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Synthesis of α-amino acid derivatives and amines *via* activation of simple alkyl halides by zinc in water

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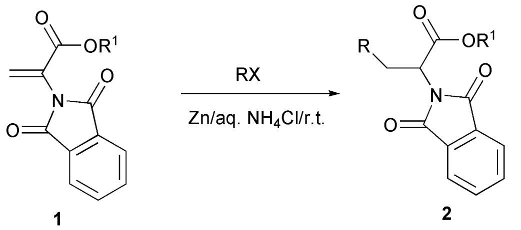
A method for the synthesis of α-amino acid derivatives and amines is developed *via* a zinc-mediated conjugate addition reaction of alkyl halides to α-phthalimidoacrylate derivatives and nucleophilic addition to imines in the presence of NH_4Cl in water. No reaction was observed in the absence of water.

Amino acids and amines are the fundamental building blocks of peptides and proteins and their physiological importance ensures a sustained interest in their chemistry.[1] Synthesis of α-amino acids *via* displacement reactions on α-halo acids, the Strecker synthesis, *via* hydantoins and *via* oxazolones have played key roles in the early days of amino acid chemistry.[2] The Petasis boronic acid method,[3] the Alper double carbonylation method,[4] Lewis acid catalyzed imine additions,[5] and the catalytic hydrogenation of amino acrylates[6] are among the recent methods developed for the synthesis of α-amino acids.

Currently, there is a wide interest in searching for alternative media and processes for chemical and organic synthesis. As a result of the natural abundance of water as well as the inherent advantages of using water as a solvent, interest has been growing in studying organic reactions in water.[7] Recently, we have developed a novel synthesis of α-amino acids *via* rhodium-catalyzed conjugate addition of electron-deficient α-aminoacrylates with organotin,[8a] organoboron,[8b] organosilane[8c] and organobismuth[8a] reagents under ambient conditions of air and water. However, these reagents are limited to aryl and vinyl derivatives. Although the metal-mediated C–X bond activation of allyl and aryl halides in aqueous media has been studied relatively intensively during the past decade, few efforts have been made to activate the C–X bond of alkyl halides by a metal in water because of the instability of alkyl organometallic reagents towards water. For a long time, we have been intrigued by the possibility of activating the C–X bond of alkyl halides by using a simple metal in water. The study would possibly extend the scope of aqueous metal reactions. However, in view of the high reactivity of alkyl organometallic reagents toward water, it is doubtful that metal could be used for such a purpose. Herein, we wish to report that the C–X bond activation of simple alkyl halides can be carried out with zinc powder in aqueous NH_4Cl, which leads to a novel synthesis of α-amino acid derivatives **2** *via* conjugate addition[9] to α-aminoacrylates **1** (eqn. (1)).



1 **2** (1)

Electron-deficient α-phthalimidoacrylate derivatives[8a] were selected because of their stability in water and enhanced reactivity towards nucleophiles. When ethyl α-phthalimidoacrylate was stirred with 2-iodopropane (3 equivalents) and zinc powder (6 equivalents, < 10 μm, 98+%) at room temperature in water, the desired conjugate addition product was isolated in 22% yield. An attempt to improve the addition yield by changing the temperature was not successful. However, when the reaction was carried out in (acidic) aqueous ammonium chloride solution, the yield of the desired addition product was improved to some extent. The concentration of ammonium chloride in water was found to have a significant effect on the yield and rate of the reaction (Table 1). In saturated NH_4Cl aqueous solution, a quantitative yield of the Michael adduct was obtained only after 4 h at room temperature. It is important to mention that no reaction actually occurred between the acrylate and 2-iodopropane without water in dry organic solvents including CH_2Cl_2, dioxane, or a protic solvent such as methanol. These results indicated that water, as the solvent, played a key role in promoting the reaction.[10] Using indium instead of zinc gave a moderate yield of the adduct in water, whereas InCl-mediated conjugate addition[11] of 2-iodopropane to ethyl α-phthalimidoacrylate afforded an 85% yield of the desired product. No reaction was observed with other metals such as tin, bismuth, samarium, magnesium or nickel in either water or saturated aqueous NH_4Cl solution. The use of surfactant, SDS, improved the yield of the desired product slightly.

Subsequently, various alkyl halides were examined in saturated aqueous NH_4Cl solution, and the results are listed in Table 2. Both secondary and tertiary alkyl groups such as linear (2-butyl, 2-propyl, 2-pentyl), cyclic (cyclohexyl, cyclopentyl, cycloheptyl), and bulky ones (*tert*-butyl) were all transferred to the substrate successfully. It should be noted that even simple primary iodides (entries 17–19) and methyl iodide (entry 20) provided the desired products in good yields, which opens the door for a variety of metal-mediated C–C bond formations in water. As expected, alkyl iodides provided a much higher yield

Table 1 Effect of reaction conditions[a]

Entry	Reaction conditions	Yield[b] (%)
1	*i*-PrI/In/H_2O + MeOH (2 : 1)/12 h	63
2	*i*-PrI/In/H_2O/12 h	63
3	*i*-PrI/In/H_2O/SDS/4 h	18
4	*i*-PrI/In/H_2O/SDS/12 h	73
5	*i*-PrI/Zn/H_2O/4 h	Trace (22)[c]
6	*i*-PrI/Zn/0.1 M aq. NH_4Cl/4 h	6
7	*i*-PrI/Zn/0.4 M aq. NH_4Cl/4 h	35
8	*i*-PrI/Zn/0.8 M aq. NH_4Cl/4 h	65
9	*i*-PrI/Zn/sat. aq. NH_4Cl/4 h	93
10	*i*-PrI/Sn/H_2O/12 h	0 (0)[c]
11	*i*-PrI/Mg/H_2O/12 h	0 (0)[d]
12	*i*-PrI/Bi/H_2O/12 h	0 (0)[d]
13	*i*-PrI/Sm/H_2O/12 h	0 (0)[d]
14	*i*-PrI/Mn(Cu)/H_2O/12 h	0 (0)[d]
15	*i*-PrI/InCl/H_2O/12 h	81
16	*i*-PrI/Ni/H_2O/12 h	0
17	*i*-PrI/Zn/CH_2Cl_2/12 h	0
18	*i*-PrI/Zn/MeOH/12 h	Trace
19	*i*-PrI/Zn/dioxane/12 h	0

[a] These reactions were performed at room temperature. [b] Isolated yields. [c] The reaction was run over 4 days. [d] Saturated aqueous NH_4Cl solution was used instead of water.

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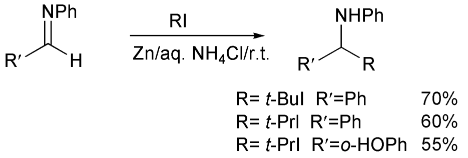
Table 2 Synthesis of α-amino acid derivatives *via* the C–X activation of alkyl halide

Entry	RX	R$_1$	Method	Yield[a] (%)
1	2-Iodobutane	Et	A	94
2	2-Iodobutane	Et	B	69
3	2-Iodobutane	Et	C	81
4	2-Iodo-2-methylpropane	Et	A	86
5	2-Iodo-2-methylpropane	Et	B	57
6	2-Iodo-2-methylpropane	Et	C	72
7	1-Iodocyclohexane	Et	A	96
8	1-Iodocyclohexane	Et	B	61
9	1-Iodocyclohexane	Et	C	79
10	1-Iodocyclopentane	Et	A	97
11	1-Iodocyclopentane	Et	B	65
12	1-Iodocyclopentane	Et	C	81
13	2-Iodopropane	Et	A	93
14	2-Bromopropane	Et	A	47
15	1-Iodocycloheptane	Et	A	62
16	1-Iodocyclopentane	Me	A	85
17	1-Iodobutane	Me	A	47
18	1-Iodopentane	Me	A	49
19	1-Iodohexane	Me	A	51
20	Iodomethane	Me	A	31

Conditions: A: zinc was used; B: indium was used; C: InCl was used instead of zinc or indium metals.[a] Isolated yields.

of the adduct than the corresponding alkyl bromides, which is consistent with the relative reactivities of organic halides. An attempt to transfer the seemingly more reactive benzyl group to the substrate did not succeed. The reason for this failure is still not clear.

In addition to the conjugate additions, the method was also successful for imine additions, which generated amines in water



(2)

A tentative mechanism for the reaction involves activation of the C–X bond in an alkyl halide to generate an alkylzinc species, and a subsequent conjugate addition of the resulting alkylzinc reagent to α-phthalimidoacrylate derivatives or nucleophilic addition to imines in water. However, an alternative mechanism involving a single-electron transfer (SET)[12] process could not be excluded.

In conclusion, a method for the synthesis of natural and unnatural α-amino acid derivatives and amines has been developed *via* a zinc-mediated conjugate addition of alkyl halides to α-aminoacrylates and nucleophilic addition to imines in the presence of NH$_4$Cl in water. The reaction did not proceed in the absence of water. The current reaction of transfering an alkyl group to α-phthalimido acrylates also complements our previous work on α-amino acids *via* the conjugate addition of (vinyl) aryl–metal reagents catalyzed by rhodium.[8] The scope (such as asymmetric synthesis), mechanism, and synthetic applications of this reaction are currently under investigation.

A typical experimental procedure is as follows: a suspension of α-phthalimidoacrylate (0.25 mmol), organic halide (0.75 mmol) and zinc powder (98 mg, 1.5 mmol) in 3 mL of aqueous saturated NH$_4$Cl aq. solution was stirred for 3–12 h at room temperature. After the reaction was completed (monitored by TLC), 15 mL of ethyl acetate was added. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (15 mL), dried over MgSO$_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (eluent: hexane–EtOAc = 10 : 1).

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Notes and references

1 *Chemistry and Biochemistry of the Amino Acids*, ed. G. C. Barrett, Chapman & Hall, London, 1985.

2 (*a*) R. M. Williams, in *Organic Chemistry Series, Volume 7: Synthesis of Optically Active α-Amino Acids*, ed. J. E. Baldwin, P. D. Magnus, Pergamon Press, Oxford, 1989; (*b*) O. R. Duthaler, *Tetrahedron*, 1994, **50**, 1539; (*c*) H. Kunz, in *Stereoselective Synthesis*, ed. G. Helmechen, R. W. Hoffmann, J. Mulzer and E. Schaumann, Georg Theime Verlag, Stuttgart, 1995, **vol. E21b**, 1931; (*d*) J. K. Whitesell, *Acc. Chem. Res*, 1985, **18**, 280 and references therein.

3 (*a*) N. A. Petasis and I. A. Zavialov, *J. Am. Chem. Soc.*, 1997, **119**, 445; (*b*) N. A. Petasis and I. A. Zavialov, *J. Am. Chem. Soc.*, 1998, **120**, 11798.

4 Y. S. Li and H. Alper, *Angew. Chem., Int. Ed.*, 2001, **40**, 779.

5 M. J. O'Donnell and W. D. Bennett, *Tetrahedron*, 1988, **44**, 5489.

6 (*a*) M. J. Burk, *Chemtracts: Org. Chem.*, 1998, **11**, 787; (*b*) M. T. Reetz and G. Mehler, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 3889; (*c*) M. van den Berg, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.*, 2000, **122**, 11539.

7 (*a*) C. J. Li and T. H. Chan, *Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, 1997; (*b*) *Organic Synthesis in Water*, ed. P. A. Grieco, Blackie Academic & Professional, Glasgow, 1998.

8 (*a*) T. S. Huang and C. J. Li, *Org. Lett.*, 2001, **3**, 2037; (*b*) T. V. Nguyen and C. J. Li, unpublished results (*c*) T. S. Huang and C. J. Li, *Chem. Commun.*, 2001, **22**, 2348.

9 For a zinc–copper couple mediated conjugate addition, see: (*a*) M. Roth, W. Damm and B. Giese, *Tetrahedron Lett*, 1996, **37**, 351; (*b*) C. Petrier, C. Dupuy and J. L. Luche, *Tetrahedron Lett.*, 1986, **27**, 3149.

10 For a review of water-promoted reactions, see: S. Ribe and P. Wipf, *Chem. Commun.*, 2001, 299.

11 Very recently, Naito reported an indium-mediated alkyl addition to C=N and C=C bonds in aqueous methanol. See: H. Miyabe, M. Ueda, A. Nishimura and T. Naito, *Org. Lett.*, 2002, **4**, 131.

12 T. H. Chan, *Pure Appl. Chem.*, 1996, **52**, 5643.