A green method for the self-aldol condensation of aldehydes using lysine†

Yutaka Watanabe,* Kazue Sawada and Minoru Hayashi

Received 7th September 2009, Accepted 30th November 2009
First published as an Advance Article on the web 13th January 2010
DOI: 10.1039/b918349c

A self-condensation of aldehydes has been conveniently accomplished by the catalytic action of lysine in water or a solvent-free system under specific emulsion conditions to give α-branched α,β-unsaturated aldehydes in good yields.

Introduction

The quest for environment friendly or green methods for chemical synthesis is attracting more and more attention.[1] To achieve such a green process, especially for industrial applications it is desirable (1) either to adopt a solvent-free system or to use water as solvent, (2) to use biogenic catalysts but not petroleum products, (3) to avoid heating, and (4) to follow a simple work-up procedure and waste treatment. Aldol condensation is an important synthetic method widely used in organic synthesis.[2] A typical process involves the self-condensation of aldehydes catalyzed by alkalis or acids.[3] Several alternative methods for aldol condensation have been reported.[4] However, in an era when green methods are warranted, many of these methods are not satisfactory with respect to reaction temperature, reaction time, solvent, yield, and simplicity of the catalyst. Aldol condensation is an industrially important process. For example, the condensation product of butanal is the important synthetic intermediate in the preparation of 2-ethylhexanol which is widely used for making plasticizers, surfactants, *etc*. The industrial process for the self-aldol condensation of aldehydes is usually carried out in an aqueous alkaline solution. While condensation of medium carbon-chain aldehydes such as octanal and nonanal can be conducted by heating under alkaline conditions,[5] water-insoluble higher aldehydes are not suitable for the alkaline process. A unified procedure for aldol condensation that can be applied to all kinds of aldehydes is lacking. We herein report a very general and an environmentally benign method for aldol condensation of all range of aldehydes (medium to high carbon aldehydes). The use of biogenic lysine (Lys) as the catalyst and the solvent-free/aqueous conditions make this method very attractive.

Results and discussion

In addition to the common self-aldol condensation of aldehydes using an alkali, the majority of the reported procedures employ secondary amines and their derivatives as catalysts. As exceptional cases, simple aldehydes such as butanal and acetaldehyde were shown to be converted to the condensation products by the catalysis of α-amino acids in the mechanistic studies.[6] We have now found that Lys and ornithine (Orn) catalyze the self-condensation of aldehydes in water. Thus, the treatment of 10 mol% of Lys in water with 3-phenylpropanal (1 M) for 2 h at room temperature, resulted in the formation of the condensation product in 65% yield (Table 1). Orn also yielded the same product in a comparable yield (59%). However, arginine, despite being a comparably basic amino acid, was not as effective as Lys and Orn (only 24% yield). From this, it is very clear that the presence of an amino group in the side chain is essential for smooth reaction.

In order to investigate the effect of concentration of the aldehyde in the feasibility of reaction, the condensation reaction was carried out at different molar concentrations of the aldehyde. It was found that as the concentration of the aldehyde increases, the yield also increased. For example, 0.25 M, 0.5 M, 1 M and 2 M nonanal in water gave 13%, 21%, 62% and 64% yield of the condensation product, respectively. After various experimental studies, 1–2 M solution of aldehydes with more than seven carbons underwent condensation smoothly in the presence of 10 mol% of Lys at room temperature (Table 1). Even water-insoluble solid octadecanal (entry 9) was found to furnish the coupling product in 61% although a larger amount of Lys and longer reaction time were required.

In order to understand the role of water, we next carried out the reaction without water. Thus, treatment of higher aldehydes (more than C_6) with 10 mol% of Lys with stirring at room temperature for 2 h gave the condensation products in good yields, which are comparable with those in the reactions in aqueous medium (Table 2). The solvent-free condensation of hexanal (C_6) gave a yield identical to that obtained in the water solvent system, in which concentration of the aldehyde was exceptionally higher (8 M), as shown in Table 2. It is noteworthy that the short chain aldehydes such as pentanal (C_5) and butanal (C_4) provided the condensation product in moderate yields under solvent-free conditions, but when the reaction was done in water (1 M), the yields dropped by half.

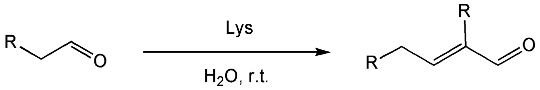
The Lys-catalyzed self-condensation of aldehydes in water or without a solvent, as described, would be a synthetically useful alternative; it can be applied to various aldehydes with low to high carbon numbers, in contrast to the common alkaline condensation that requires heating in the case of moderate chain aldehydes (C_7–C_9) and is not suitable for higher chain ones. The reaction is especially emphasized to be a green procedure judging from the following: (1) the solvent-free or aqueous condition, (2) the catalyst used, Lys, is of bio-origin, (3) no heating is required, (4) short reaction time and simple work-up

---

Department of Materials Science and Biotechnology, Graduate School of Science and Engineering, Ehime University, Matsuyama, 790-8577, Japan. E-mail: wyutaka@dpc.ehime-u.ac.jp; Fax: +81-89-927-9921

† Electronic supplementary information (ESI) available: ^{1}H- and ^{13}C-NMR spectra and data. See DOI: 10.1039/b918349c

Table 1 Lys-catalyzed self-condensation of various aldehydes in water



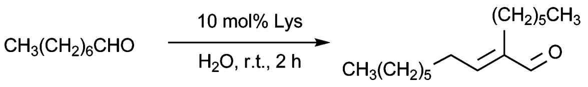
Entry	Aldehyde	Conc./M	Lys (mol%)	Time/h	Yield (%)	*E*/*Z*
1	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CHO$	1.0	10	2	70	94/6
2	$n\text{-}C_9H_{19}CHO$	1.0	10	2	75	99/1
3	$n\text{-}C_8H_{17}CHO$	2.0	10	2	64	98/2
4	$n\text{-}C_7H_{15}CHO$	2.0	10	2	68	98/2
5	$n\text{-}C_6H_{13}CHO$	2.0	10	2	69	98/2
6	$n\text{-}C_5H_{11}CHO$	8.0	10	2	63	95/5
7	$Ph(CH_2)_2CHO$	1.0	10	2	65	98/2
8	$n\text{-}C_{12}H_{25}SCH(CH_3)CH_2CHO$	1.0	10	2	78	25/75
9	$n\text{-}C_{17}H_{35}CHO$	1.0	30	10	61	99/1

Table 2 The self-condensation of aldehydes in no solvent[a]

		Yield (%)	
Entry	Aldehyde	No solvent	H_2O (conc.)
1	$n\text{-}C_9H_{19}CHO$	74	
2	$n\text{-}C_8H_{17}CHO$	66	
3	$n\text{-}C_7H_{15}CHO$	62	
4	$n\text{-}C_6H_{13}CHO$	64	
5	$n\text{-}C_5H_{11}CHO$	62	63 (8 M)
6	$n\text{-}C_4H_9CHO$	52	23 (1 M)
7	$n\text{-}C_3H_7CHO$	46	23 (1 M)

[a] A mixture of an aldehyde and 10 mol% Lys was stirred for 2 h (3 h in the case of entries 6 and 7) at r.t.

Table 3 Concentration *vs.* yield



Entry	Concentration/M	Yield (%)
1	0.25	21
2	0.5	15
3	1.0	53
4	2.0	68

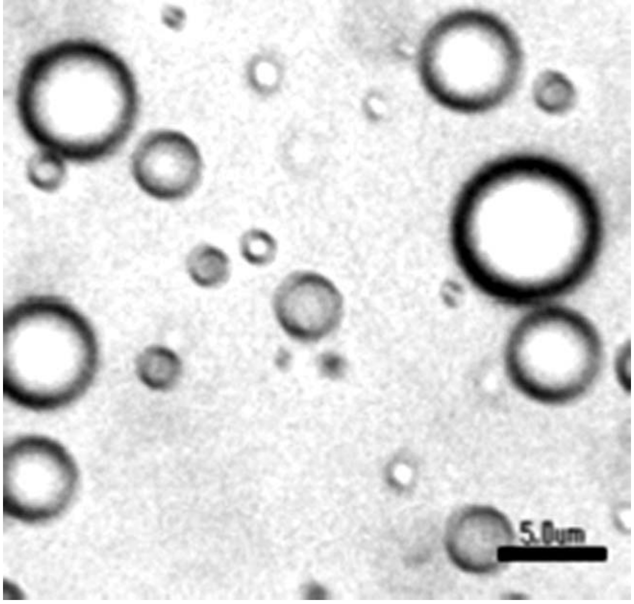
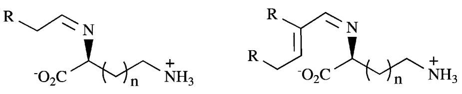


Fig. 1 Optical micrograph of the mixture of 3-phenylpropanal and Orn in water (scale bar = 5 μm).

procedure, and (5) the waste, containing the basic amino acid, is non-toxic. Furthermore, since by-products were highly polar in all cases carried out this time, chromatographic isolation was accomplished without using a large amount of elution solvents and silica gel. Although the solvent-free process is greener than the reaction in water, when the starting aldehyde is a solid, the water media is essential to promote the condensation.

The reaction mixture in water formed an emulsion. This observation suggests that a micelle or micelle-like colloidal aggregate is formed by assembly of an amphiphilic imine **1** derived from Lys or Orn and aldehyde (Scheme 1). Indeed, the formation of spherical droplets in water was observed by an optical microscope (Fig. 1). The yield of the condensation products depended remarkably upon the concentration of an aldehyde and carbon number of its chain. Thus, 1.0 and 2.0 M of octanal gave the dimer in 53 and 68% yields, respectively, while in the case of the concentration of 0.25 and 0.5 M, 21 and 15% of the product were obtained (Table 3). This tendency was observed in the case of aldehydes with more than seven carbon atoms. These results suggest that the reaction of heptanal and higher aldehydes has a critical concentration between 1.0 and 0.5 M for reaction promotion. On the other hand, in the case of hexanal and lower aldehydes, yields for 1.0 M concentration decreased dramatically and to gain yields similar to those in higher aldehydes, higher concentration around 4.0–8.0 M was required. Based on these findings, the present aqueous reaction is indicated to occur in assembled particles. Recently, there have been many reports on the reactions in colloidal particles like micelles.[7] Such media were generally constructed by adding a surfactant to a reactant and a catalyst in water.[8] Catalysts themselves are sometimes designed to behave as surfactants.[9] In contrast to these reports, the present emulsion is formed by the



1 **2**

Scheme 1

reaction intermediate imine **1** and its condensation product **2**, and the reaction proceeds in assembled sphere. The solvent-free process also proceeds under emulsified conditions. The water to form the emulsion may be generated by imine formation.

Conclusion

The Lys-promoted reaction of aldehydes in water or under solvent-free conditions has furnished the corresponding condensation products in good yields. The reaction takes place in the emulsion media, which assemble both lipophilic aldehydes and hydrophilic Lys in the same specific micelles, resulting in the promotion of smooth reaction, in spite of an aqueous system. This process is environmentally benign and applicable to various aldehydes, especially to long-chain aldehydes. Therefore, the procedure would provide a practical synthetic method for the self-condensation of aldehydes.

Experimental

Lys was purchased from Aldrich Chemical Co, and dried by heating (120 °C, for a few hours) *in vacuo*. Normal tap water was used for the reaction. Aldehydes were purchased and distilled under reduced pressure. Some aldehydes were prepared by usual 1,4-addition of thiol to crotonaldehyde (entry 8 in Table 1) and Swern oxidation of stearyl alcohol (entry 9).

General procedure for the Lys-catalyzed condensation of aldehydes in water

An aldehyde (10 mmol) was added to a solution of Lys (1.0 mmol) in water (10 mL) under vigorous stirring, and the resulting emulsion was stirred for 2 h at room temperature. After addition of water and extraction with ether, the condensation product was isolated by chromatography or distillation. In order to facilitate the extraction, the emulsion was eliminated by adding NaCl to the aqueous layer in some cases.

General procedure for the solvent-free condensation of aldehydes

To an aldehyde (10 mmol), Lys (1.0 mmol) was added and the mixture was vigorously stirred for 2 h at room temperature. The work-up and isolation procedure were the same as described above.

Acknowledgements

We thank Venture Business Laboratory (VBL) and Institute for Cooperative Science (INCS), Ehime University for NMR and elemental analysis.

Notes and references

1 P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, 1998; R. Mestres, *Green Chem.*, 2004, **6**, 583; C.-J. Li and B. M. Trost, *Proc. Natl. Acad. Sci. U. S. A.*, 2008, **105**, 13197; R. A. Sheldon, *Chem. Commun.*, 2008, 3352.
2 A. T. Nielsen and W. J. Honlikan, *Org. React.*, 1968, **16**, 1.
3 M. Häussermann, *Helv. Chim. Acta*, 1951, **34**, 1482.
4 M. J. Astle and J. A. Zaslowsky, *Ind. Eng. Chem.*, 1952, **44**, 2867; R. D. Offenhauer and S. F. Nelsen, *J. Org. Chem.*, 1968, **33**, 775; T. Takahashi and H. H. O. Schmid, *Chem. Phys. Lipids*, 1969, **3**, 185; R. Mahrwald and H. Schick, *Synthesis*, 1990, 592; T. Ishikawa, E. Uedo, S. Okada and S. Saito, *Synlett*, 1999, 450; C. P. Mehnert, N. C. Dispenziere and R. A. Cook, *Chem. Commun.*, 2002, 1610; K. Shimizu, E. Hayashi, T. Inokuchi, T. Kodama, H. Hagiwara and Y. Kitayama, *Tetrahedron Lett.*, 2002, **43**, 9073; S. Kiyooka, H. Fujimoto, M. Mishima, S. Kobayashi, K. Md. Uddin and M. Fujio, *Tetrahedron Lett.*, 2003, **44**, 927; J. Hamaya, T. Suzuki, T. Hoshi, K. Shimizu, Y. Kitayama and H. Hagiwara, *Synlett*, 2003, 873; H. Hagiwara, J. Hamaya, T. Hoshi and C. Yokoyama, *Tetrahedron Lett.*, 2005, **46**, 393; A. Arnold, M. Markert and R. Mahrwald, *Synthesis*, 2006, 1099.
5 F. Robert, J. Héritier, J. Quiquerez, H. Simian and I. Blank, *J. Agric. Food Chem.*, 2004, **52**, 3525.
6 For a model study on aldolase action, kinetic experiments of the reaction of butanal (Lys/K_2CO_3/50 °C at pH around 9.0) have been carried out: A. A. Yasnikov, T. S. Boiko, N. V. Volkova and I. V. Mel'nichenko, *Biokhimiya*, 1966, **31**, 969, (*Biochem. USSR*, 1966, **31**, 841). For a model study on the investigation of the contents in atmospheric aerosols, the aldol condensation of acetaldehyde was demonstrated by the catalysis of amino acids such as Gly, Ala, Ser, Pro and Arg, but not Lys and Orn, in the presence of inorganic salts:; B. Nozière, P. Dziedzic and A. Córdova, *Geophys. Res. Lett.*, 2007, **34**, L21812; B. Nozière and A. Córdova, *J. Phys. Chem. A*, 2008, **112**, 2827.
7 G. Oehme, E. Paetzold and R. Selke, *J. Mol. Catal.*, 1992, **71**, L1; S. Tascioglu, *Tetrahedron*, 1996, **52**, 11113; J. B. F. N. Engberts and M. J. Blandamer, *Chem. Commun.*, 2001, 1701; U. M. Lindström, *Chem. Rev.*, 2002, **102**, 2751; T. Dwars, E. Paetzold and G. Oehme, *Angew. Chem., Int. Ed.*, 2005, **44**, 7174.
8 B. H. Lipshutz and S. Ghorai, *Aldrichim. Acta*, 2008, **41**, 59.
9 K. Manabe, Y. Mori, T. Wakabayashi, S. Nagayama and S. Kobayashi, *J. Am. Chem. Soc.*, 2000, **122**, 7202; K. Manabe, X.-M. Sun and S. Kobayashi, *J. Am. Chem. Soc.*, 2001, **123**, 10101.