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A tandem Aldol condensation/dehydration co-catalyzed by acylase and *N*-heterocyclic compounds in organic media

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ABSTRACT

A tandem Aldol condensation/dehydration of aldehydes and ketones could be performed under D-aminoacylase and *N*-heterocyclic compounds used as co-catalyst in organic media. Some control experiments have been designed to demonstrate that either acylase or *N*-heterocyclic compounds could not catalyze the tandem reaction. The acylase showed the highest activity in the presence of imidazole and has been used to catalyze the tandem Aldol condensation/dehydration between different aldehydes and ketones. This method has provided a new strategy to perform the tandem Aldol condensation/dehydration and expanded the application of biocatalysts.

1. Introduction

Biocatalytic promiscuity focuses on the enzyme catalytic activities with unnatural substrates and alternative chemical transformations [1a–f]. To the best of our knowledge, several hydrolase-catalyzed basic reactions, such as Aldol condensation [2a–c], Mannich reaction [3], Michael additions [4a–c], Markovnikov additions [5a–c] and Henry reactions [6a–b], have been reported. Furthermore, a new area was established that using the single-enzyme catalyzed tandem reactions base on the multifunction of enzyme. Lipase could catalyze domino kinetic resolution/intramolecular Diels–Alder reactions [7a–b]. Klaas et al. have reported a combined multistep process of deprotection, acetylation and epoxidation catalyzed by CAL-B [8]. Our group has reported the two-step enzymatic synthesis of *N*-substituted imidazole derivatives containing glucose mediated by protease [9] and one-pot synthesis of pyrimidine-saccharide complexes catalyzed by D-aminoacylase [10]. Several methods have been reported to improve the performance of enzymes in organic solvent. Additives are quite simple and nearly universally scalable technique. For example, adding *N*-methylimidazole caused a significant activation of the lipase acrylic resin from *Candida antarctica* (CAL B) in acylation [11]. Methyl-β-cyclodextrin improved the activity and enantioselectivity of subtilisin [12]. Sodium dodecyl sulfate showed influence on lipase MY catalyzed the hydrolysis of ester [13]. The group of Itoh used ionic liquid to enhance enantioselectivity of lipase [14].

Claisen–Schmidt condensation was thought to be a classical method to prepare α, β-unsaturated ketones from aromatic aldehydes and aliphatic ketones [15]. The products of Claisen–Schmidt were useful intermediates for further transformations, such as Diels–Alder reactions, Stetter reactions, Michael additions, Baylis–Hillman reactions, Juliaĭ–Colonna epoxidations and Robinson annulations. The traditional methods employed a relatively strong base such as metal hydroxide or metal alkoxide, but these methods suffered from several side reactions and the narrow substrate diversity [16]. The heterogeneous catalysts have also been used for the Claisen–Schmidt condensation, including L-proline – TEA [17], $H_3PW_{12}O_{40}/SiO_2$ [18], ionic liquids [19–20], $Zr(HSO_4)_4/SiO_2$ [21], micrometer-sized nanostructured magnesium oxide [22]. However these methods always used toxic catalysts and an excess of solvent.

In this paper, a tandem Aldol condensation/dehydration of aldehydes and ketones catalyzed by D-aminoacylase and *N*-heterocyclic compounds in organic media has been discovered. A novel and effective approach to achieve tandem Aldol condensation/dehydration was established (Scheme 1). After optimization of the stepwise process, a number of α, β-unsaturated ketones were successfully synthesized.

2. Experimental

^{1}H spectra were recorded on a Bruker AVANCE DMX-400 spectrometer at 400 MHz, respectively. Chemical shifts are reported

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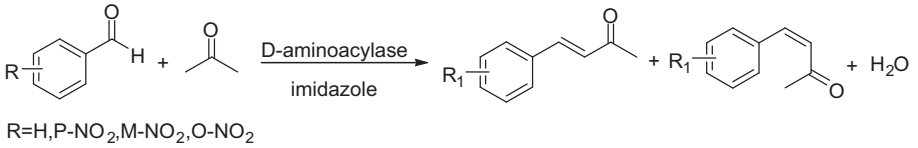


Scheme 1. D-aminoacylase and imidazole co-catalyzed tandem Aldol condensation/dehydration between ketones and aldehydes.

in ppm (δ), relative to the internal standard of tetramethylsilane (TMS). IR spectra were measured with a Nicolet Nexus FTIR 670 spectrophotometer. HPLC was carried out using a Agilent 1100 series column (methanol/water = 32/68, 1.0 ml/min and 274 nm). D-aminoacylase from *Escherichia coli* (DA), acylase "Amano" from *Aspergillus oryzae* (AA) and lipase from acrylic resin from *Candida antarctica* (CAL B) were purchased from Amano Enzyme Inc. (Japan). Bovine serum albumin (BSA) was obtained from Wuxi Enzyme Co. Ltd., Wuxi, PR China. Lipase from *Candida cylindracea* (CCL) and lipase from *Mucor jiavanicus* (MJL) and lipozyme immobilized from *Mucor miehei* (MML) were purchased from Fluka. All chemicals were obtained from commercial suppliers. For all reactions dry (molecular sieve), analytical grade solvents were used. Solvents for column chromatography were not distilled before use.

2.1. General procedure for the Claisen–Schmidt reaction of 4-nitrobenzaldehyde and acetone

A suspension of 4-nitrobenzaldehyde (100 mg), imidazole (50 mg), acetone (1.5 ml) and D-aminoacylase 100 mg in octane (10 ml) was incubated at 50 °C and 200 r.p.m. (orbitally shaken) for 48 h. Then, solvent was evaporated under vacuum to dryness. The crude residue was purified by flash column chromatography on silica gel using petroleum/ethylacetate mixtures. Product-containing fractions were combined, concentrated, and dried to give 1. All the compounds were spectroscopically characterized (IR, ^{1}H NMR).

2.1.1. (3E)-4-(4-nitrophenyl)-3-buten-2-one [23]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 8.8 Hz, 2H), 7.68 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 16.0 Hz, 1H), 6.81 (d, J = 16.4 Hz, 1H), 2.41 (s, 3H); IR (neat): 1677, 1612, 1525, 1346, 974.

2.1.2. (3E)-4-(3-nitrophenyl)-3-buten-2-one [23]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.0 Hz, 1H), 7.84 (s, 1H), 7.34 (t, J = 16.0, 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 4.38 (d, J = 6.0 Hz, 1H), 4.02 (d, J = 6.4 Hz, 1H), 2.43 (s, 3H); IR (neat): 1660, 1615, 1354.

2.1.3. (3E)-4-(2-nitrophenyl)-3-buten-2-one [24]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 16.0, 8.0 Hz, 1H), 7.44 (t, J = 16.0, 8.0 Hz, 1H), 5.68 (d, J = 9.6 Hz, 1H), 3.12 (d, J = 9.6 Hz, 1H), 2.24 (s, 3H); IR (neat): 1677, 1612, 1525, 1346.

2.1.4. (3E)-4-phenyl-3-buten-2-one [24]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 16.0 Hz, 2H), 7.51 (d, J = 16.0 Hz, 1H), 7.39 (t, J = 6.4, 3.2 Hz, 3H), 6.71 (d, J = 16.0 Hz, 1H), 2.38 (s, 3H); IR (neat): 1659, 1616, 1354, 761, 694.

2.1.5. (3E)-4-(4-chlorophenyl)-3-buten-2-one [23]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 16.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 6.67 (d, J = 16.0 Hz, 1H), 2.36 (s, 3H); IR (neat): 1652, 1626, 1341, 826.

2.1.6. (3E)-4-(3-chlorophenyl)-3-buten-2-one [25]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.42 (d, J = 16.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.34 (t, J = 16.0, 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 16.0 Hz, 1H), 2.37 (s, 3H); IR (neat): 1671, 1613, 1359, 983.

2.1.7. (3E)-4-(2-chlorophenyl)-3-buten-2-one [23]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (t, J = 8.8, 4.4 Hz, 1H), 7.48 (t, J = 8.8, 4.4 Hz, 1H), 7.46 (d, J = 16.4 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.59 (d, J = 16.4 Hz, 1H), 2.35 (s, 3H); IR (neat): 1673, 1609, 1359, 975.

2.1.8. (3E)-4-(4-hydroxylphenyl)-3-buten-2-one [28]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.53 (d, J = 16.0 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H) 6.61 (d, J = 16.4 Hz, 1H), 2.40 (s, 3H); IR (neat): 3150, 1666, 1629, 1364, 971.

2.1.9. (3E)-4-(3-hydroxylphenyl)-3-buten-2-one [27]

^{1}H NMR (400 MHz, $CDCl_3$) δ7.65 (s, 1H), 7.47 (d, J = 16.0 Hz, 1H), 7.24 (t, J = 8.0, 15.6, 7.6 Hz, 1H), 7.05-7.08 (m, 2H), 6.95 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 16.0 Hz, 1H), 2.39 (s, 3H); IR (neat): 3170, 1645, 1615, 1356, 997.

2.1.10. (3E)-4-(2-hydroxyphenyl)-3-buten-2-one [28]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 16.8 Hz, 1H), 7.72 (s, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.26 (t, J = 8.8, 4.4 Hz, 1H), 7.02 (d, J = 16.0 Hz, 1H), 6.94 (t, J = 7.6, 14.8, 7.2 Hz, 2H), 2.43 (s, 3H); IR (neat): 3358, 1673, 1619, 1356, 972.

2.1.11. (3E)-4-(4-methoxyphenyl)-3-buten-2-one [24]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 16.4 Hz, 1H), 6.90 (d, J = 8.0 Hz, 2H), 6.59 (d, J = 16.4 Hz, 1H), 3.83 (s, 3H), 2.35 (s, 3H); IR (neat): 1663, 1624, 1356, 974.

2.1.12. (3E)-4-(4-tolyl)-3-buten-2-one [25]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 16.4 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 6.68 (d, J = 16.4 Hz, 1H), 2.39, (s, 3H), 2.38 (s, 3H); IR (neat): 1679, 1612, 1317, 970.

2.1.13. E-2-(4-nitrobenzylidene)cyclohexanone [26]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 7.6 Hz, 2H), 7.49 (d, J = 7.6 Hz, 2H), 5.47 (s, 1H), 2.62 (t, J = 8.8, 16.8, 8.0 Hz, 2H), 2.57 (t, 2H), 2.09 (m, 2H), 1.83 (m, 2H); IR (neat): 1658, 1633, 1359, 973.

2.1.14. 3-Methyl-5-(4-nitrophenyl)cyclohex-2-enone [29]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 6.03 (s, 1H), 3.47 (m, 1H), 2.71-2.56 (m, 4H), 2.05 (s, 3H); IR (neat): 1661, 1606, 1596, 1521, 1346, 853; GC–MS: m/z = 231.

3. Results and discussion

When 4-nitrobenzaldehyde and acetone was catalyzed by D-aminoacylase and imidazole in hexane at 50 °C, two products were observed. The structures of these two products were approved by IR and ^{1}H NMR. Based on the observation, we envisioned that D-aminoacylase and imidazole could serve as co-catalyst for direct preparation of the synthetically useful α, β-unsaturated carbonyl compounds from aldehydes and ketones.

Table 1
Direct tandem Aldol condensation/dehydration of 4-nitrobenzaldehyde and acetone catalyzed by different enzymes in hexane[a].

Entry	Enzyme	Yield[b] (%)	*E*/*Z*
1	Blank	–[c]	–
2	Blank[d]	2.2	12/1
3	DA	33.5	15/1
4	DA[e]	6.4	16/1
5	DA (denature)[f]	6.0	1/5
6	AA	3.3	9/1
7	BSA	–	–
8	CCL	2.9	1/10
9	MJL	1.6	1/13
10	MML	1.8	5/1
11	CAL B	–	–

[a] Reaction conditions: Enzyme (10 mg), 4-nitrobenzaldehyde (10 mg), acetone (0.15 ml), imidazole (5 mg), hexane (1 ml), 50 °C, reaction time (48 h).
[b] Determined by HPLC.
[c] Not detected.
[d] Without D-aminoacylase.
[e] Without imidazole.
[f] Pretreated with urea at 100 °C for 8 h.

Some control experiments were designed to demonstrate that the tandem Aldol condensation/dehydration between 4-nitrobenzaldehyde and acetone was catalyzed by D-aminoacylase and imidazole. As seen from Table 1, the tandem Aldol condensation/dehydration between 4-nitrobenzaldehyde and acetone did not take place without D-aminoacylase and imidazole (entry 1, Table 1). Imidazole could not catalyze tandem reaction efficiently (entry 2, Table 1). The reaction of 4-nitrobenzaldehyde and acetone with D-aminoacylase, but in the absence of imidazole, led to very low yield (entry 4, Table 1) after 48 h. When the reactants were incubated with denatured D-aminoacylase and bovine serum albumin (BSA), the yield were lower than 7% (entries 5 and 7, Table 1), ruling out the possibility that the amino acid distribution on the protein surface promoted the process. Several widely used hydrolases, such as AA, CCL, MJL, MML and CAL B, could not accelerate the reaction efficiently in hexane (entries 6 and 8–11, Table 1). However, the reaction yield was 33.5% under the catalysis of D-aminoacylase and imidazole (entry 3, Table 1). All these results suggest that the specific catalytic site of D-aminoacylase and imidazole were responsible for promoting the Claisen–Schmidt condensation.

Some conventional organic solvents with different log *P* values were surveyed for this tandem reaction and the results are shown in Table 2. In these solvents, such as DMSO, THF, chloroform and toluene, the yields of this tandem reaction were less than 10% (entries 1–4, Table 3). In cyclohexane and hexane, the yields were improved to 32.4% and 33.5% (entries 5 and 6, Table 3). Better results were obtained in isooctane or octane (entries 7 and 8,

Table 2
The tandem Aldol condensation/dehydration between 4-nitrobenzaldehyde and acetone under different solvents[a].

Entry	Solvent	Log *p*	Yield[b] (%)	*E*/*Z*
1	DMSO	−1.3	–[c]	–
2	THF	0.56	3.3	12/1
3	Chloroform	1.95	–	–
4	Toluene	2.61	–	–
5	Cyclohexane	3.35	32.4	12/1
6	Hexane	3.9	33.5	15/1
7	Isooctane	4.5	67.9	16/1
8	Octane	4.9	67.8	38/1

[a] Reaction conditions: D-aminoacylase (10 mg), 4-nitrobenzaldehyde (10 mg), acetone (0.15 ml), imidazole (5 mg), solvent (1 ml), 50 °C, reaction time(48 h).
[b] Determined by HPLC.
[c] Not detected.

Table 3
Screening of *N*-heterocyclic for the tandem Aldol condensation/dehydration of acetone and *p*-nitrobenzaldehyde[a].

Entry	*N*-heterocyclic	Yield[b] (%)	*E*/*Z*
1	None	6.4	1/16
2	Imidazole	67.8	38/1
3	*N*-methylimidazole	29.9	20/1
4	Benzoimidazole	20.7	10/1
5	Pyridine	3.7	7/1
7	2-Methyl-5-nitroimidazole	0.6	1/3

[a] Reaction conditions: D-aminoacylase (10 mg), 4-nitrobenzaldehyde (10 mg), acetone (0.15 ml), *N*-heterocyclic (5 mg), octane (1 ml), 50 °C, reaction time (48 h).
[b] Determined by HPLC.

Table 3). Considering the high selectivity of the elimination, octane was chosen as the medium for further investigation.

The effect of varieties *N*-heterocyclic compounds was also evaluated (Table 3). The product could be furnished with yields of 20.7% and 29.9%, when *N*-methylimidazole and benzoimidazole was added. Other *N*-heterocyclic compounds, such as pyridine and 2-methyl-5-nitroimidazole, did not exhibit promising result. However, imidazole showed a unique property and could enhance the activity of D-aminoacylase for this tandem reaction obviously. The yield could be up to 67.8%.

The yields with different concentrations of imidazole are shown in Fig. 1. The amount of imidazole exhibited an obviously influence on the yield and selectivity of the reaction. In the absence of imidazole, the reaction did not take place. However, the reaction yield decreased as the dosage of imidazole increasing from 5 to 50 mg ml^{-1}. A similar phenomenon was observed for the reaction selectivity. The best concentration of imidazole was 5 mg ml^{-1}. It can be concluded that the imidazole showed dual role in this enzymatic reaction. One side, imidazole could catalyze the tandem reaction with D-aminoacylase at the appropriate amount. On the other side, when excessive imidazole was added, the deactivation of DA occurred, which has been proved by a further investigation. As seen from Fig. 2, the reaction was improved as increasing the D-aminoacylase with a fixed concentration of the imidazole at the beginning. Then, the plateau was reached after D-aminoacylase exceeding 10 mg ml^{-1}. It proved that D-aminoacylase could not catalyze this reaction without the assistant of imidazole. Therefore, the optimum quality ratio of D-aminoacylase and imidazole was 2/1.

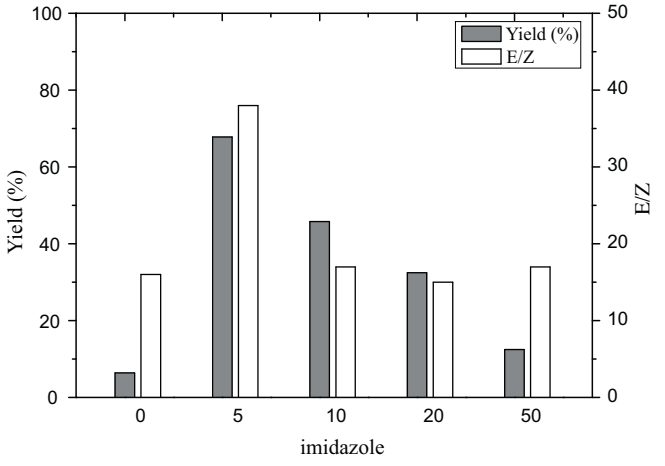


Fig. 1. Effect of different imidazole concentrations on the reaction of tandem Aldol condensation/dehydration between 4-nitrobenzaldehyde and acetone in octane. Reaction conditions: D-aminoacylase (10 mg), 4-nitrobenzaldehyde (10 mg), acetone (0.15 ml), octane (1 ml), 50 °C, reaction time (48 h). Yields were determined by HPLC.

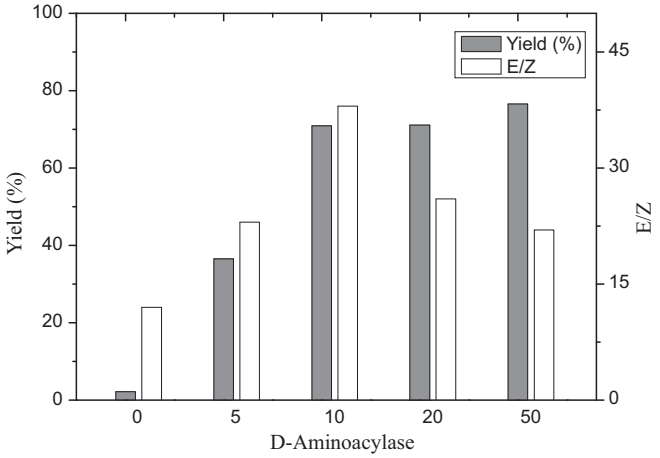


Fig. 2. Effect of different enzyme concentrations on the reaction of tandem Aldol condensation/dehydration between 4-nitrobenzaldehyde and acetone in octane. Reaction conditions: 4-nitrobenzaldehyde (10 mg), acetone (0.15 ml), imidazole (5 mg), octane (1 ml), 50 °C, reaction time (48 h). Yields were determined by HPLC.

The influence of catalyst loading on the reaction efficiency was investigated. The quality concentration of D-aminoacylase and imidazole in the reaction system were increased in the same proportion. As shown in Fig. 3, with the concentration of D-aminoacylase changed from 0 to 10 mg ml^{-1}, the yield increased from 49.7% to 67.8%, but it decreased remarkably with the concentration of D-aminoacylase increased from 20 to 50 mg ml^{-1}. We found that a by-product was formed with the concentration of D-aminoacylase at 50 mg ml^{-1} by TLC. The by-product was 3-methyl-5-(4-nitrophenyl)-cyclohex-2-enone by analyzed IR, ^{1}H NMR and GC–MS. From Figs. 1–3, it demonstrated that imidazole and D-aminoacylase can catalyze carbon–carbon double bond formation.

As shown in Fig. 4, when the concentration of *p*-nitrobenzaldehyde was changed from 5 to 10 mg ml^{-1}, the yield increased from 21.1% to 67.8% and *E*/*Z* increased from 18 to 38. Decreased in yields and *E*/*Z* were observed as the concentration continually varied from 20 to 50 mg ml^{-1}.

The time course of tandem Aldol condensation/dehydration between 4-nitrobenzaldehyde and acetone catalyzed by D-aminoacylase and imidazole was tested in octane. The progress

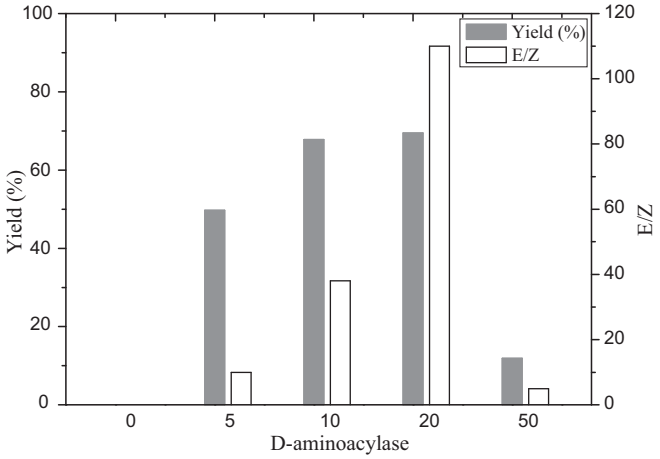


Fig. 3. Co-effect of different enzyme and imidazole concentrations on the reaction of tandem Aldol condensation/dehydration between 4-nitrobenzaldehyde and acetone in octane. Reaction conditions: 4-nitrobenzaldehyde (10 mg), acetone (0.15 ml), $m_{(\text{D-aminoacylase})}/m_{(\text{Imidazole})}$ = 2/1, octane (1 ml), 50 °C, reaction time (48 h). Yields were determined by HPLC.

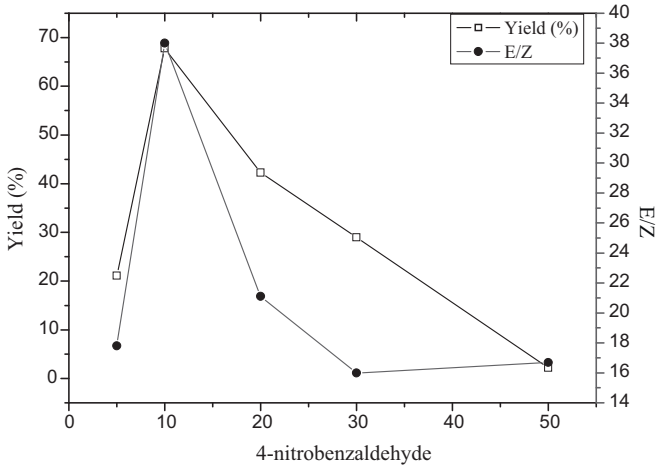


Fig. 4. Influence of different substrates concentration on the reaction of tandem Aldol condensation/dehydration between 4-nitrobenzaldehyde and acetone in octane. Reaction conditions: D-aminoacylase (10 mg), imidazole (5 mg), $n_{(\text{4-nitrobenzaldehyde})}/n_{(\text{acetone})}$ = 1/30, octane (1 ml), 50 °C, reaction time (48 h). Yields were determined by HPLC.

curves are shown in Fig. 5. The yield increased as the reaction time prolonged. 88.9% of 4-(4-nitrophenyl)-3-buten-2-one was obtained after 72 h with the ratio of *E* to *Z* being 1/154.

Having established optimal reaction conditions, we probed the generality of the process. The tandem reaction between different aldehydes and ketones in octane at 50°C in the presence of D-aminoacylase and imidazole was conducted. Results are summarized in Table 4. Examination of electron-withdrawing groups was revealed that a pronounced steric effect is evident in the ortho position (entries 3 and 7, Table 4) than other positions of aromatic aldehydes (entries 1–2 and 5–6, Table 4). The electronic effect showed slight influence on the reactions (entries1, 4, 5, 11 and 12, Table 4). Compared with benzaldehyde, electron-donating group could enhance the reactivity of substrates (entries 4, 11 and 12, Table 4). However, electron-withdrawing group showed negative effect on the reaction (entry 1, Table 4). Slight decrease in yields was observed. Chlorine had two kinds of electronic effects. Thus, an excellent result was obtained (entry 5, Table 4). When the aldehydes, containing hydroxyl group were used as substrates, the tandem reactions hardly took place except the hydroxyl group on the ortho position (entries 8–10 and 13–14, Table 4). It may

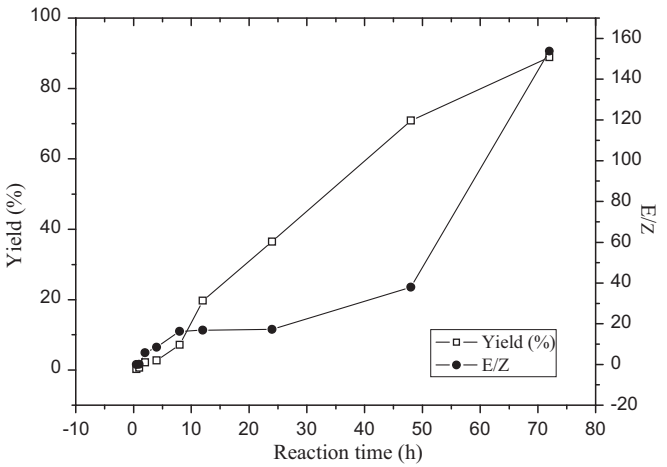
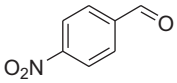
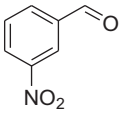
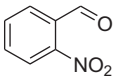
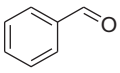
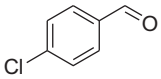
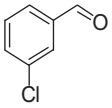
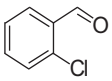
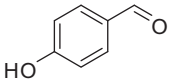
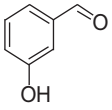
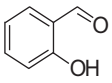
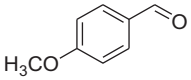
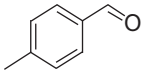
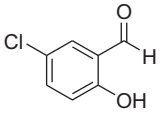
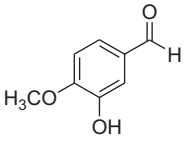
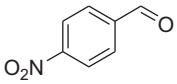
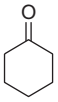


Fig. 5. The progress curve of different time that D-aminoacylase catalyzed 4-nitrobenzaldehyde and acetone in octane. Reaction conditions: D-aminoacylase (10 mg), 4-nitrobenzaldehyde (10 mg), acetone (0.15 ml), imidazole (5 mg), octane (1 ml), 50 °C. Yields were determined by HPLC.

Table 4
Direct tandem Aldol condensation/dehydration between other aromatic aldehydes and ketones[a].

Entry	Aldehydes	Acetones	Yield[b] (%)	*E*/*Z*
1			67.8	38/1
2			88.8	224/1
3			44.4	1/1
4			74.3	245/1
5			90	*E*
6			99.6	57/1
7			39	282/1
8			8.5	90/1
9			0.6	*E*
10			20.4	*E*
11			89.8	19/1
12			87.1	12/1
13			–[c]	–
14			–	–
15			70.8	*E*

[a] Reaction conditions: D-aminoacylase (10 mg), aldehydes (10 mg), ketones (0.15 ml), imidazole (5 mg), octane (1 ml), 50 °C, reaction time (48 h).
[b] Determined by HPLC.
[c] Not detected.

be due to the hydrogen bond between the hydroxyl of aldehydes and the nitrogen of imidazole, which leading to affect the function of imidazole. For the 2-hydroxylbenzaldehyde, the hydrogen of hydroxyl can form intramolecular hydrogen bond with carbonyl, which reduce the hydrogen bond between aldehyde and imidazole. So the 2-hydroxylbenzaldehyde can react with acetone and got the yield in 20.4% (entry 10, Table 4). The tandem reaction between *p*-nitrobenzaldehyde and cyclohexanone was also investigated and the high yield was observed (entry 15, Table 4).

4. Conclusions

A facile method to perform tandem Aldol condensation/dehydration between aldehydes and ketones has been developed by D-aminoacylase and *N*-heterocyclic compounds as co-catalyst in octane. The relationship of D-aminoacylase and imidazole was demonstrated by the combination of different control experiments. To make summarize, the quality ratio of D-aminoacylase and imidazole should be 2/1 and the tandem reaction between aldehydes and ketones was carried out in octane at 50 °C. After the optimization of the stepwise process, series of α, β-unsaturated ketones were prepared efficiently using D-aminoacylase and imidazole via tandem condensation/dehydration reaction.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcatb.2010.09.014.

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