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Proline catalyzed aldol reactions in aqueous micelles: an environmentally friendly reaction system

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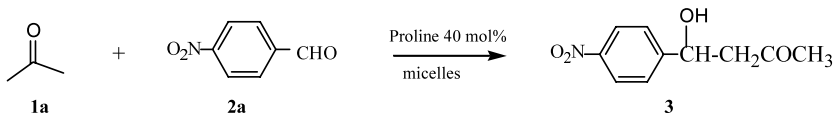
Abstract—The proline catalyzed aldol reactions of nitrobenzaldehydes with various ketones in aqueous anionic micelles were investigated. Both the selectivities and reaction yields were observed to be higher than those of the corresponding reactions in organic solvents. A reaction mechanism is proposed that is somewhat different from that in organic solvents.

Since the discovery of its roles as a good small-organic-molecule catalyst in intramolecular aldol reactions,[1,2] proline has drawn considerable attention[3] in synthetic chemistry due to its similarity to the type I aldolases.[4] Recently, List and others have reported some new direct asymmetric intermolecular reactions catalyzed by proline, including aldol,[5] Mannich,[6] Michael,[7] and other analogous reactions.[8] Additionally, some non-proline catalyzed aldol reactions in aqueous media have been reported due to the increasing concerns regarding environmental issues. In most cases, these reactions require Lewis acid activation of the acceptors and the use of silyl enol ethers as aldol donors.[9] In one case, aldol reactions were catalyzed by a proline-like molecule in a buffer solution with 10% DMSO.[10] Except for one recent example, proline catalyzed aldol reactions in aqueous micelles have not been reported.[11] Herein we wish to present our recent results regarding environmentally benign aldol reactions catalyzed directly by proline in aqueous anionic micelles.

Initially, the aqueous aldol reaction of acetone (**1a**) with 4-nitrobenzaldehyde (**2a**) in the absence of surfactant was studied by mixing **1a** (20 mmol), **2a** (4 mmol) and proline (0.16 mmol, 40 mol%) in pure water (15 ml). After five days at 40°C, the anticipated aldol product, 4-hydroxy-4-(4-nitrophenyl)-2-butanone (**3**), was obtained in only 15% yield (Table 1, entry 1). When an anionic surfactant, sodium dodecyl sulfate (20 mol% SDS), was added to the reaction system, 87% yield of aldol product **3** was obtained in only 24 h (entry 2). This yield is substantially higher than that of the corresponding reaction in organic solvents (68%).[5a,b] This reaction is very efficient, with only one by-product formed, the α,β-unsaturated ketone, in a trace amount.[12] When only SDS was used (no proline, entry 3), the yield of **3** was only 12%. The above results indicate that both proline and anionic surfactant SDS play important roles in this reaction.

To examine the effects of different surfactants on the reaction, several other micelles, including anionic, non-ionic, and cationic systems, were applied under comparable conditions. The results are shown in Table 1.

As shown in Table 1, satisfactory yields were observed with anionic surfactant micelles, e.g. SDS (entry 2, 87%), SDBS (entry 4, 87%), and SLS (entry 5, 63%). Other surfactants, including nonionic (entry 6) and cationic (entries 7–10) did not efficiently promote the reaction and the observed yields were much lower.



1a **2a** **3**

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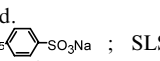
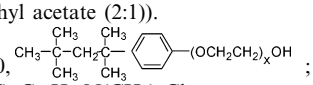
Table 1. Proline catalyzed aldol reactions in different aqueous surfactants micelles

Entry	Surfactant	*T* (h)	Yield (%)[a]	Entry	Surfactant	*T* (h)	Yield (%)
1	H_2O	120	15	6	Trtion-100[c]	120	Trace
2	SDS	24	87	7	CTAB[c]	120	7
3	SDS(only)[b]	120	12	8	OTAC[c]	120	Trace
4	SDBS[c]	5	87	9	DDBAC[c]	120	29
5	SLS[c]	60	63	10	DTAC[c]	120	Trace

[a] Yields based on isolation with column chromatography (petroleum/ethyl acetate (2:1)).
[b] Proline was not added.
[c] SDBS denotes  ; SLS, $C_{12}H_{25}OSO_3Na$; Trtion-100,  ; CTAB, $C_{16}H_{33}N(CH_3)_3Br$; OTAC, $C_{18}H_{37}N(CH_3)_3Cl$; DDBAC, $C_{12}H_{25}N(CH_3)_2(CH_2C_6H_5)Cl$ and DTAC, $C_{12}H_{25}N(CH_3)_3Cl$.

In order to explore the generality of this reaction, a range of substrates was examined. The results of these reactions are presented in Table 2. Inspection of Table 2 shows that among the aldehydes examined, only nitrobenzaldehydes performed well (entries 1–3). The reactions of 3- and 2-nitrobenzaldehydes gave the corresponding aldol products **4** (74%, entry 2) and **5** (52%, entry 3) in reasonable yields.

On the basis of these observations, we extended the study to the reactions of nitrobenzaldehydes with other ketones in SDS micelles (Table 2 entries 4–13). First, the reactions of cyclopentanone and cyclohexanone were investigated. The results indicate that both of these cyclic ketones underwent the desired cross-aldolization with **2**, and afforded *syn*/*anti*-mixtures of the aldol products **12**–**17** in reasonable yields. The diastereoselectivity of these reactions is quite good. The *anti*-products are favored, as indicated by the *anti*/*syn* ratios of about 80:20 (entries 7–11) and 97:3 (entry 12). These results are much better than those of the corresponding reactions in organic solvent, where the *anti*/*syn* ratios of the reactions of 4-nitrobenzaldehyde with cyclohexanone and cyclopentanone were found to be only 41/24 and 46/27, respectively.[5b]

Next, reactions of 2-butanone were investigated. An interesting feature of these reactions is that this substrate resulted in two regioisomeric forms, one of which gave *syn*/*anti* isomers. Upon stirring an aqueous mixture of nitrobenzaldehyde 2-butanone, proline, and SDS at 40°C, the corresponding aldol products **6**, **8**, and **10** (from nucleophilic attack of the methyl group) were formed in yields of 23, 17 and 7%, respectively. Products **7**, **9** and **11** (from nucleophilic attack of the methylene group) were also formed, but in higher yields (66, 42 and 13%). This is in contrast to the previous observation that only products **6**, **8**, and **10** were observed in organic solvent.[5b] The higher yields of the methylene aldol products yields indicate that in this reaction the thermodynamically more stable enamine **20** is favored over the kinetically more stable enamine **19** (Fig. 1). It should be noted that the yields of the *anti*-products are higher than those of the corresponding *syn* products (39/27 for **7**, 22/20 for **9**, and 10/3 for **10**).

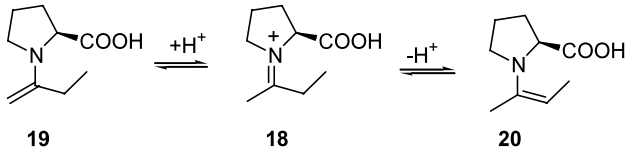


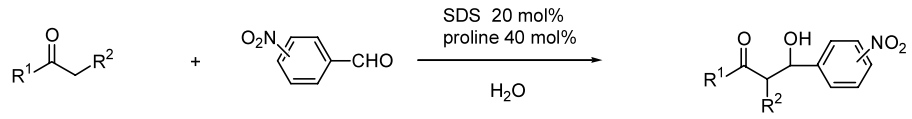
Figure 1. Proposed iminium and enamine intermediates.

In contrast to the reaction of benzyl methyl ketone, where no reaction was observed (entry 13), moderate to excellent yields of the aldol products were obtained for aliphatic ketones and activated aromatic substrates such as nitrobenzaldehyde (Table 2). Among substrate **2**, the yields of the reactions of **2a** are the highest, followed those by **2b** and then **2c**. The differences in reaction yields and in required reaction times (Table 2, column 4) may be accounted for by the steric effect of the nitro substituent. Importantly, the diastereoselectivity and the chemical yields of these aldol reactions in micelles are much better than those of the corresponding reactions in organic solvent.[5b]

In organic solvent, the reaction was proposed to proceed by an amine base and Brønsted acid co-catalyzed mechanism, where both the pyrrolidine ring (in L-proline) and carboxylic acid group are required.[5b] The hydrogen bonds in the complexes **21** and **25** (Scheme 1) were found to be the reaction driving force.[5a,b]

However, we found that only the pyrrolidine ring (in L-proline) was required in micelles, so the carboxylic acid group (in L-proline) may not be involved. In other experiments, we found that L-proline methyl ester and L-hydroxyproline can catalyze the same aldol reaction in micelles, giving the aldol product **3** with yields of 82 and 70%, respectively. Most other natural L-amino and some D-amino acids were also examined, only giving trace or no aldol products. The above results imply that the reaction mechanism in micelle may be different from that in organic solvents. On this basis, an amine catalyzed mechanism for the aldol reaction in micelles was proposed (Scheme 1). The hydrogen bond between the carboxylic acid and substrates in organic solvent (vide supra) may be substituted by a stronger hydrogen bond between water and substrate in the micelles. The reaction driving force in micelles may be related to the

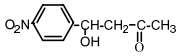
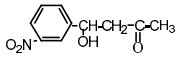
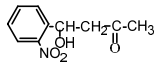
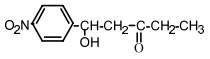
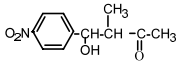
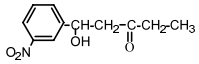
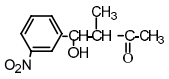
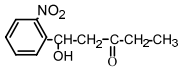
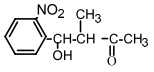
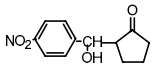
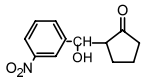
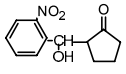
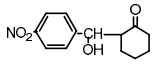
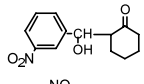
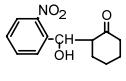
Table 2. Aldol reactions of ketones with nitrobenzaldehydes in SDS micelle



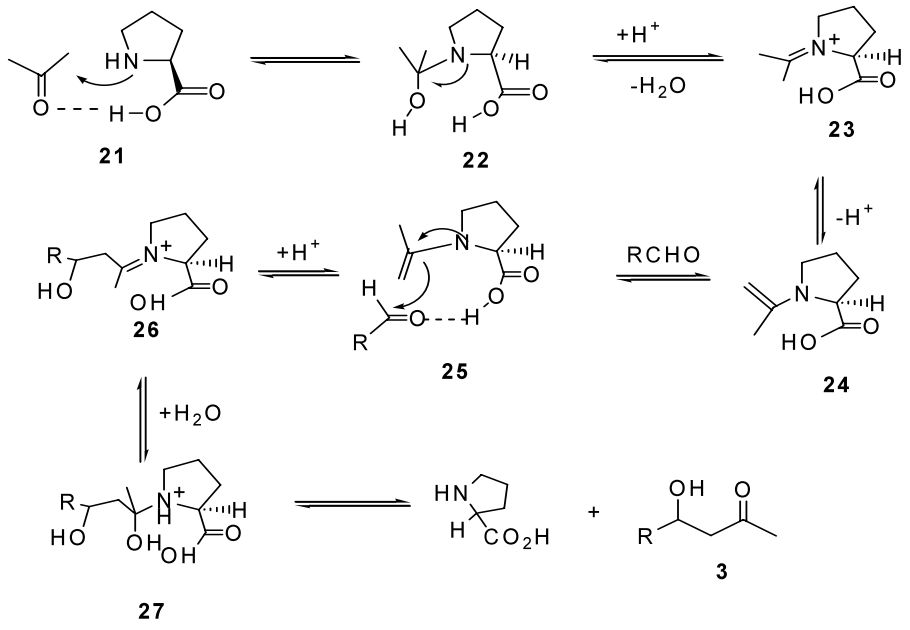
1 **2** **3- 17**

1a: acetone
1b: 2-butanone
1c: cyclopentanone
1d: cyclohexanone
1e: benzylmethylketone

2a: *p*-nitro
2b: *m*-nitro
2c: *o*-nitro

Entry	Ketone	Aldehyde	Time/h	Product		Yield (%)[a]
1	**1a**	**2a**	24		**3**	87
2	**1a**	**2b**	72		**4**	74
3	**1a**	**2c**	120		**5**	52
4	**1b**	**2a**	96		**6**	23
					**7**	66 (39 : 27)[b]
5	**1b**	**2b**	120		**8**	17
					**9**	42 (22 : 20)[b]
6	**1b**	**2c**	192		**10**	7
					**11**	13 (10 : 3)[b]
7	**1c**	**2a**	120		**12**	81 (80:20)[b]
8	**1c**	**2b**	144		**13**	51 (81:19)[b]
9	**1c**	**2c**	168		**14**	44 (78:22)[b]
10	**1d**	**2a**	96		**15**	78 (74:26)[c]
11	**1d**	**2b**	144		**16**	68 (78:22)[c]
12	**1d**	**2c**	192		**17**	24 (93:7)[b]
13	**1e**	**2a**	144			No reaction

[a] Yields based on isolation with column chromatography (petroleum/ethyl acetate (2:1)).
[b] *anti*/*syn* ratio detected by NMR.
[c] *anti*/*syn* ratio based on isolation with column chromatography.



Scheme 1. A proline directly catalyzed aldol reaction mechanism in micelles.

hydrophobic force[13] which compresses the reactants together in a highly compact arrangement of complexes **21** and **25**. The strong substituent steric effect of the nitro group on the reaction can also be explained by the compressed compact substrates in a restricted hydrophobic domain. The detailed reaction mechanism is currently under investigation.

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