Lithium Acetate Catalyzed Aldol Reaction between Aldehyde and Trimethylsilyl Enolate in a Dimethylformamide–H_2O Solvent

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Lithium acetate catalyzed aldol reaction between trimethylsilyl enolates and aldehydes in a DMF–H_2O (50:1) solvent proceeded smoothly to afford the corresponding aldols in good to high yields. It is noted that trimethylsilyl enolates derived from carboxylic esters behaved as excellent nucleophiles in the above reaction.

Since the crossed aldol reaction between silyl enolates and aldehydes by the promotion of Lewis acid was reported from our laboratory,[1] the aldol reactions using silyl enolates have widely been utilized for constructing carbon skeltons. Recently, new Lewis base-catalyzed aldol reactions of trimethylsilyl (TMS) enolates with aldehydes in a *N*,*N*-dimethylformamide (DMF) solvent were reported, which afforded the corresponding aldols in high yields by using lithium diphenylamide, lithium pyrrolidone or lithium acetate (AcOLi).[2] It is interesting to note that the nucleophilic attack of AcOLi onto silicon atom at low temperatures effectively activated simple and commonly-employed TMS enolates though the above acetate is a weaker nucleophile compared with lithium diphenylamide or pyrrolidone. In order to exhibit the usefulness of a mild and readily-available AcOLi catalyst, the aldol reaction in DMF that contained water in the presence of the above catalyst was studied. An acetate anion which is stable in water was then considered to work as effective catalyst at low temperatures whereas the anion generated from Lewis bases such as lithium diphenylamide or pyrrolidone does not even exist nor exhibit any catalytic effects. In this communication, we would like to report on lithium acetate (AcOLi)-catalyzed aldol reaction between trimethylsilyl enolates and aldehydes in a DMF–H_2O (50:1) solvent, which afforded the corresponding aldols in high yields.

The aldol reactions in water or water-containing organic solvents attracted much attention in a sense related to economical and environmentally benign synthetic methods. Although several methods of aldol reactions using silyl enolates in water or water-containing organic solvents have been reported,[3–7] there are few that used silyl enolates derived from carboxylic esters due to their extreme sensitivity toward water.[3,7b] Of the few reactions, one was carried out in emulsified sphere using surfactants[3] and the other proceeded with restrictive use of highly reactive acceptor aldehydes.[7b]

In the first place, reaction of benzaldehyde and TMS enolate derived from methyl isobutyrate **1** was tried in the presence of 10 mol% of AcOLi at −45 °C in DMF–H_2O (10:1), and the aldol adduct was obtained in 71% yield. Then, the reaction conditions were carefully screened so as to improve the yields. Finally, the corresponding aldol was obtained in high yield when the reaction was carried out by using two equivalents of **1** in DMF–H_2O (50:1) (Eq 1). In the absence of the catalyst, on the other hand, the aldol adduct was obtained only in 17% yield under the same reaction conditions. These results indicated that the AcOLi behaved as an effective Lewis base catalyst in this aldol reaction.

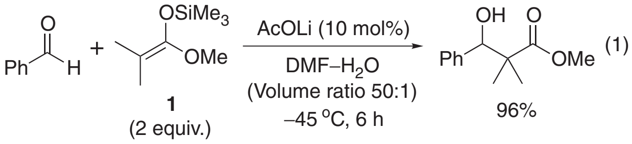
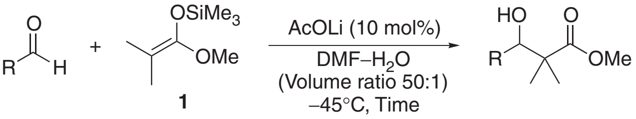
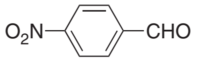
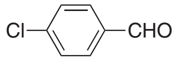
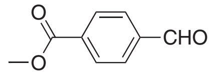
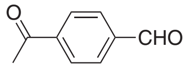
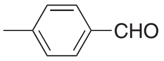
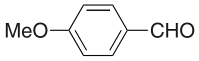
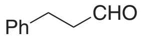
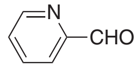
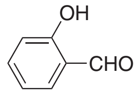
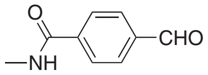
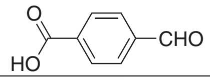


Table 1.

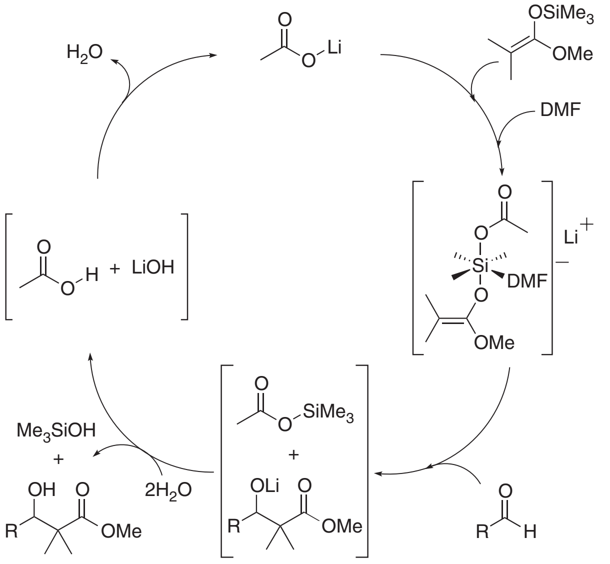


Entry	Aldehyde	Time /h	Yield[a] /%
1		3	97[b](69)
2		3	94 (63)
3		3	99
4		3	93[b]
5		16	78 (84)
6		17	62 (94[b])
7		18	84[b](65[b])
8		2.5	97 (84)
9		14	84
10		3	92[b]
11[c]		24	52

[a]Yield was determined by ^{1}H-NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. Numbers in parentheses were yields under non-aqueous condition (ref 2b). [b]Isolated yield. [c]Reaction temperature was gradually warmed up to rt.

Next, the reactions of TMS enolate **1** with various aldehydes were tried (see Table 1).[8] In every case, the aldol adducts were obtained in high yields. It is remarkable that both aromatic aldehydes having electron-withdrawing groups and an aliphatic aldehyde, 3-phenypropionaldehyde, reacted smoothly to afford the desired aldols in high yields while the corresponding aldols were obtained in moderate yields in non-aqueous solvent (Entries 1–2 and 7).[2b] 2-Pyridinecarboxaldehyde afforded the aldol adduct in high yield, on the other hand, the reaction did not generally proceed by using Lewis acids (Entry 8). One of the most characteristic points of the present reaction carried out in a water-containing DMF solvent is that the aldehydes having free amide, hydroxy, or even carboxylic functions reacted smoothly to afford the desired aldols in moderate to high yields although such functions were incompatible with metal enolates or Lewis acids (Entries 9–11).

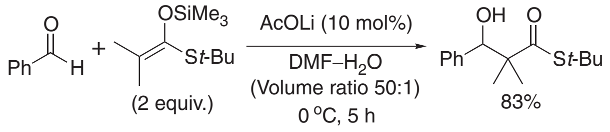
Assumed catalytic cycle of the present reaction was illustrated in Scheme 1. The same reaction pattern may be considered until lithium aldolate is formed via a hexacoodinated hypervalent silicate under non-aqueous conditions.[2] In case of the reaction carried out in a water-containing DMF solvent, the initially formed lithium aldolate and silyl acetate are rapidly hydrolyzed to produce lithium hydroxide and acetic acid. Subsequent neutralization should afford lithium acetate to establish a catalytic cycle.



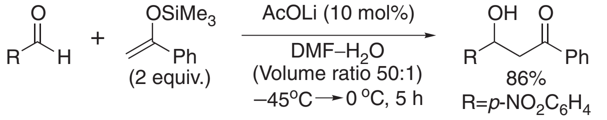
Scheme 1.

Under non-aqueous conditions, the initially formed lithium aldolate was converted into its TMS ether with trimethylsilyl acetate and the catalyst was regenerated.[2] Aromatic aldehydes having electron-withdrawing groups and 3-phenypropionaldehyde afforded silyl acetals as co-products via the reaction with lithium aldolates because they were more electrophilic than benzaldehyde.[9] Thereby, yields of the desired aldols were moderate under non-aqueous conditions. In the presence of water, on the other hand, lithium aldolates were rapidly hydrolyzed and formations of the above-mentioned silyl acetals were restrained; therefore, the desired aldols were obtained in high yields.

This catalytic aldol reaction can also be performed smoothly by using other TMS enolates. For example, TMS enolates derived from *S-tert*-butyl isobutanethioate and acetophenone afforded the corresponding aldols in good yields (Eqs 2 and 3).



(2)



(3)

Thus, lithium acetate catalyzed aldol reaction between TMS enolates and aldehydes in a water-containing DMF solvent was established. This is the first example of Lewis base-caralyzed aldol reaction which afforded aldol adducts even when silyl enolates derived from carboxylic esters were used in a water-containing organic solvent. This method is quite practical and is applicable to the synthesis of various aldols since the reaction is carried out under the conditions not strictly anhydrous and uses such a mild, readily-available and inexpensive Lewis base catalyst. Further development of this reaction is now in progress.

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References and Notes

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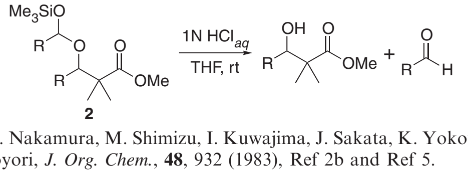
8 Typical experimental procedure is as follows (Table 1, Entry 1): to a stirred solution of AcOLi (2.6 mg, 0.04 mmol) in DMF (0.5 mL) and H_2O (0.06 mL) were added successively a solution of 4-nitrobenzaldehyde (60.4 mg, 0.4 mmol) in DMF (1.5 mL) and a solution of silyl enolate **1** (139.5 mg, 0.8 mmol) in DMF (1.0 mL) at −45 °C. The mixture was stirred for 3 h at the same temperature, and quenched with 1.0 N HCl. The mixture was extracted with Et_2O and organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration and evaporation of the solvent, the crude product was purified by preparative TLC to give the corresponding aldol (98.3 mg, 97%) as a white powder.

9 Although a small amount of acetal **2**, a co-product, was obtained under the non-aqueous condition, it was easily converted to normal aldol and starting aldehyde on treatment with 1 N HCl.



See: E. Nakamura, M. Shimizu, I. Kuwajima, J. Sakata, K. Yokoyama, and R. Noyori, *J. Org. Chem.*, **48**, 932 (1983), Ref 2b and Ref 5.