] Isolated yield. [c] Thiophenol was used as a nucleophile to react with carbonylimidazolide.

based exchange processes,[7] have been developed recently for the synthesis of ureas and carbamates which are environmentaly more benign, a standard method for rapid library generation of urea and carbamate involves use of a transfer reagent such as phosgene, triphosgene,[4b] 1,1′-carbonylimidazole,[4b] carbonylimidazolium salt,[8] chloroformates, or some carbamoyl cation equivalent such as

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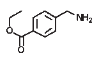
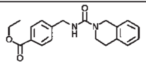
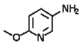
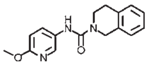
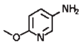
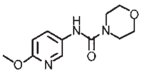
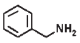
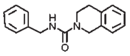
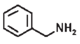
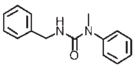
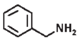
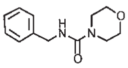
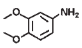
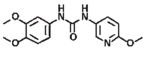
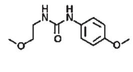
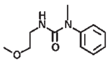
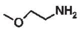
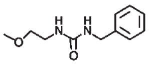
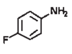
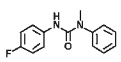
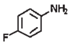
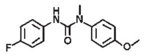
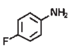
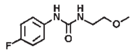
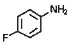
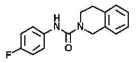
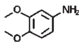
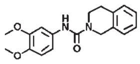
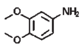
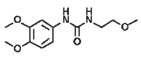
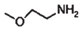
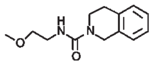
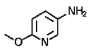
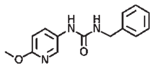
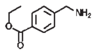
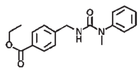
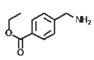
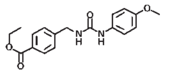
(7) (a) Han, C.; Porco, J. A., Jr. *Org. Lett.* **2007**, *9*, 1517. (b) Leung, M. K.; Lai, J. L.; Lau, K. H.; Yu, H. H.; Hsiao, H. J. *J. Org. Chem.* **1996**, *61*, 4175. (c) For general review on chemistry of dialkyl carbonates, see: Tundo, P.; Selva, M. *Acc. Chem. Res.* **2002**, *35*, 706. (d) Belfadhel, H. A.; Brack, H.; Godoy-Lopez, R.; Willemse, D. J. P. M. U.S. Patent 20100113819.

Table 4. Preparation of Urea by in Situ Generation of Carbonylimidazole in Water[a]

entry	R-NH$_2$	product		yield(%)[b]
1			2a	86
2			2b	82
3			2c	80
4			2d	81
5			2e	73
6			2f	70
7			2g	85
8			2h	93
9			2i	95
10			2j	97
11			2k	62
12			2l	78
13			2m	73
14			2n	91
15			2o	87
16			2p	83
17			2q	88
18			2r	95
19			2s	77
20			2t	82

[a] CDI (12 mmol) was added to the solution of amine (10 mmol) in water at 0 °C and monitored by TLC. The reaction mixture was then warmed up to room temperature. The second amine (12 mmol) was added. The reaction mixture was stirred at room temperature and was monitored by TLC. [b] Isolated yield.

isocyanates[4b] or carbamoylchlorides. There are significant drawbacks associated with many of these reagents. Carbamoylchlorides and isocyanates have limited commercial availability, whereas phosgene and triphosgene are highly toxic and highly moisture sensitive making the process more tedious. Among these 1,1′-carbonyldiimidazole (CDI) is comparatively mild and the most widely used reagent. However, CDI is moisture sensitive and is reported to react with water with evolution of carbon dioxide.[9] We observed a complete decomposition of CDI to imidazole in 10 min at 0 °C. CDI is known to react with amines to give N-substituted 1*H*-imidazole-1-carbonyl-(carbonylimidazolide), which can be converted to urea, carbamate, or thiocarbamate. Preferred solvents for such conversions are CH_2Cl_2, THF, or CH_3CN preferably under anhydrous conditions.[9] We have investigated the same reaction in water and found that CDI, though unstable in water, rapidly reacts with amine to give good yields of respective imidazole-*N*-carboxamides (N-substituted carbonylimidazolide) (Scheme 1). CDI mediated amidation of unprotected α-amino acids[10] and, recently, a solvent-free CDI mediated amidation are reported.[11] However, to the best of our knowledge, there is no precedence for the preparation or reaction of carbonylimidazolide in water.

CDI on treatment with the solution of benzylamine in water at room temperature yielded symmetric urea. The same reaction when carried out at low temperature (0 °C) gave *N*-benzylcarbonylimidazolide (entry 2, Table 1) as a sole product. Both, primary and secondary amines undergo "In Water" imidazocarbonylation to give the corresponding carbonylimidazolide. This method was used to make a number of carbonylimidazolides (Table 1). In most cases the product precipitates out from the reaction mixture. The product could be isolated in pure form by just filtration. It has been observed that an aromatic amine with a deactivated ring does not undergo this reaction even at elevated temperature (entries 9 and 10, Table 1). This could be attributed to the low nucleophilicity of such amines.

The effect of solvent in the preparation of carbonylimidazolide was studied by reacting tetrahydroisoquinoline with CDI. As shown in Table 2, the reaction goes to completion within 10 min with water as a solvent, which is comparatively much faster than the reaction in other solvents.

Carbonylimidazolides obtained from primary amines are less reactive as compared to CDI and do not undergo

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(8) (a) Grzyb, J. A.; Shen, M.; Ishii, Y.; Chi, W.; Brown, R. S.; Batey, R. A. *Tetrahedron* **2005**, *61*, 7153. (b) Review on carbamate preparation: Chaturvedi, D. *Curr. Org. Chem.* 2011, *15*, 1593

(9) (a) *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley: Chichester, 2005; Vol. 2, pp 1006–1010. (b) NMR of CDI in D_2O shaw complete decomposition of CDI at 0 °C in 10 min.

(10) Sharma, R. K.; Jain, R. *Synlett* **2007**, 603.

(11) Verma, S. K.; Ghorpade, R.; Pratap, A.; Kaushik, M. P. *Tetrahedron Lett.* **2012**, *53*, 2373.

further substitution to yield symmetric urea at low temperatures. Carbonylimidazolides obtained from secondary amines are very stable and does not react further to give urea, carbamate, or thiocarbamate. The method is therefore not suitable for the preparation of tetrasubstituted ureas, and carbamates or thiocarbamates derived from secondary amines. Adamantylamine under similar conditions does not react with CDI to yield any product.

In water, hydrogen bonding of imidazole rings and the carbonyl group of CDI with a water molecule makes the carbonyl carbon highly electrophilic. Electron densities in imidazole rings are reduced because of H-bonding, thereby increasing the nucleofugality of the imidazole group. In addition to this, the nucleophilic reactivity of amine is very high in water compared to organic solvents.[12] These together explain the very high reaction rate of amine with CDI in water as compared to the rate of decomposition of CDI in water due to the nucleophilic attack by the water molecule.

Carbonylimidazolide derived from the primary amine reacts in situ with a nucleophile such as phenol, thiophenol, and amine to give the corresponding carbamate (Table 3), thiocarbamate (Table 3), and urea (Table 4). Alcohols, thiols, and electron-deficient amines such as nitrobenzene do not react with carbonylimidazolide under similar conditions.

In summary, we have developed an "in water" imidazolecarbonylation reaction that provides a highly efficient and general method for preparing ureas, carbamates, and thiocarbamates, which essentially removes the usage of anhydrous solvent and an inert atmosphere. The product precipitates out from the reaction mixture and can be obtained in high purity by filtration, making the method simple and scalable. Water is an inexpensive, nontoxic, and environmentally benign solvent. In addition, unique reactivities observed in water can be regarded as a paradigm shift where highly moisture sensitive reagent 1,1′-carbonyldiimidazole undergoes "in water" reaction. The results discussed are unprecedented and add value to the current knowledge of organic reactions in water.

Supporting Information Available. Experimental procedure and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] Brotzel, F.; Chu, Y. C.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 3679.

The authors declare no competing financial interest.