

Lithium Pyrrolidone Catalyzed Aldol Reaction between Aldehyde and Trimethylsilyl Enolate

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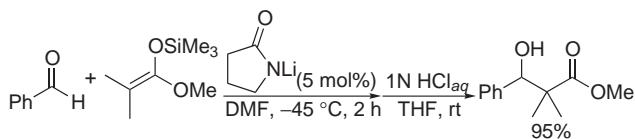
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Lithium pyrrolidone catalyzed aldol reaction between trimethylsilyl enolates and aldehydes proceeded smoothly in a DMF or pyridine solvent to afford the corresponding aldols under weakly basic conditions.

In synthetic organic chemistry, aldol reaction is one of the most important and frequently employed tools for carbon–carbon bond formation.¹ Silyl enolates have been recognized as isolable aldol donors and have frequently and effectively been employed in constructing carbon skeleton ever since the crossed aldol reaction between aldehydes and silyl enolates promoted by Lewis acids such as titanium tetrachloride was reported from our laboratory.² Since silyl enolate is a weakly nucleophilic reagent, there are two general approaches known to perform aldol reaction: namely, i) to activate aldon acceptors such as aldehydes or acetals with Lewis acid to let them behave as electrophiles,² ii) to activate a silyl enolates to let them behave as nucleophiles, e.g., a) formation of metal enolates by transmetallation of silyl enolates with several metal salts that are from long-standing MeLi to recently utilized transition metals,³ b) formation of enolate anions by nucleophilic cleavage of a Si–O bond with a fluoride ion⁴ or phosphines,⁵ and c) formation of the activated coordinate complexes on a silicon atom^{6,7} with Lewis bases. Concerning Lewis base catalyzed activation, Denmark et al. established an aldol reaction using trichlorosilyl enolates and phosphoramides, Lewis bases,⁸ while Hosomi et al. recently reported an aldol reaction using a combination of dimethylsilyl enolate and CaCl_2 in an aqueous DMF solvent.⁹

It was revealed in the previous communication that the lithium diphenylamide was effective Lewis base catalyst for the acceleration of aldol reaction between aldehydes and trimethylsilyl enolates in a dimethylformamide (DMF) or pyridine solvent.¹⁰ This catalyst, however, still leaves a problem of separating the catalyst from the resulting reaction mixture. With the activation of a simple and popular silyl enolate as trimethylsilyl enolate in mind, the other Lewis base catalyst which is easily removed from an organic layer by simple extraction with water was considered. And then, readily-available and inexpensive 2-pyrrolidone was chosen as a precursor of the catalyst because pK_a value of its N–H bond was shown to be close to that of diphenylamine by the measurement in DMSO^11 and was easy-to-solve in water. In this communication, we would like to report a catalytic aldol reaction between trimethylsilyl enolates and aldehydes by using lithium pyrrolidone as a Lewis base.



When benzaldehyde and trimethylsilyl enolate derived from methyl isopropionate were allowed to react in the presence of a stoichiometric amount of lithium pyrrolidone in THF at 0 °C, the aldol adduct was afforded only in 39% yield. In our previous paper, it was shown that DMF and pyridine were the suitable solvents for lithium diphenylamide catalyzed aldol reaction between aldehydes and silyl enolates. Then, the above mentioned aldol reaction was tried at -45 °C in DMF by adding 1 mol% or 5 mol% of lithium pyrrolidone or at 0 °C in pyridine using 5 mol% of lithium pyrrolidone, and the desired aldol was obtained in 81% or 95% yield in DMF or 78% in pyridine, respectively. These results indicated that the anion of 2-pyrrolidone had a Lewis base character to catalyze the above aldol reaction.

The scope of acceptor aldehydes was examined by using 10 mol% of lithium pyrrolidone in DMF or pyridine (see Table 1). Trimethylsilyl enolate derived from methyl isopropionate smoothly reacted with various aromatic aldehydes to afford the corresponding aldols in high yields. Aromatic aldehyde having an electron-withdrawing group such as *p*-nitrobenzaldehyde and aliphatic aldehyde also afforded aldol adducts in moderate yields.

Table 1.

Entry	Aldehyde	Solv.	Time / h	Temp / °C	Yield ^a / %
1	<i>p</i> -MeC ₆ H ₄ CHO	DMF	1.5	-45	95
2	<i>p</i> -MeC ₆ H ₄ CHO	Pyridine	3	0	93
3	<i>p</i> -MeOC ₆ H ₄ CHO	DMF	2	-45	92
4	<i>p</i> -MeOC ₆ H ₄ CHO	Pyridine	3	0	95
5	1-NpCHO ^c	DMF	4	-45	91 ^b
6	1-NpCHO ^c	Pyridine	5	0	83 ^b
7	<i>p</i> -NO ₂ C ₆ H ₄ CHO	DMF	3 d	-45 → rt	57
8	<i>p</i> -CNC ₆ H ₄ CHO	DMF	3	-45	78
9	<i>p</i> -CNC ₆ H ₄ CHO	Pyridine	5	0	89
10	<i>p</i> -ClC ₆ H ₄ CHO	DMF	2	-45	87
11	<i>p</i> -ClC ₆ H ₄ CHO	Pyridine	30	0	82
12	<i>p</i> -BrC ₆ H ₄ CHO	DMF	3	-45	92
13	<i>p</i> -BrC ₆ H ₄ CHO	Pyridine	30	0	88
14	PhCH ₂ CHO	DMF	4	-45	55 ^b

^aYield was determined by ¹H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. ^bIsolated yields.

^c1-Naphthaldehyde.

The present Lewis base catalyzed reaction has distinctive advantage to the formation of aldols especially when aldehydes having basic functions in the molecule were used. In order to demonstrate the utility, these Lewis base catalyzed aldol reactions of aldehydes having basic functions and trimethylsilyl enolates

Table 2.

Entry	Aldehyde	Time /h	Yield ^a /%
1		1	97
2		2	91
3		3	97 ^b

^aYield was determined by ¹H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. ^bIsolated yield.

derived from methyl isopropionate were tried by using 10 mol% of lithium pyrrolidone in a DMF solvent. The reactions proceeded smoothly at -45°C and the corresponding aldol adducts were obtained in high yields (Table 2).

Several silyl enolates were further studied in this lithium pyrrolidone catalyzed aldol reaction (see Table 3). In the first place, enolates generated from *S*-ethyl ethanethioate and acetophenone were employed, and the corresponding aldol adducts were obtained in good yields (Entry 1, 2). On the other hand, only a trace amount of the desired aldol was detected when sterically hindered triethylsilyl enolate derived from methyl isopropionate was employed instead of the above trimethylsilyl enolate (Entry 3). This result indicated that the reaction proceeded via the activation of trimethylsilyl enolate by forming hypervalent silicate between lithium pyrrolidone and the silicon atom of enolate.^{7,10} Further, it was observed that the silyl enolate derived from methyl propionate gave the aldols with moderate *syn*-diastereoselectivity irrespective of the geometry of the two isomeric silyl enolates (Entry 4–9). This indicated that the

Table 3.

Entry	Silyl enolates	Solv.	Temp. / $^{\circ}\text{C}$	Time /h	Yield ^a /%	syn:anti
1		DMF	-45	2	95	–
2		DMF	-45	3	77	–
3		DMF	-45	3	trace	–
4		DMF	-45	3	42	1.7 : 1
5		DMF	0	3	50	1.6 : 1
6		Pyridine	-19 → 0	18	4	1.6 : 1
7		DMF	-45	3	88	2.7 : 1
8		DMF	0	3	95	2.4 : 1
9		Pyridine	-19 → 0	18	70	2.4 : 1

^aYield was determined by ¹H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

reaction proceeded mostly via acyclic transition states.^{5,7}

In order to examine the solvent effect, aldol reaction of benzaldehyde with trimethylsilyl enolate of methyl isopropionate using 5 mol% of lithium pyrrolidone was tried in pyridine and in its substituted ones such as 4-picoline, 2-picoline and 2,6-lutidine whose yields were 54%, 18%, trace, respectively. Reactivity of this reaction diminished remarkably by steric hindrance around nitrogen atom of the solvent. This meant that the coordination of the solvent to the silicon atom played an important role in this reaction. Since this reaction did not take place in the absence of the catalyst in pyridine at 0°C ,¹⁰ it is assumed to proceed via the following mechanism: in the first place, lithium pyrrolidone coordinated to the silicon atom of trimethylsilyl enolate to form pentacoordinated hypervalent silicate. The solvent was further coordinated to the silicon atom of thus formed pentacoordinated silicate to produce hexacoordinated hypervalent silicate, which reacted with carbonyl compounds to form the desired aldol via acyclic transition states.

Thus, a new catalytic aldol reaction between trimethylsilyl enolates and aldehydes was established by using lithium pyrrolidone in a DMF or pyridine solvent. Further expansion of this reaction is now in progress.

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