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Arginine- or Lysine-catalyzed Michael Addition of Nitromethane to α,β-Unsaturated Ketones in Aqueous Media

Seongsoon Park

Department of Chemistry, Center for NanoBio Applied Technology, Institute of Basic Sciences, Sungshin Women's University, Seoul 142-732, Korea. E-mail: spark@sungshin.ac.kr
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"Green catalysts" are garnering much more interest because of increasing environmental concerns. One of the requirements for the "green catalysts" is harmlessness to living systems and decomposability in nature. For this, amino acids are the best candidate because amino acids are natural components of living systems as well as bio-degradable materials.[1] Recently, it has been discovered that amino acids can catalyze numerous reactions including the aldol reaction, the Mannich reaction, an α-amination, an α-aminoxylation, the Diels Alder reaction, and an asymmetric conjugate addition.[2] Besides, the salts of proline or modified amino acids exhibit catalytic activities towards Michael addition of nitroalkanes to enones or enals.[3] The products of Michael addition of nitroalkanes provide a variety of key building blocks for various compounds, such as an amine, ketone, alkane, and alkene.[4]

The most widely studied amino acid as a catalyst is proline. The reaction mechanisms of the proline-catalyzed reactions with carbonyl compounds are mainly involved in the initial formation of imine (or iminium ion) and then conversion to enanmine.[5] Such activation process of carbonyl substrates can be employed to other types of reactions. For instance, our group recently reported that a basic amino acid can catalyze the epoxidation of α,β-unsaturated ketone with hydrogen peroxide.[6] Sixteen amino acids were screened but only three basic amino acids, such as arginine, histidine, and lysine, catalyzed the epoxidation. The basic amino acids presumably have a dual role such as a base to abstract a proton from hydrogen peroxide and an activator of the carbonyl group through imine formation. More critical role of such basic amino acids in the epoxidation is the subtraction of a proton from hydrogen peroxide to provide an activated nucleophile, hydrogen peroxide anion, because the other amino acids including proline did not show the catalytic activity towards the epoxidation. The amino acids that exhibited the highest activity were arginine and lysine. The amino acids possess similar pK_a (12.5 and 10.8, respectively) to that of hydrogen peroxide (pK_a = 11.6).[7,8] Based on the previous results, it can be hypothesized that the basic amino acids may catalyze the other type of reactions involved in nucleophiles possessing similar pK_a. For example, nitromethane possesses similar pK_a (*i.e.* 10.2) to those of arginine and lysine, and thus nitromethane can be deprotonated by the amino acids and utilized as a nucleophile to react with α,β-unsaturated ketone.

Table 1. Screening amino acids as a catalyst in the Michael addition of cyclohex-2-enone[a]

Entry	Amino acid	Time (h)	Conversion (Yield)[b]	Ratio of **1** to **2** (**1** : **2**)[c]
1	not added	48	n.d.[d]	n.d.
2	Arginine	48	94% (86%)	1.0 : 1
3	Histidine	48	48% (21%)	7.4 : 1
4	Lysine	48	97% (73%)	0.90 : 1

[a]Reaction conditions: cyclohex-2-enone (0.5 mmol, 48 μL), amino acid (0.05 mmol), CH_3NO_2 (2.5 mmol, 134.5 μL), *t*-amyl alcohol (5.5 μL, internal standard), water (1,812 μL), 25 °C. [b]The conversions were determined by GC. The values in parentheses refer to the isolated yields. The yields were calculated based on the total amount of **1** and **2**. Only racemic products were obtained, although L-amino acids were used for the screening. [c]The ratios were determined by NMR. [d]n.d. = not detected.

In the current study, the hypothesis is explored in Michael addition of nitromethane to α,β-unsaturated ketones. Although the salts or modified forms of amino acids with an assistance of a base can perform the Michael addition of nitroalkane, the free-amino-acid-catalyzed Michael addition with nitroalkane has rarely been studied.[9] The direct use of unmodified amino acids as a catalyst provides benefits in economical and environmental concerns. Cyclohex-2-enone and nitromethane were chosen as model substrates, although it has been reported that nitromethane exhibited poor activity in the proline-salt-catalyzed Michael addition in organic solvents.[3] In addition, water was selected as the reaction media because water is regarded as the best solvent for "green technology" and the pK_a of a compound generally increases in organic solvents. It has been assumed that maintaining pK_a is an important factor to activate the nucleophile by the abstraction of a proton. Thus, water could be a superior medium over organic solvents in the current approach.

First, L-amino acids were screened towards the Michael addition of cyclohex-2-enone with nitromethane (5 eq.) in water (Table 1). Sixteen amino acids were chosen for screening because the other four amino acids (*i.e.* tryptophan, tyrosine, glutamic acid, and aspartic acid) exhibit poor aqueous solubility.[6] Cyclohex-2-enone (250 mM), amino acid (25 mM), nitromethane (1,250 mM), and *t*-amyl alcohol (internal

Table 2. Effect of the varied amounts of nitromethane on the ratio of the products[a]

Nitro-methane (equiv.)	Time (h)	Conversion		Ratio of **1** to **2** (1 : 2)	
		Arginine	Lysine	Arginine	Lysine
1	24	50%	60%	8.0 : 1	6.0 : 1
1.1	24	52%	62%	5.2 : 1	5.5 : 1
1.5	24	60%	67%	3.5 : 1	3.4 : 1
2	24	64%	71%	3.0 : 1	2.6 : 1
3	24	68%	77%	1.9 : 1	1.6 : 1
5	24	84%	87%	1.1 : 1	1.0 : 1

[a]Reaction conditions: identical to the method in Table 1 except reducing the reaction time (24 h) and using varied amount of nitromethane.

standard, 25 mM) were mixed and stirred at 25 °C for 48 h in water (2 mL). The reactions were monitored by gas chromatography and the reaction conversions were calculated by comparing a decrease of the integration area of cyclohex-2-enone with that of the internal standard. The reaction without any amino acids did not produce the product compound. Among sixteen amino acids, three basic amino acids (*i.e.*, arginine, histidine, and lysine) converted cyclohex-2-enone to the products including 3-(nitromethyl)cyclohexanone (**1**). The reactions by arginine and lysine showed 94% and 97% conversion, respectively, while the conversion by histidine is only 48%. Probably, arginine or lysine abstracts a proton more easily from nitromethane due to their higher pK_a than that of histidine. Unlike the basic amino acids, proline, which is the most commonly used amino acid as a catalyst, did not convert cyclohex-2-enone to the product compound in the current reaction condition. Probably, the nitrogen atom of proline is protonated by a proton from the carboxyl group at neutral pH and it is probably difficult to form an initial iminium ion to activate the carbonyl group or work as a base to subtract a proton from nitromethane. Therefore, the salt form of proline or an addition of a base is mostly used for Michael addition. In contrast, those basic amino acids possess a basic side chain, and the side chain can presumably take a proton from the carboxyl group. Therefore, no protonation occurs on the nitrogen atom at α-position. The unprotonated

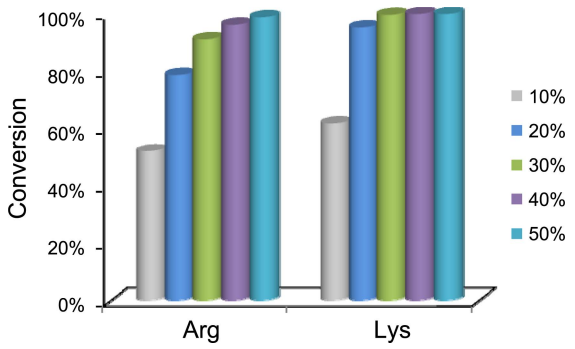


Figure 1. The effect of the varied amount of amino acid. The reaction condition is identical to that in the Table 1 but a slightly excess amount of nitromethane (1.1 eq.) was used. The reactions were performed for 24 h. The ratios of the products (**1** : **2**) were obtained as 5-7 : 1.

nitrogen atom is now free to form the initial imine intermediate and can also work as a base for activation of nitromethane. For further studies, arginine- and lysine-catalyzed reactions were investigated because the histidine-catalyzed reaction exhibited the lowest conversion.

After the reaction mixtures were extracted with MTBE (*t*-butyl methyl ether), a detailed analysis of the products exhibited that a considerable amount of an unexpected by-product, 1,3-bis(nitromethyl)cyclohexanol (**2**), was formed. The by-product was formed from a successive nitro-aldol reaction of the Michael-addition product because an excess amount of nitromethane was used. To identify the effect of the amount of nitromethane used on the formation of the by-product, a series of reactions using varied amount of nitromethane were performed. Table 2 shows that the formation of the by-product (**2**) increased with the improvement of the reaction conversion according to the addition of more amount of nitromethane. Utilizing equivalent or 1.1-fold amount of nitromethane exhibited the highest selectivity to the Michael addition product (5.2-8 : 1), although those reaction conditions provided lower reaction conversions. For reaction completion, the reaction condition using 1.1-fold excess amount of nitromethane was employed for further investigation. To accelerate the reaction, the effect of the varied amount of amino acids on the reaction was examined. As a typical catalytic reaction, increase of the amount of the amino acid accelerated the reaction (Figure 1). When 50% of arginine or lysine was used, the reaction conversions reached 99% or > 99% for 24 h, respectively. The use of 50% amino acid of arginine or lysine was decided for the further investigation because utilizing a large amount of amino acids did not increase the reaction cost much.

Although the solubility of cyclohex-2-enone is high enough to be homogenous in water, many substrates are less or not soluble in water. Thus, particular co-solvents may be required to dissolve such insoluble substrates. We examined four water-miscible solvents, such as acetonitrile, ethanol, 2-propanol, and THF, in the current reaction system (Table 3). The co-solvents (1 mL) were added to the reaction mixture instead of the same volume of water. Interestingly, the highest but little lower conversion (94%) compared to that in water was obtained from the reactions in more polar solvents, such as ethanol or 2-propanol,[10] for arginine-catalyzed reactions, while all four lysine-catalyzed reactions reached 99%

Table 3. Effect of co-solvent on the amino-acid-catalyzed Michael addition[a]

Entry	Co-solvent	Time (h)	Conversion	
			Arginine	Lysine
1	Acetonitrile	24	79%	> 99%
2	Ethanol	24	94%	> 99%
3	2-Propanol	24	94%	> 99%
4	THF	24	87%	> 99%

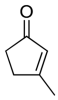
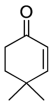
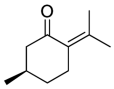
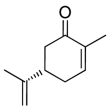
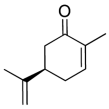
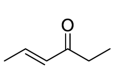
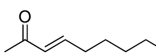
[a]Reaction conditions: cyclohex-2-enone (0.5 mmol, 48 μL), amino acid (0.25 mmol), CH_3NO_2 (0.55 mmol, 30 μL), *t*-amyl alcohol (5.5 μL, internal standard), water (916.5 μL), co-solvent (1 mL), 25 °C.

conversion for 24 h. More polar solvents probably maintain near the pK_a of a compound and thus nitromethane is more easily deprotonated to be an activated form in alcohols. Although, the conversions are similar in both reactions in ethanol and 2-propanol, ethanol was chosen as a co-solvent for further investigation because it has been reported that ethanol is more polar and less toxic than 2-propanol.[11]

The optimized current reaction condition was employed to the reactions with a series of substrates including smaller sized (entries 1-3 in Table 2), structurally similar (entries 4-7), bulkier (entries 8-10), and linear compounds (entries 11-14). Arginine and lysine were only utilized as a catalyst. The compounds (entries 5, 6, 8-10, 13, and 14) are water-insoluble, and thus ethanol was added as a co-solvent, which makes the reaction mixture homogeneous (Table 3). Cyclopent-2-enone (entry 1) is water soluble and smaller sized than cyclohex-2-enone. The reaction with cyclopent-2-enone exhibited similar reaction conversion to that with cyclohex-2-enone: reached > 99% for 24 h. Structurally similar substrates (entries 3, 5, and 6) possessing methyl group on the α- or γ-positions exhibited moderate to high reaction conversions (40-81%), while the cases with substrates (entries 2, 4, and 7) possessing methyl group on the reaction center (*i.e.* the β-position) exhibited low to moderate reaction conversions (0-50%). Especially, the reaction with 3,5,5-trimethylcyclohex-2-enone (entry 7) did not proceed. Perhaps, three substituents including one at the reaction center hinder the approach of the amino acid to form an imine intermediate or the approach of the nucleophile. In addition, the reaction towards one of the bulkier substrates did not occur either (pulegone, entry 8). Pulegone possesses non-parallel electro-configuration of π-electrons of the double bond to π-electrons of the carbonyl group. Presumably, the non-parallel π-electrons of the carbonyl group cannot assist the activation of the double bond to proceed the reaction. Unlike these substrates, the reactions with carvone (2-methyl-5-(prop-1-en-2-yl)cyclohex-2-enone, entries 9 and 10) occurred, although the reaction conversions are lower (18-29%). Linear substrates (entries 10-14) were converted to the corresponding products with moderate to high conversions (45-91%).

In summary, it has been demonstrated that basic amino acids, such as arginine and lysine, catalyze the Michael addition of nitromethane to α,β-unsaturated ketones. The reaction is presumably initiated through an abstraction of a proton from nitromethane by the basic amino acid. The higher pK_a of arginine and lysine than that of the other amino acids provides a suitable power to abstract a proton from nitromethane. In addition, the substrate investigation exhibited that steric hindrance of substituents and parallel electro-configuration between π-electrons of the carbonyl group and the double bond are important factors for the reaction to proceed.

Table 4. Amino-acid-catalyzed Michael addition of nitromethane to α,β-unsaturated ketones[a]

Entry	Substrate	Amino acid	Time (h)	Conversion (yield)[b]	
				Method A	Method B
1		Arginine	24	>99% (86%)	
		Lysine	24	>99% (82%)	
2		Arginine	48	21%	
		Lysine	48	28%	
3		Arginine	48	79% (39%)	
		Lysine	48	81% (77%)	
4		Arginine	48	30% (24%)	
		Lysine	48	50% (30%)	
5		Arginine	48		61% (57%)
		Lysine	48		80% (73%)
6		Arginine	48	40% (25%)	
		Lysine	48	45% (37%)	
7		Lysine	48		nr
		Arginine	48		nr
8		Arginine	48		nr
		Lysine	48		nr
9		Arginine	48		24% (13%)
		Lysine	48		28% (24%)
10		Arginine	48		18% (16%)
		Lysine	48		29% (23%)
11		Arginine	48	53% (10%)	
		Lysine	48	89% (16%)	
12		Arginine	48	45% (41%)	
		Lysine	48	48% (27%)	
13		Arginine	48		83% (76%)
		Lysine	48		86% (61%)
14		Arginine	48		82% (62%)
		Lysine	48		91% (49%)

[a]Reaction conditions: See the detailed method in the experimental section. [b]The yields were calculated from the amount of the Michael-addition product isolated.

Experimental

A General Method for Michael Addition with Cyclohex-2-enone.

Method A: In a 4-mL vial, cyclohex-2-enone (0.5 mmol, 48 μL), internal standard (*t*-amyl alcohol, 0.05 mmol, 5.5 μL), amino acid (625 μL of 400 mM), nitromethane (0.55 mmol, 30 μL) were added in water (1311.5 μL). The reaction mixture was stirred at 25 °C. After 24 or 48 h, the reaction mixture (100 μL) was retrieved and extracted with MTBE (1 mL). The MTBE layer was analyzed by gas chromatography.

Method B: In a 4-mL vial, cyclohex-2-enone (0.5 mmol, 48 μL), internal standard (*t*-amyl alcohol, 0.05 mmol, 5.5 μL), amino acid (625 μL of 400 mM), nitromethane (0.55 mmol, 30 μL) were added in water (311.5 μL). After addition of ethanol (1 mL), the reaction mixture was stirred at 25

°C. After 24 or 48 h, the reaction mixture (100 μL) was retrieved and extracted with MTBE (1 mL). The organic layer was analyzed by gas chromatography.

For purification of the products, first the reaction was quenched by an addition of a HCl solution (1 M, 50 μL), and the reaction mixture was saturated with sodium chloride. Then, reaction mixture was extracted several times with ethyl acetate (9 mL) until no products found in the water layer by TLC. The organic layers were combined and dried over anhydrous Na_2SO_4. The product was purified by preparative TLC (ethyl acetate : hexane = 1 : 3). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40-4.33 (dd, 2H), 2.68-2.65 (m, 1H), 2.53-2.45 (m, 2H), 2.34-2.27 (m, 1H), 2.21-2.11 (m, 2H), 2.05-1.99 (m, 1H), 1.77-1.73 (m, 1H), 1.59-1.48 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.36, 80.28, 44.71, 41.10, 37.44, 28.5, 24.44; MS (EI): *m/z* 157 (M^+).

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