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An efficient method for direct aldol reactions catalyzed by pyrrolidine/catechol The influence of cooperation of Brønsted acidity and hydrogen-bond on the reaction

Changyun Ji [a], Yungui Peng [a,*], Chengzhi Huang [a], Ning Wang [a], Zhen Luo [a], Yaozhong Jiang [b]

[a] *The School of Chemistry and Chemical Engineering, Southwest Normal University, Beibei, Chongqing 400715, China*
[b] *Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, China*

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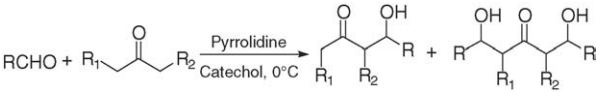
Abstract

The aldol reactions of aromatic aldehydes with ketones catalyzed by pyrrolidine were accelerated by addition of a series of Brønsted acids to the reaction medium and found that the catechol was the most effective co-catalyst. The combination of pyrrolidine and catechol are very efficient for catalyzing the reaction to proceeding under mild conditions with high yield in short time.



Keywords: Aldol reaction; Pyrrolidine; Catechol; Bifunctional catalysis

1. Introduction

The direct aldol reaction is one of the most powerful and efficient methods for carbon–carbon bond formation [1–3]. These developments include: (i) Lewis acid-catalyzed Mukaiyama-type [4–9] and Lewis base-catalyzed [8–13] aldol reactions. (ii) Bimetallic and heterobimetallic bifunctional Lewis acid/Brønsted base catalyzed [14–16] direct aldol reactions. (iii) Small organic molecules [1,2,17–30] catalyzed direct aldol reactions. However, some of the classical and conventional aldol reaction has not been well exploited due to the following reasons: (1) side reactions such as self-condensation of the ketone or/and dimerization of the aldehyde can be a problem; (2) the hash reaction conditions employed which, usually require a strong acid, such as *p*-TsOH [2], HCl or base, such as KOH [31] and NaOH [12,13] makes it unattractive in the synthesis of complex molecules which possess acid or base sensitive functional groups; (3) the desired aldol products is usually accompanied by dehydration side products [8,9,12,13,31]; (4) unsatisfactory yield [16] is observed in most of the case and (5) long reaction time is required. Therefore, mild reaction conditions are much sought after to overcome some, if not all, the above problems.

Nature's catalytic systems (enzymes, antibodies as well as others) are more efficiency and apparently do not need long reaction time under mild conditions. Chemists have learned much from Nature and have very successfully been using the catalytic antibody approach including evolutions [32]. It is clear that the recognition process in such systems relies on hydrogen bonding and hydrophobic interactions [32,33]. Barbas and co-workers have screened a series of acid and found that the combination of pyrrolidine/acetic acid (pKa = 4.8) was superior to proline in the reactivity when used them in the aldol reaction [1]. The success of such reaction relies on enamine intermediate, which was formed in situ between ketone and pyrrolidine. In our laboratory, we have studied systematically the influence of acidity on different catalytic circle stages of the direct aldol reaction and

* Corresponding author. Tel.: +86 23 68252927; fax: +86 23 68254000.
E-mail address: pengyungui@hotmail.com (Y. Peng).

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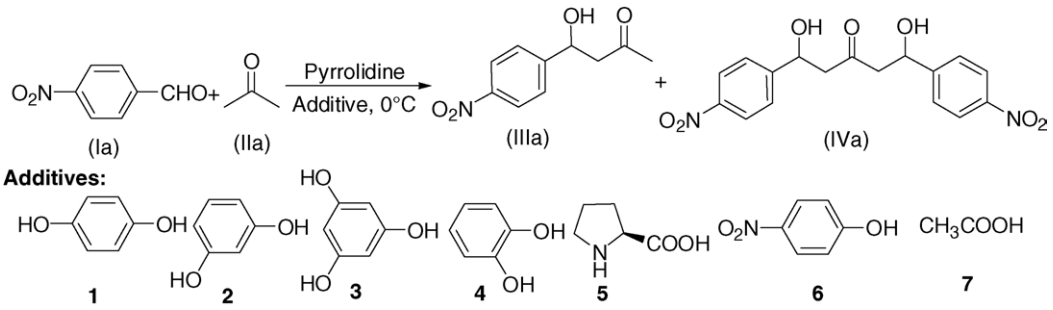


Scheme 1. Screening of additives of the aldol reaction.

found that the match of the acidity and basicity is very important to obtained good reactivity and high yield [34]. Except for the acidity, hydrogen bonding, especially double hydrogen bonding can also play an important role in modulating the reactivity. In order to find more mild and efficient catalytic system, we try to study the influence of the multi-phenol (p*K*a = 9.4–10.5) on the reactivity because those hydroxyl groups can simultaneously act as Brønsted acids and form different type of mono- or double-hydrogen-bonds to the carbonyl of aldehydes, both can activate the carbonyl group's towards nucleophilic attack.

2. Results and discussion

We report the study of the aldol reaction of acetone with *p*-nitrobenzaldhyde, which catalyzed by those acid additives/pyrrolidine (Scheme 1). The results are shown in Table 1.

Table 1
The influence of additive on the direct aldol reaction[a]

Entry	Additive	p*K*a (25 °C)	Time (min)	**IIIa** (%)	**IVa** (%)	Chemoselectivity, **IIIa**/(**IIIa** + **IVa**) (%)	Total yield (%)[b]
1	–	–	90	15.8	38.9	28.9	54.7
2	1	10.4 (20 °C)	90	56.8	33.0	63.2	89.8
3	2	9.4	30	42.0	45.4	48.0	87.4
4	3	7	50	51.2	44.4	53.6	95.6
5	4	9.4	30	74.4	16.1	82.2	90.5
6[c]	5		120	67.6	8.6	88.7	76.2
7	6	7.2	50	64.6	29.7	68.5	94.3
8	7	4.8	60	63.2	22.4	73.8	85.6

[a] The reaction was carried out in neat dried acetone with a concentration of 0.4 mol/L at 0 °C; *p*-nitrobenzaldehyde/additives/pyrrolidine = 1:0.4:0.2.
[b] Isolated yield.
[c] Without pyrrolidine.

Table 2
The influence of conditions on the reaction

Entry	C (mol/L)	*T* (°C)	H_2O (eq)	Pyrrolidine/catechol (eq)	Time (min)	**IIIa** (%)	**IVa** (%)	Chemoselectivity, **IIIa**/(**IIIa** + **IVa**) (%)	Total yield (%)[a]
1	0.4	0	–	0.2/none	90	15.8	38.9	28.9	54.7
2	0.4	0	–	0.2/0.2	30	43.2	53.2	44.8	96.4
3	0.4	0	–	0.2/0.3	30	50.1	43.9	53.3	94.0
4	0.4	0	–	0.2/0.4	30	74.4	16.1	82.2	90.5
5	0.4	0	–	0.2/0.5	60	53.8	41.9	56.2	95.7
6	0.4	0	–	0.2/0.6	60	51.1	31.8	61.7	82.8
7	0.2	0	–	0.2/0.4	40	61.2	36.7	62.5	97.9
8	0.8	0	–	0.2/0.4	30	33.7	50.3	40.1	84.0
9	0.4	0	–	0.1/0.2	30	52.3	45.6	53.4	97.9
10	0.4	0	–	0.05/0.1	30	48.3	48.3	50.0	96.6
11	0.4	0	0.2	0.2/0.4	30	75.5	20.0	79.1	95.5
12	0.4	0	0.3	0.2/0.4	30	75.6	18.3	80.5	93.9
13	0.4	0	0.4	0.2/0.4	30	81.3	17.2	82.5	98.5
14	0.4	0	0.5	0.2/0.4	30	68.9	23.3	74.7	92.2
15	0.4	0	0.6	0.2/0.4	30	67.5	27.2	71.3	94.7
16	0.4	0	0.8	0.2/0.4	30	65.6	28.9	69.4	94.5
17	0.4	22	0.4	0.2/0.4	30	44.5	32.8	57.6	77.3
18	0.4	−12	0.4	0.2/0.4	30	56.0	32.2	63.5	88.2

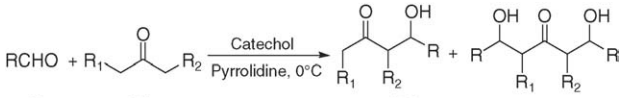
[a] Isolated yield.

When pyrrolidine was independently used as catalyst, the aldol products **IIIa** and **IVa** were obtained in 54.7% after 1.5 h (Table 1, entry 1). With the addition of 0.4 equivalent additives **1–4** as co-catalyst, the total yield was up to 87.4–95.6% (Table 1, entries 2–5). These additives were also superior to proline in the catalytic reactivity (Table 1, entry 6). Cathechol was founded to be particular effective and prominently superior to resorcinol which with the same p*K*a. When use catechol as additive, the product was obtained in 82.2% chemoselectivity and 90.5% yield (Table 1, entry 5). Only 48.0% chemoselectivity and 87.4% yield were obtained when used resorcinol as additive (Table 1, entry 3). This may be due to the capable of forming double-hydrogen-bond between catechol and aldehyde. Only mono-hydrogen-bond was formed in the presence of resorcinol.

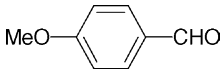
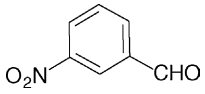
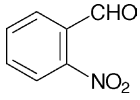
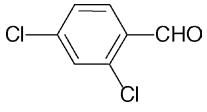
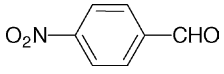
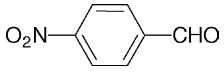
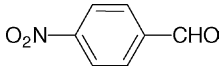
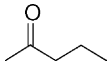
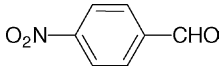
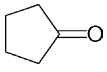
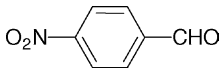
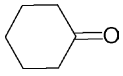
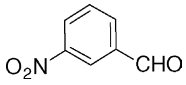
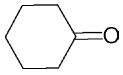
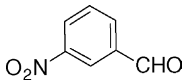
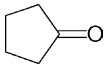
In order to increase the reactivity and chemoselectivity, several reaction parameters had to be optimized. A series of solvents including DMSO, DMF, CH_2Cl_2, $CHCl_3$, MeOH, $Cl(CH_2)_2Cl$, C_6H_6 and CH_3COCH_3 were screened. And the best solvent was found to be acetone. The most suitable pyrrolidine/catechol ratio was found to be 1:2 for effective rate acceleration and high chemoselectivity; if the ratios greater or less than 1:2 significantly reduced the chemoselectivity (Table 2, entries 1–6). The optimum reaction concentration was found to be 0.4 mol/L for high yield and high chemoselectivity (Table 2, entries 4, 7 and 8). We also found that the catalytic amount of pyrrolidine (0.2 equivalent) and catechol (0.4 equivalent) were necessary and sufficiently enough for the reaction (Table 2, entries 4, 9 and 10). Furthermore, proper amount of water is benefit for this reaction,

Table 3

Direct aldol reactions of aldehydes with ketones catalyzed by pyrrolidine/catechol[a]



(I) (II) (III) (IV)

Entry	R-CHO	(II)	Time (min)	(III) (%)	(IV) (%)	Total yield (%)[b]
1[c]			240	77.3		77.3
2[d]			40	56.5	37.2	93.7
3			40	50.7	38.3	89.0
4			120	47.8	45.6	93.4
5			30	81.3	17.2	98.5
6			40	41.7/50.7[d]		92.4
7			30	84.4		84.4
8			30	76.6	15.5	92.1
9			30	92.8		92.8
10			30	94.8		94.8
11			30	87.7	7.8	95.5

[a] The reaction was carried out in neat ketone with a concentration of 0.4 M at 0 °C; aldehyde/catechol/pyrrolidine = 1:0.4:0.2:0.4.
[b] Isolated yield.
[c] Reaction temperature = 18 °C.
[d] Reaction at the methyl.

the chemoselectivity improved with the increasing of the amount of water (Table 2, entries 11–13). When the equivalent changing to 0.4, the chemoselectivity is up to a good level 82.5% (Table 2, entry 13). Further increasing the amount of water, the increasing of chemoselectivity was not obviously (Table 2, entries 14–16). The optimum reaction temperature was found to be 0 °C (Table 2, entries 4, 17 and 18).

To extend the scope of the reaction further, a series of aromatic aldehydes which including electron-withdrawing (NO_2 and Cl) and electron-donating (OMe) substituents were reacted with ketones under the optimal conditions. The results are presented in Table 3. The aromatic aldehydes reacted very well with acetone and the aldol adducts were all formed in high yields (77.3–98.5%) (Table 3, entries 1–5). Even the 2,4-dichlorobenzaldehyde and *p*-methoxybenzaldehyde, which has shown lower reactivity in other catalytic system, the yields were, respectively, up to 93.4% at 0 °C for 2 h and 77.3% at 18 °C for 4 h (Table 3, entries 1 and 4). Other ketones could also be successfully employed as the aldol donors and afford the aldol products in good yields (Table 3, entries 6–11). Especially, ketones, such as butan-2-one, pentan-2-one and cyclohexanone have showed high chemoselectivity (Table 3, entries 6, 7, 9 and 10). It should be noted that no dehydrated products were observed in any of the reactions, and all of the reactions completed in 30–40 min except 2,4-dichlorobenzaldehyde and *p*-methoxybenzaldehyde required longer reaction times.

3. Conclusions

We have explored the influence of multi-phenol on the reactivity and found that the double-hydrogen-bond and a small amount of water are very important to obtained good reactivity and high yield. The pyrrolidine–catechol bifunctional catalytic system, which utilizes inexpensive chemicals and does not require preactivation of the donor and the acceptor, can activate the aldol reaction to proceeding smoothly under mild reaction conditions. Further studies focusing on the full scope of this catalyst system are currently under investigation and will be reported in due course.

Acknowledgements

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