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# Note

## Pyrrolidine catalyzed regioselective and diastereoselective direct aldol reaction in water

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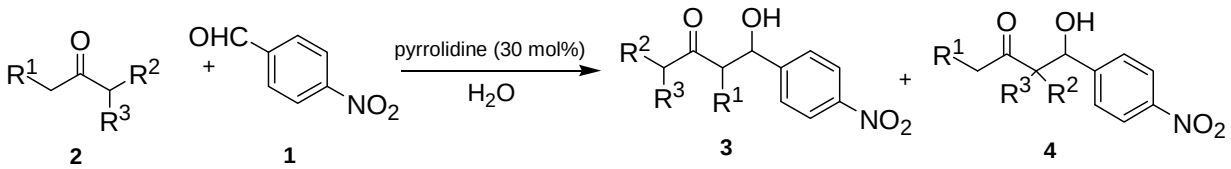
Pyrrolidine catalyzed direct aldol reaction of methyl ketones other than acetone with 4-nitrobenzaldehyde in water affords linear aldol addition product arising from the selective attack of the unsubstituted carbon of the unsymmetrical ketone. The present methodology provides an experimentally simple and green process for regioselective synthesis of β-hydroxyketones in water.

**Keywords**: Direct aldol reaction, pyrrolidine catalysis, regioselective synthesis, diastereoselective synthesis, aqueous media, organocatalysis

Aldol reactions involve the generation of new carbon-carbon bond with simultaneous formation of stereocenter at carbinol carbon in aldol product[1]. All aldol reactions are potentially stereogenic, with certain combinations of enol or enolate and carbonyl resulting in the creation of two chiral centers in the product. In earlier time, this was a big limitation as number of products and their isomers were obtained in final step due to uncontrolled selectivity (Regio-, diastereo- and enantioselectivity). Also, dehydration of the aldol addition product leading to thermodynamically more stable α,β-unsaturated carbonyls under the reaction conditions restricted the synthetic application of aldol reaction. The last three decades have witnessed a renaissance in the aldol reaction. The principal factor for the rebirth of the aldol reaction as modern method of synthesis is probably the discovery that its stereochemistry can be controlled quite effectively with the chemoselective formation of the β-hydroxy carbonyls[2]. As a result, aldol reaction has come up as a principal chemical reaction for the stereoselective construction of complex polyol structures and become one of the most venerable organic reactions in organic synthesis[3].

We have been interested in stereoselective synthesis in water. Recently, we have reported pyrrolidine as an effective organocatalyst in water for the direct aldol addition reaction between acetone and range of aromatic and heterocyclic aldehydes providing β-hydroxyketones in high yields and in a short reaction time of 5 min[4]. The study of the reaction mechanism revealed the involvement of the reactive enamine intermediate in pyrrolidine catalyzed direct aldol reaction in water. Based on which the chiral version of the pyrrolidine catalysis for direct aldol reaction has also been developed in water[5]. It is envisaged that the direct aldol reactions of unsymmetrical donor ketones with aromatic aldehydes under pyrrolidine catalysis will be of particular interest since they could form two regioisomer products, one of which gives rise to possible *syn/anti* isomers.

We report herein the extended scope of the pyrrolidine catalyzed direct aldol reaction in water with regioselective and diastereoselective direct aldol reaction of methyl ketones and 4-nitrobenzaldehyde in water. The reactions of different donor ketones (**2a-h**) with 4-nitrobenzaldehyde **1**, using pyrrolidine as catalyst (**Scheme I**) have been performed. The results of these investigations have been tabulated in **Table I**. The conversions in all the cases are 93-99%. The rate of reaction is sensitive to the presence of bulkier substituents at the α-carbon of the donor ketones as compared with the reaction time of 5 min for the direct aldol reaction of acetone[5]. The reaction of 2-butanone **2a** with 4-nitrobenzaldehyde **1** in the presence of pyrrolidine provide products **3a** and **4a** with a regioselectivity of 76:24 and overall conversion of 98% in a reaction time of 30 min (**Table I**, **entry 1**). While the same reaction with 2-pentanone **2b** as donor ketone affords **3b** and **4b** with regioselectivity of 95:5 and 99% conversion (**Entry 2**). Aldol reaction of 2-octanone **2c**, 4-phenyl-2-butanone **2d** and pyruvaldehyde-1,1-dimethylacetal **2e** affords **3c**, **3d** and **3e** respectively, as sole product with >99% regioselectivity resulting from the nucleophilic attack of the methyl group of the respective ketones (**Entry 4-6**). The observed regioselectivity in favour of linear aldol products possibly originates from the greater reactivity of the




**2** **1** **3** **4**

**a**; $R^1$ = H, $R^2$ = $CH_3$, $R^3$ = H
**b**; $R^1$ = H, $R^2$ = $CH_2CH_3$, $R^3$ = H
**c**; $R^1$ = H, $R^2$ = -$(CH_2)_4CH_3$, $R^3$ = H
**d**; $R^1$ = H, $R^2$ = -$CH_2Ph$, $R^3$ = H
**e**; $R^1$ = H, $R^2$ = $R^3$ = $OCH_3$
**f**; $R^1$ =$CH_3$, $R^2$ = $CH_3$, $R^3$ = H
**g**; $R^1R^2$ = -$(C H_2)_3$-, $R^3$ = H
**h**; $R^1R^2$ = -$(CH_2)_2$-, $R^3$ = H

**Scheme I**

**Table I —** Pyrrolidine catalyzed reaction of ketones (**2a-h**, 40 mmoles) with **1** (2 mmoles)

| Ketone | Time | Conversion† % | Yield (%)‡ | | Regioselectivity† | dr†syn/anti |
|---|---|---|---|---|---|---|
| | | | 3 | 4 | 3:4 | |
| a | 30 min | 98 | 71 | 11 | 76:24 | 1:2 |
| b | 105 min | 99 | 87 | 5 | 95:5 | 1:4 |
| c | 12h | 99 | 87 | - | >99 | - |
| d | 4h | 99 | 93 | - | >99 | - |
| e | 20 min | 99 | 87 | - | >99 | - |
| f | 12h | 99 | 92 | - | - | 1:2 |
| g | 5h | 93 | 73 | - | - | 4:1 |
| h | 30 min | 99 | 89 | - | - | 1:2 (1:19)* |

† Determined from $^1$H NMR.
‡ Isolated yield after column chromatography
* After single crystallization.

less substituted enamine intermediate (kinetically stable) vis-à-vis more substituted enamine intermediate (thermodynamically stable). These results suggest that under these experimental conditions, kinetic control prevails leading to linear isomer as major product[6]. Thus we propose that regioselective formation of the enamine intermediate is a kinetic phenomenon under pyrrolidine catalysis in water. This observed regioselection is contrary to that reported for aldol addition reaction in the presence of alkali metal bicarbonates and L-proline in aqueous media[7]. Earlier reports on the aldol reaction of 2-butanone **2a** with 4-nitrobenzaldehyde **1** in aqueous media catalyzed by proline as organocatalyst favours non-linear regioisomer as the major product[7]. The regioselectivity of the aldol reaction with unsymmetrical ketones in favour of linear isomer is a rarity. The antibody 84G3 catalyzed aldol reaction in buffer[8] and proline catalyzed aldol reaction in organic media at ambient conditions[6] and at 2 GPa[9] has recently been shown to be highly regioselective for linear isomer. Other than these, no known organocatalysts display similar level of the regio-control at ambient conditions.

The diastereoselectivity of non-linear aldol products (**4a** and **4b**) arising from their respective unsymmetrical donor ketones (**2a** and **2b**) is in favour of *anti* diastereomer. The symmetrical donor ketones such as 3-pentanone **2f**, cyclopentanone **2g** and cyclohexanone **2h** gave product **3f**, **3g** and **3h** with good diastereoselectivity (**Entry 3**, **7** and **8**, respectively). The diastereoselectivity of cyclopentanone and cyclohexanone follows the normal trend, cyclopentanone as donor ketone favours the *syn* product whereas cyclohexanone favours the *anti*[10]. The *anti* isomer of the product with cyclohexanone as donor ketone can be obtained in >95% diastereomeric excess through fractional crystallization as *anti* isomer crystallizes in preference to its *syn* counterpart from the crude product.

## Experimental Section

### General procedure of aldol reaction of 1a with different donor ketones 10

To a stirring mixture of **1** (302 mg, 2 mmoles) and aliphatic ketone **2** (40 mmoles) in water (3 mL), pyrrolidine (30 mol%) was added as catalyst. The reaction was monitored by TLC and on completion was ceased by the addition of saturated $NH_4Cl$ solution (25 mL) followed by extraction with 100 mL of $CH_2Cl_2$ (2 × 50 mL). The organic layer was washed with water (2 × 50 mL) and dried over anhydrous $Na_2SO_4$ and evaporated to obtain crude product.

Column chromatography of the crude on silica gel (60-120) using mixture of ethyl acetate and hexane in varying proportions as eluent, gave pure product.

**1-Hydroxy-1-(4′-nitrophenyl)-pentan-3-one[7c] (3a)** Yield, 71% (304 mg); Pale yellow liquid; $R_f$ 0.3 (ethyl acetate: hexane, 1:3); $^1$H NMR ($CDCl_3$): δ 1.07 (t, 3H, *J* = 7.2 Hz, $CH_3$), 2.46 (q, 2H, *J* = 7.2 Hz, $CH_2$), 2.75-2.79 (m, 2H, $CH_2$), 5.25-5.29 (m, 1H, CH), 7.50 (d, 2H, *J* = 8.6 Hz, ArH), 8.17 (d, 2H, *J* = 8.6 Hz, ArH); $^{13}$C NMR ($CDCl_3$): δ 7.47, 36.8, 50.2, 69.1, 123.7, 126.4, 126.8, 127.5, 147.3, 150.2, 211.3.

**1-Hydroxy-1-(4′-nitrophenyl)hexan-3-one[8] (3b)** Yield, 87% (388 mg); Yellow crystalline solid, mp: 56-71°C; $R_f$ 0.3 (ethyl acetate:hexane, 1:3); MS (*m/z*) FAB: 223 ($M^+$); IR ($CHCl_3$): 3446, 1701, 1517 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 0.92 (t, 3H, *J* = 7.4 Hz, $CH_3$), 1.59 (sextet, 2H, *J* = 7.4 Hz, $CH_2$), 2.40 (t, 3H, *J* = 7.4 Hz, $CH_2$), 2.73-2.76 (m, 2H, $CH_2$), 3.58 (d, 1H, *J* = 3.0 Hz, OH), 5.22 (m, 1H, CH), 7.50 (d, 2H, *J* = 8.6 Hz, ArH), 8.18 (d, 2H, *J* = 8.6 Hz, ArH); $^{13}$C NMR ($CDCl_3$): δ 13.7, 16.9, 45.4, 50.7, 68.9, 123.6, 126.4, 147.3, 150.3, 210.4.

**1-Hydroxy-1-(4′-nitrophenyl)nonan-3-one (3c)** Yield, 87% (485 mg); Yellow liquid; $R_f$ 0.3 (ethyl acetate:hexane, 1:2); MS (*m/z*) FAB: 279 ($M^+$); Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.46; H, 7.85; N, 5.70; IR ($CHCl_3$): 3414, 2930, 1707, 1522 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 0.88 (t, 3H, *J* = 6.9 Hz, $CH_3$), 1.27 (br s, 6H, 3 × $CH_2$), 1.58 (br t, 2H, $CH_2$), 2.44 (t, 2H, *J* = 7.8 Hz, $CH_2$), 2.80-2.87 (m, 2H, $CH_2$), 5.26 (dd, 1H, *J* = 7.8 and 4.2 Hz, CH), 7.53 (d, 2H, *J* = 8.7 Hz, ArH), 8.21 (d, 2H, *J* = 8.7 Hz, ArH); $^{13}$C NMR ($CDCl_3$): δ 13.9, 23.3, 23.3, 28.6, 31.4, 43.5, 50.5, 68.9, 123.6, 126.3, 147.1, 150.3, 210.9.

**1-Hydroxy-1-(4′-nitrophenyl)-5-phenylpentan-3-one (3d)** Yield, 93% (556 mg); Yellow liquid; $R_f$ 0.2 (ethyl acetate:hexane, 1:2); MS (*m/z*) FAB: 299 ($M^+$). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.05; H, 5.79; N, 5.03; IR ($CHCl_3$): 3448, 3028, 2927, 1709, 1618, 1346 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.76-2.80 (m, 4H, 2 × $CH_2$), 2.92 (t, 2H, *J* = 6.9 Hz, $CH_2$), 3.57 (br s, 1H, OH), 5.23 (t, 1H, *J* = 6.0 Hz, CH), 7.14-7.31 (m, 5H, ArH), 7.48 (d, 2H, *J* = 8.4 Hz, ArH), 8.19 (d, 2H, *J* = 8.4 Hz, ArH); $^{13}$C NMR ($CDCl_3$): δ 29.5, 45.0, 50.9, 68.9, 123.6, 123.7, 126.3, 127.0, 128.2, 128.5, 128.6, 128.7, 128.8, 140.3, 147.3, 149.9, 209.7.

**4-Hydroxy-1,1-dimethoxy-4-hydroxy-4-(4′-nitrophenyl)butan-2-one 3e** Yield, 87% (468 mg); pale yellow liquid; $R_f$ 0.3 (ethyl acetate:hexane, 1:3); MS (*m/z*) FAB: 269 ($M^+$); MS ES-TOF: Exact mass calculated for $C_{12}H_{15}NO_6$: 269.0899, Found: 268.0848 (M-H)$^-$; IR ($CHCl_3$): 3419,1713, 1520 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.98-3.00 (m, 2H, $CH_2$), 3.43 (s, 3H, $OCH_3$), 3.44 (s, 3H, $OCH_3$), 4.46 (s, 1H, CH), 5.29 (t, 1H, *J* = 6.3 Hz, CH), 7.55 (d, 2H, *J* = 8.4 Hz, ArH), 8.21 (d, 2H, *J* = 8.4 Hz, ArH); $^{13}$C NMR ($CDCl_3$): δ 45.8, 55.3, 68.7, 104.3, 123.7, 126.5, 147.4, 150.0, 204.9.

**1-Hydroxy-2-methyl-1-(4′-nitrophenyl)pentan-3-one[10] 3f** Yield, 92% (409 mg) mixture of diastereomers (*syn:anti*, 1:2); pale yellow liquid; $R_f$ 0.3 (ethyl acetate:hexane, 1:3); $^1$H NMR ($CDCl_3$): δ 0.96-1.08 (m, 6H, 2 × $CH_3$), 2.33-2.89 (m, 3H, CH and $CH_2$), 4.81 (d, 1H, CH of *anti* diastereomer), 5.18 (d, 1H, CH of *syn* diastereomer), 7.47 (d, *J* = 8.8 Hz, 2H, Ar-H), 8.16 (d, *J* = 8.8 Hz, 2H, Ar-H); $^{13}$C NMR ($CDCl_3$): δ 7.2 (+ve), 7.3 (+ve), 9.9 (+ve), 14.1 (+ve), 35.0 (-ve), 36.2 (-ve), 51.5 (+ve), 52.1 (+ve), 72.0 (+ve), 75.3 (+ve), 123.2 (+ve), 123.4 (+ve), 126.7 (+ve), 127.3 (+ve), 147.2, 149.3, 149.6, 215.4, 216.8.

**2-[Hydroxy-(4′-nitrophenyl)methyl]-cyclopentanone 3g** Yield, 73% (324 mg) as a mixture of two diastereomers (*syn:anti*, 4:1); pale yellow liquid; $R_f$ 0.2 (ethyl acetate: hexane,1:3); $^1$H NMR ($CDCl_3$): δ 1.17-2.47 (m, 7H, CH and 3 × $CH_2$), 4.81 (d, 1H, *J* = 9.0 Hz, CH of *anti* diastereomer), 5.40 (d, 1H, *J* = 2.7 Hz, CH of *syn* diastereomer), 7.51 (d, 2H, *J* = 9.0 Hz, ArH), 8.19 (d, 2H, *J* = 9.0 Hz, ArH); $^{13}$C NMR ($CDCl_3$): δ 24.3, 24.6, 25.5, 27.5, 30.2, 42.4, 42.5, 56.3, 57.0, 69.8, 73.5, 123.0, 123.0, 126.5, 127.2, 147.4, 147.9, 149.2, 213.5, 214.6.

**2-[Hydroxy-(4′-nitrophenyl)methyl]-cyclohexanone 3h** Yield, 89% (401 mg) as a mixture of two diastereomers (*syn:anti,* 1:2); pale yellow liquid; $R_f$ 0.2 (ethyl acetate:hexane, 1:3); $^1$H NMR ($CDCl_3$): δ 1.24-2.54 (m, 9H, CH and 4 × $CH_2$), 4.90 (d, 1H, *J* = 8.4 Hz, CH of *anti* diastereomer), 5.46 (br s, 1H, CH of *syn* diastereomer), 7.50 (d, 2H, *J* = 8.8 Hz, ArH), 8.21 (d, 1H, *J* = 8.8 Hz, ArH); $^{13}$C NMR ($CDCl_3$): δ 24.5, 24.6, 25.8, 27.5, 27.6, 30.6, 42.4, 42.5, 56.7, 57.0, 69.9, 73.8, 123.3, 123.4, 126.5, 127.8, 147.4, 148.3, 149.2, 213.9, 214.6.

## Conclusion

The scope of pyrrolidine catalyzed direct aldol reaction in water using methyl ketones other than acetone, which afford linear aldol addition product

arising from the unsubstituted carbon of the unsymmetrical ketone have been studied. The present methodology provides an experimentally simple and green process for regioselective synthesis of β-hydroxyketones in water. The symmetrical ketones provide the aldol addition product in moderate to good diastereoselectivity. The aldol addition product of cyclohexanone and 4-nitrobenzaldehyde can be obtained in high diastereoselectivity after a single crystallization of the crude product.

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