An Environment-Friendly and Efficient Method for Aldol Condensation Catalyzed by L-Lysine in Pure Water

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Abstract: This is a new example of a nonmetallic small-molecule catalyst for direct intermolecular aldol reactions. We found L-lysine is an effective catalyst for this condensation between unmodified acetone and a variety of aldehydes in the presence of pure water. This green catalyst system could be reused.

Keywords: L-lysine, organo-catalysis, aldol reaction, green chemistry.

Green chemistry, which is defined as the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances, generated extensive interest in both industrial and academic research years ago. In this regard, synthetic chemists have great interest to develop highly efficient transformations for the preparation of organic compounds. One of the main themes of contemporary synthetic organic chemistry is using environmentally benign solvent and catalysts. Obviously, the use of water with positive effects in terms of cost, safety, and environmental impact as reaction solvent instead of organic solvent is preferred to decrease environmental contamination [1]. Organo-catalysis became a new research area in synthetic chemistry several years ago, which is one of the most important contents for green chemistry. Driven by environmental concerns, there is great interest and need for cheap and readily available, recyclable and reusable organocatalysts that promote reactions in pure water to expand the scope of organocatalysis as part of an environmentally benign approach to fine chemical synthesis, especially large scale reactions.

Aldol condensation plays an important role in nature as a source of carbohydrates and is used for the synthesis of chiral β -hydroxy carbonyl compounds or α , β -unsaturated ketones, which in turn have great potential and valuable intermediates in organic synthesis [2]. This powerful and atom-economic C-C bond forming reaction is usually carried out in organic solvents catalyzed by strong acids, bases [3], or some metal salts [4]. Recently ionic liquid was used as the solvent [5]. Yet, the application of ionic liquids in the industrial syntheses of fine chemicals is still problematic because of the relatively high cost of these solvents. Lproline was first reported as the organocatalyst in aldol reactions [6]. Since then many papers have been published on this topic [7]. However, it should be noted that among all the reported systems most catalysts work in organic solvent [8] or mixed aqueous organic solvent [9], and there is also a method in the both secondary amine and mesoporous silica, which are present but the yield is low [10]. To our delight, Llysine, which is very cheap, was found to have at least equally good catalytic activity in water as compared to proline. The relevant reactions proceeded very smoothly in pure water with no need to add surfactant or organic solvent.

To achieve the best results for this reaction (Scheme 1), we select the reaction between acetone and pnitrobenzaldehyde as a model to optimize the reaction conditions. For each reaction condition, conversion of acetone (0.8ml) and p-nitrobenzaldehyde (1mmol) to 4-Hydroxyl-4-(4-nitrophenyl)-2-butanone was measured by HPLC. As is shown in Table 1, with the amount of catalyst increased, the yield will get the best and don't increase any more, though the reaction time reduces a little.

Scheme 1.

 Table 1.
 Effect of Catalyst on the Reaction of 4-Nitrobenzaldehyde with Acetone

Entry	Amount of Catalyst	Time	Yield ^a
1	5 mol%	24 h	31%
2	20 mol%	15 h	79%
3	40 mol%	15 h	79%
4	60 mol%	15 h	79%
5	80 mol%	13 h	75%

^αHPLC yield.

A series of aromatic aldehydes was studied instead of pnitrobenzaldehyde under the same conditions. The results are presented in Table 2. Despite the extremely low solubility of aldehydes in water, the lysine-catalyzed aldol reactions proceeded efficiently at ambient temperature $(30-37^{\circ}C)$. The electron-deficient aldehydes proceeded much faster than the electron-rich ones. In some cases, dehydration occurred and in other cases the hydroxyketone was isolated. Perhaps this is because the products formed by the electron-deficient

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Entry	Aldehyde	Main product	Time (h)	Yield ^{a,b} (%)
1	O ₂ N — CHO	O ₂ N OH O	19	86
2	O ₂ N CHO	O ₂ N OH O	20	88
3	CHO NO ₂	NO ₂ OH O	20	88
4	Н ₃ С-СНО	H ₃ C	48	62
5	Н ₃ СО — СНО	H ₃ CO	45	79
6	СІ—СНО		24	81
7	СІ		24	83
8	Cl CHO		22	83
9	Br	Br	22	84
10	Н ₃ СО Н ₃ СО	H ₃ CO H ₃ CO	24	85
11	СНО		26	83
12	NC-СНО	NC	24	83

 Table 2.
 L-Lysine Catalyzed Aldol Reactions between Acetone and Arylaldehydes in Pure Water

(Table 2). Contd.....

Entry	Aldehyde	Main product	Time (h)	Yield ^{a,b} (%)
13	Вг СНО	OH O Br	24	81
14	Br — CHO	Br - OH	22	84
15	OH H ₃ CO CHO	H ₃ CO	50	79
16	СНО	OH OH	28	76

^aIsolated yields after column chromatography.

^bA mixture of an aldehyde (1.0mmol), acetone(0.5mL), and L-lysine(20 mol%) in 4 mL of water was stirred in a 10 ml, round-bottomed flask at ambient temperature. The reaction was followed and monitored by TLC. When the reaction was completed, ethyl acetate (10mL×3) was added into the flask to extract the product. Then the reaction mixture was partitioned between aqueous and ethyl acetate. The organic layer was separated and concentrated, then the residue was purified by column chromatography eluting with petroleum/ethyl acetate to give aldol product.

aldehydes are easier to form a carbanion. Or they are more likely to carry out E1cB elimination. The experimental results also show that there will be more beta elimination product, if we extend the reaction time. In addition, different sensitivity of the products to temperature changes may also a factor. We didn't pay attention to the optical activity at a specific reaction temperature. Vigorous stirring was required for the success of the reaction. Both electron-deficient and electron-rich aldehydes can react with acetone, giving excellent yields. Our findings reflect the wide applicability and usefulness of the method.

We also investigated the reusability of this system of water and L-lysine. After the reaction was completed, the product was extracted out by filling in ethyl acetate. Amazingly, the aqueous solution could be reused without any loss of its activity even after five runs. (Table 3).

In conclusion, we choose L-lysine as organocatalyst, which can promote the direct aldol reaction of aldehydes and acetone in large amount of water. And this catalytic amount of lysine is reusable, nonmetallic small-molecule catalyst. From a green chemistry perspective, this highly effective and

Table 3. Recycling Experiments with L-Lysine^a

Run	1	2	3	4	5
Yield(%) ^b	86	85	86	86	85

^aReactions performed with p-nitrobenzaldehyde (1.0 mmol), acetone(0.5 mL), and L-lysine (20mol%) in pure water (4 mL) and stirred for 19 h at r.t. ^bIsolated yields after column chromatography.

environmentally benign synthetic methodology can be regarded as a goal in modern organic chemistry.

The spectra data of the compounds **Entry 1-16** are as follows.

Entry 1

 $R_{\rm f}$ 0.30 (1:3 EtOAc/Petroleum); IR (KBr) 3455, 2907, 1714, 1600, 1521, 1341, 1241, 1165, 1079, 858, 839 cm $^{-1}$; 1 H-NMR(500MHz, CDCl₃): δ 2.23(s, 3H, COCH₃), 2.86(t, J=5.6 Hz, 2H, CH₂), 3.58(br s, 1H, OH), 5.27(t, 1H, J=6.2 Hz, CH), 7.54(d, 2H, J=8.6 Hz, Ar-H), 8.19(d, 2H, J=8.7 Hz, Ar-H).

Entry 2

 R_f 0.32 (1:3 EtOAc/Petroleum); ¹H-NMR(500MHz, CDCl₃): δ 2.15(s, 3H, COCH₃), 2.83(t, 2H, J=8.6 Hz, CH₂), 4.03(s, 1H, OH), 5.19(q, 1H, J=3.6 Hz, CH), 7.44(t, 1H, J=7.9 Hz, Ar-H), 7.63(d, 1H, J=7.7 Hz, Ar-H), 8.0(q, 1H, J=1.4 Hz, Ar-H), 8.14(s, 1H, Ar-H).

Entry 3

 $R_{\rm f}$ 0.31 (1:3 EtOAc/Petroleum); 1 H-NMR(500MHz, CDCl₃): δ 2.24(s, 3H, COCH₃), 2.74(dd, 1H, J=9.4, 9.4 Hz, one H of CH₂CO), 3.12(dd, 1H, J=2.0, 2.0 Hz, the other one H of CH₂CO), 3.76(br s, 1H, OH), 5.68(dd, 1H, J=1.8, 1.8 Hz, CH), 7.42-7.46(m, 1H, Ar-H), 7.67(t, 1H, J=7.4 Hz, Ar-H), 7.89(d, 1H, J=7.8 Hz, Ar-H), 7.94(t, 1H, J=7.6 Hz, Ar-H).

Entry 4

 R_f 0.60 (1:4 EtOAc/Petroleum); ¹H-NMR(500MHz, CDCl₃): δ 2.31(d, 6H, J=4.9 Hz, six H of the two CH₃), 6.62(d, 1H, J=16.3 Hz, one H of CH), 7.14(d, 2H, J=8.0 Hz, Ar-H), 7.38(d, 2H, J=8.1Hz, Ar-H), 7.43(d, 1H, J=16.3Hz, the other one H of CH); ¹³C-NMR(125MHz, CDCl₃): δ 21.4, 27.3, 126.2, 128.3, 129.7, 131.7, 140.9, 143.4, 198.3.

Entry 5

 $R_{\rm f}$ 0.51 (1:4 EtOAc/Petroleum); IR (KBr) 1656, 1633, 1601, 1574, 1511, 1423, 1360, 1245, 1177, 1029, 836, 806 cm $^{-1}$; 1 H-NMR(500MHz, CDCl₃): δ 2.36(s, 3H, COCH₃), 3.84(s, 3H, CH₃O), 6.60(d, 1H, J=16.3 Hz, one H of CH), 6.91(d, 2H, J=8.8 Hz, Ar-H), 7.46-7.50(m, 3H, the other one H of CH and Ar-H).

Entry 6

 R_f 0.50 (1:4 EtOAc/Petroleum); ¹H-NMR(500MHz, CDCl₃): δ 2.37(s, 3H, COCH₃), 6.67(d, 1H, J=16.3 Hz, one H of CH), 7.35(d, 2H, J=8.5 Hz, Ar-H), 7.44(d, 1H, J=16.3 Hz, the other one H of CH), 7.46(d, 2H, J=2.1 Hz, Ar-H).

Entry 7

 R_f 0.60 (1:3 EtOAc/Petroleum); ¹H-NMR(500MHz, CDCl₃): δ 2.42(s, 3H, COCH₃), 6.67(d, 1H, J=16.4 Hz, one H of CH), 7.26-7.34(m, 2H, Ar-H), 7.43(q, 1H, J=0.8 Hz, Ar-H), 7.63(q, 1H, J=1.6 Hz, Ar-H), 7.93(d, 1H, J=16.4 Hz, the other one H of CH).

Entry 8

 R_f 0.61 (1:3 EtOAc/Petroleum); ¹H-NMR(500MHz, CDCl₃): δ 2.38(s, 3H, COCH₃), 6.70(d, 1H, J=16.3 Hz, one H of CH), 7.26-7.52(m, 5H, the other one H of CH and Ar-H).

Entry 9

 R_f 0.50 (1:2 EtOAc/Petroleum); ¹H-NMR(500MHz, CDCl₃): δ 2.38(s, 3H, COCH₃), 6.70(d, 1H, J=16.3 Hz, one H of CH), 7.27(q, 1H, J=3.2 Hz, Ar-H), 7.41-7.52(m, 3H, Ar-H), 7.68(s, 1H, the other one H of CH).

Entry 10

 R_f 0.55 (1:2 EtOAc/Petroleum); IR (KBr) 1674, 1650, 1597, 1468, 1432, 1358, 1270, 1165, 1067, 977, 836 cm⁻¹; ¹H-NMR(500MHz, CDCl₃): δ 2.38(s, 3H, COCH₃), 3.82(s,

6H, CH₃O), 6.51(s, 1H, Ar-H), 6.66-6.69(m, 3H, one H of CH and Ar-H), 7.42(d, 1H, J=16.2 Hz, the other one H of CH)); MS (ESI) m/z 228.9 ([M+Na])⁺.

Entry 11

 R_f 0.66 (1:3 EtOAc/Petroleum); ¹H-NMR(500MHz, CDCl₃): δ 2.31(s, 3H, COCH₃), 6.65(d, 1H, J=16.3 Hz, one H of CH), 7.33(q, 3H, J=3.3 Hz, Ar-H), 7.44(s, 1H, the other one H of CH), 7.48(q, 2H, J=2.8 Hz, Ar-H).

Entry 12

 $R_{\rm f}$ 0.37 (1:2 EtOAc/Petroleum); IR (KBr) 2225, 1673, 1624, 1481, 1365, 1225, 1209, 975, 835, 814 $\rm cm^{-1}; \ ^1H^-NMR(500MHz, CDCl_3): \delta$ 2.41(s, 3H, COCH_3), 6.78(d, 1H, J=16.2 Hz, one H of CH), 7.49(d, 1H, J=16.3 Hz, the other one H of CH), 7.63(d, 2H, J=8.2 Hz, Ar-H), 7.69(t, 2H, J=6.6 Hz, Ar-H).

Entry 13

Entry 14

 R_f 0.50 (1:2 EtOAc/Petroleum); ¹H-NMR(500MHz, CDCl₃): δ 2.15(s, 3H, COCH₃), 2.73(dd, 1H, J=3.4, 3.3 Hz, one H of CH₂CO), 2.81(dd, 1H, J=9.1, 9.1 Hz, the other one H of CH₂CO), 3.71(s, 1H, OH), 5.06(q, 1H, J=3.0 Hz, CH), 7.19(d, 2H, J=8.4 Hz, Ar-H), 7.44(d, 2H, J=8.4 Hz, Ar-H); ¹³C-NMR(125MHz, CDCl₃): δ 30.8, 51.9, 69.2, 121.4, 127.5, 131.6, 142.1, 208.8.

Entry 15

Entry 16

 R_f 0.39 (1:2 EtOAc/Petroleum); ¹H-NMR(500MHz, CDCl₃): δ 2.20(s, 3H, COCH₃), 2.91(dd, 1H, J=3.5, 3.5 Hz, one H of CH₂CO), 3.04(dd, 1H, J=8.9, 8.9 Hz, the other one H of CH₂CO), 3.49(br s, 1H, OH), 5.16(q, 1H, J=3.5 Hz, CH), 6.25(d, 1H, J=3.2 Hz), 6.32(q, 1H, J=1.9 Hz), 7.36(d, 1H, J=1.1 Hz).

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