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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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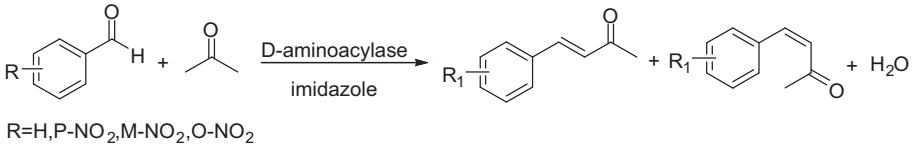

Scheme 1. D-aminoacylase and imidazole co-catalyzed tandem Aldol condensation/dehydration between ketones and aldehydes.

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.