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Direct aldol and tandem Mannich reactions in room temperature ammonia solutions

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Abstract—An economical, simple, and efficient direct aldol reaction via the double activation of both aldehydes and ketones by ammonia has been developed. An unprecedented tandem Mannich reaction was observed when hydroxybenzaldehydes, pyrrole-2-carboxyaldehyde, and indole-3-carboxyaldehyde were employed to afford 2,2-dimethyl-6-aryl-4-pyrilidinones in moderate to good yields.

The aldol reaction is one of the most powerful transformations for new carbon–carbon bond formation. The wide presence of aldol adducts in both natural products and organic synthesis has intrigued a variety of synthetic approaches, ranging from the reaction between aldehydes and preformed enolates to the direct aldol reaction between aldehydes and unmodified ketones.[1,2] In terms of atom economy,[3] the direct aldol reaction is most desirable since no atom is wasted during the coupling. Recently, amino acid (such as L-proline) and amine acid complexes[4] have been demonstrated to be efficient catalysts for the asymmetric direct aldol reaction. It is widely accepted that the reaction proceeded via the double activation of both the donor and acceptor. As a versatile and low cost nitrogen source, ammonia has been widely employed in the organic synthesis, particularly in the multi-component reactions, such as α-aminoalkylation and α-aminoallylation of carbonyl compounds.[5] To the best of our knowledge, there is no report on the direct aldol reaction carried out in ammonia solution. We envision that ammonia may function as an activator for both aldehydes and unmodified ketones and thus promote the direct aldol reaction between aldehydes and unmodified ketones. In this study, we have demonstrated that ammonia is indeed an effective activator for the direct aldol reaction between aldehydes and unmodified ketones in MeOH solution. Besides, we also have discovered an efficient and unprecedented ammonia participated multi-component construction of 2,2-dimethyl-6-aryl-4-pyrilidinonesy.

To investigate the role of ammonia in the direct aldol reaction, we chose the reaction between benzaldehyde and acetone as a model reaction for study. Commercially available 7 N ammonia in MeOH was chosen as ammonia source. Acetone (10 mmol) and benzaldehyde (1 mmol) were added to the solution of 7 N ammonia in MeOH (1 mL) in DMSO (2.5 mL) at room temperature and the solution was stirred for 16 h. After normal work-up and silica gel chromatography,[6] the desired aldol product was obtained in 45% yield. From the crude ^{1}H NMR spectrum, the ratio of four possible products was found to be **I**–**II**–**III**–**IV** = 10:1:2.6:0 (Eq. 1, Table 1, entry 1). A preliminary solvent screening revealed that MeOH was the best solvent that favored the direct aldol reaction, giving the aldol adduct in very high ratio (Table 1, entry 2). Efforts to lower the amount of ammonia by using 100 μL of 7 N ammonia in MeOH (about 0.7 mmol) led to the incompletion of the reaction (about 25% conversion). It was also found that excess of acetone (10 equiv) was crucial for the formation of the aldol adduct. It was noteworthy that the reaction carried out in 2.5 mL H_2O also afforded the aldol adduct in a relatively high ratio (Table 1, entry 3). The presence of

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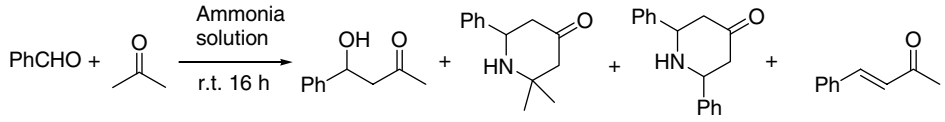
Table 1. Direct aldol reaction of benzaldehyde and acetone under different conditions



(1)

I II III IV

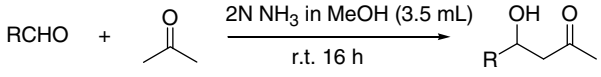
Entry	Ammonia source	Solvent	Ratios of **I–II–III–IV**[a]
1	7 N NH_3 in MeOH 1 mL	2.5 mL DMSO	10:1:2.6:0[b]
2	7 N NH_3 in MeOH 1 mL	2.5 mL MeOH	**42:3:1:0**
3	7 N NH_3 in MeOH 1 mL	2.5 mL H_2O	30:0:1:3.2[b]
4	7 N NH_3 in MeOH 1 mL	2.5 mL CH_2Cl_2	24:6:2:1[b]
5	25% NH_4OH 0.5 mL	2.5 mL H_2O	23:0:1:5
6	Ammonia gas	Neat	8:6:1:2[c]

[a] Determined based on the integration of crude ^1H NMR.
[b] The reaction cannot proceed completely within the specified time, about 5–10% benzaldehyde was observed from the crude NMR spectrum.
[c] Ammonia gas was bubbled into the mixture of benzaldehyde (1 mmol) and acetone (10 mmol) for 5 min, and then reacted at room temperature for 16 h.

water resulted in the increase of the condensation product and the incompletion of the reaction. NH_4OH solution was also studied and the same trend was observed as shown in entry 3 (Table 1, entry 5). Considering the factors of economy and operational simplicity, neat condition was studied as well. Unfortunately, no selectivity between **I** and **II** was observed (Table 1, entry 6).

With these interesting results in hand, we next studied the scope of the reaction by using different aldehydes and the results are summarized in Table 2.[11] The reaction worked smoothly for benzaldehyde derivatives with both electron-withdrawing and electron-donating functional groups (entries 2–8) and heteroaromatic aldehydes (entries 11 and 12) to afford the corresponding

Table 2. Direct aldol reaction of different aldehydes and acetone



(2)

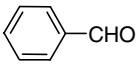
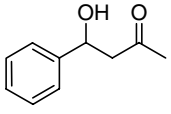
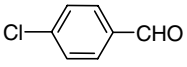
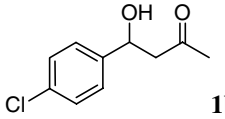
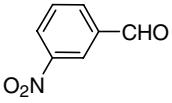
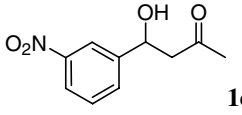
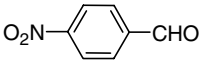
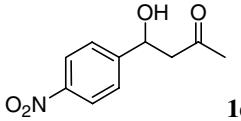
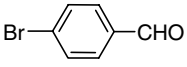
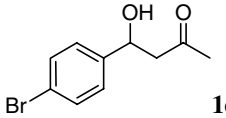
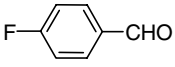
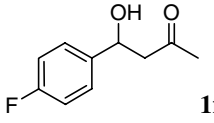
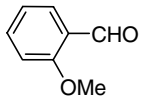
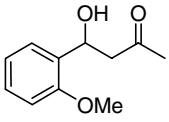
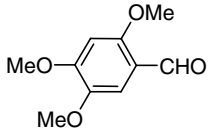
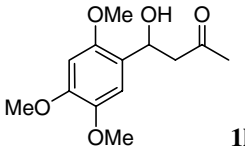
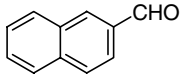
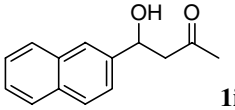
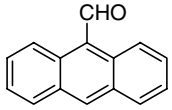
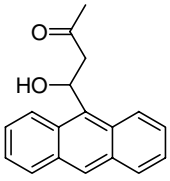
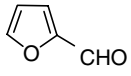
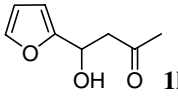
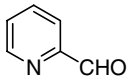
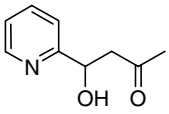
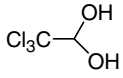
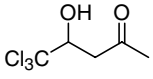
Entry	Aldehydes	Products	Yield (%)[a]
1		 **1a**	70
2		 **1b**	76
3		 **1c**	80
4		 **1d**	83
5		 **1e**	75
6		 **1f**	77

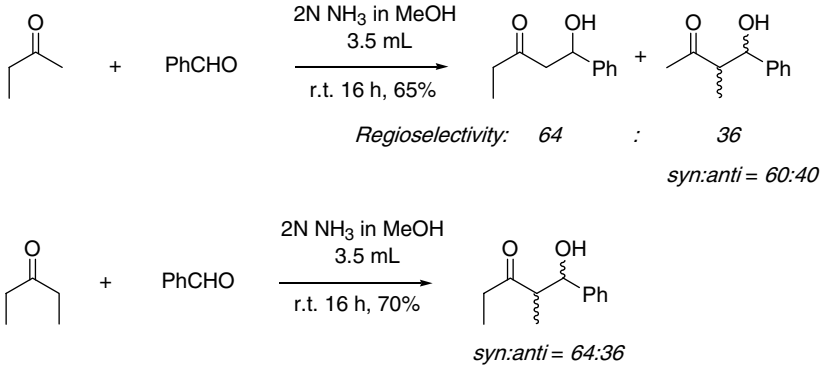
Table 2 (*continued*)

Entry	Aldehydes	Products	Yield (%)[a]
7		 **1g**	60
8		 **1h**	45
9		 **1i**	76
10		 **1j**	73
11		 **1k**	76
12		 **1l**	80
13		 **1m**	48

[a] Isolated yield.

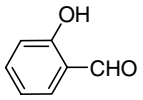
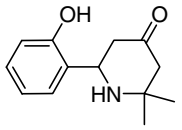
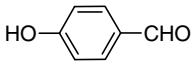
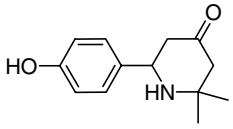
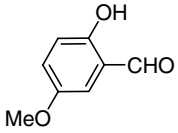
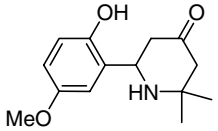
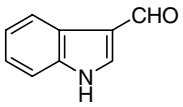
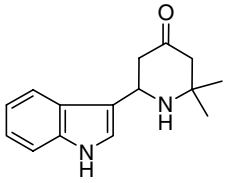
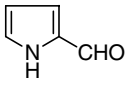
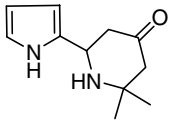
aldol products in moderate to high yields. Besides, naphthaldehyde and anthracenecarboxyaldehyde also exhibited high reactivity (entries 9 and 10). Chloral, which existed in the form of hydrate also afforded the desired aldol product in 48% yield. The reaction was also extended to 2-butanone and 3-pentanone with moderate regio- and diastereoselectivities (Scheme 1).

It is worth noting that 2,2-dimethyl-6-aryl-4-pyrilidinones were formed as major products instead of the desired aldol adducts when benzaldehyde derivatives with a hydroxy group at *ortho* or *para* position were employed in the above direct aldol reaction (Table 3, entries 1–3).[11] This provided an efficient and unprecedented synthetic route toward 2,2-dimethyl-6-aryl-4-



Scheme 1.

Table 3. Tandem Mannich reactions between aldehydes and acetone

Entry	Aldehyde	Product	Yield (%)[a]
1		 **2a**	85
2		 **2b**	80
3		 **2c**	75
4		 **2d**	45[b]
5		 **2e**	50[b]

[a] Isolated yield.
[b] The reaction was slow under the reaction condition, about 70% conversion was observed within 2 days.

pyrilidinones, which were difficult to achieve using other methods.[7] In addition to hydroxybenzaldehydes, indole-3-carboxyaldehyde and pyrrole-2-carboxyaldehyde also showed the same activity although relatively lower yields were obtained in these cases (Table 3, entries 4 and 5).

Although the precise reaction mechanism is still unclear, we speculate that the reaction might proceed through *gem*-amino-hydroxy intermediates of aldehydes formed from aldehydes and ammonia in methanol.[8] The *gem*-amino-hydroxy intermediates can either react with enamine derived from acetone and ammonia via pathway **I** to afford the aldol adducts[9] or form imines, which will react with enamine derived from acetone via pathway **II** to produce the tandem Mannich products (Fig. 1). As for hydroxybenzaldehydes, pyrrole-2-carboxyaldehyde and indole-3-carboxyaldehyde, the presence of proton on either oxygen or nitrogen may favor the formation of imines and consequently pathway **II**. To test the special role of ammonia in this reaction, we conducted the

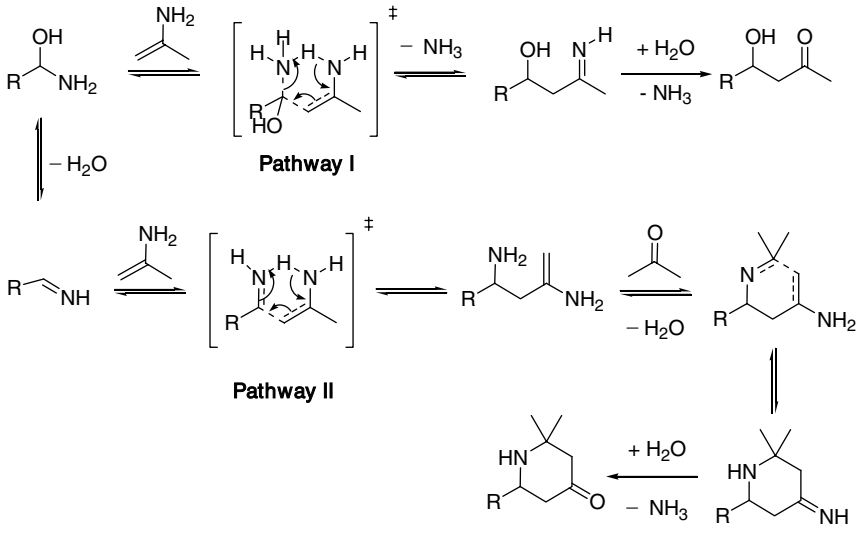


Figure 1. Proposed reaction pathway for the ammonia promoted direct aldol and tandem Mannich reaction.

reaction of benzaldehyde and acetone in 2 N solution of $MeNH_2$ in MeOH (3.5 mL) and no desired aldol adduct or tandem Mannich product was obtained. This might be due to the difficulty in forming the *gem*-amino-hydroxy intermediate.

To summarize, we have developed an economical, simple, and efficient direct aldol reaction via the double activation of both aldehydes and ketones by ammonia. Under the same condition, an unprecedented tandem Mannich reaction was observed when hydroxybenzaldehydes, pyrrole-2-carboxyaldehyde, and indole-3-carboxyaldehyde were employed to afford 2,2-dimethyl-6-aryl-4-pyrilidinones. Since the racemic aldols can be kinetically resolved using enzymes,[10] the combination of this approach with the enzyme catalyzed kinetic resolution may provide an economical process for the preparation of enantiomerically pure β-hydroxy ketones. The study on the mechanism as well as the expansion of the scope of the reaction is in progress.

Acknowledgments

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References and notes

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