One-Pot Reduction–Aldol Reaction of Esters

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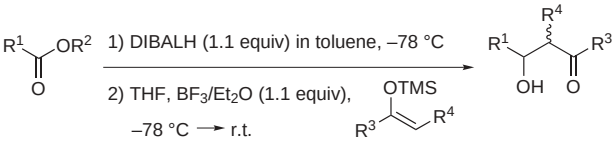
Abstract: We have developed a new protocol for making aldol adducts in a one-pot reaction between esters and silyl enol ethers in the presence of DIBALH without isolating the intermediate aldehydes. Lewis acid activation of the initially formed aluminated hemiacetals produces highly reactive electrophilic aldehyde equivalents in situ. Using this protocol, various aldol adducts can be readily obtained in up to 90% yield on a large scale.

Key words: aldol reaction, reduction, esters, aldehydes, aluminated hemiacetals, one-pot reaction

The aldol reaction is one of the most important carbon–carbon bond forming processes in contemporary organic synthesis.[1] In addition, the aldol fragments or their derivatives are often present in the structures of natural products and pharmaceuticals.[2] Typically, an aldol reaction is accomplished by reacting an aldehyde and an enolate equivalent in the presence of a Lewis acid.[3,4] The aldehydes are prepared by either oxidation of alcohols or by reduction of esters. The traditional method of generating aldol products from the ester-containing starting materials is based on reducing the ester to the corresponding aldehyde using DIBALH followed by treating the isolated aldehyde with a silyl enol ether in the presence of a suitable Lewis acid.[5] However, aldehyde isolation can be troublesome, especially on a large scale, because of the sensitivity of aldehydes and/or difficulty commonly encountered during their purification. In this regard, one-pot processes that avoid isolation of aldehyde building blocks are highly desirable, especially in the case of low boiling point aldehydes.

At the outset of our investigation, our hope was that the silyl enol ether would attack the aluminated hemiacetal which is formed upon initial reduction of the aldehyde with DIBALH.[6,7] Using this protocol, ethyl 4-pentenoate was converted to the corresponding aldol in excellent yield by the DIBALH reduction followed by the in situ aldol reaction with 1-phenyl-1-(trimethylsilyloxy)ethylene in the presence of boron trifluoride without isolating the corresponding aldehyde (Equation 1). Remarkably, the formation of α,β-unsaturated ketone was not observed in this reaction. The presence of boron trifluoride was found to be mandatory as no reaction took place in its absence.



Equation 1 One-pot reduction–aldol process

The scope of the reduction–aldol process was investigated and the results are shown in Table 1. Primary esters gave good to excellent yields (Table 1, entry 1–3 and 6), while secondary esters gave lower yields (Table 1, entry 4). The α,β-unsaturated esters gave reduced alcohols instead of the aldol adducts (Table 1, entry 5). Both aromatic and aliphatic groups (R^3) gave comparable yields (Table 1, entry 3 and 6). The 1,1,2-trisubstituted enol ethers gave lower yields with low diastereoselectivities, while typical Mukaiyama-aldol reaction gives high diastereoselectivity (Table 1, entry 7).

Table 1 The Scope of the Reduction–Aldol Reaction

Entry	R^1	R^2	R^3	R^4	Yield (%)
1[a]	CH_2=CH$(CH_2)_2$-	Et	Ph	H	90
2[a]	CH_3CH_2=CH$(CH_2)_2$-	Et	Ph	H	89
3	$PhCH_2$-	Me	Ph	H	75
4	Cyclopropyl	Me	Ph	H	25
5	PhCH=CH-	Me	Ph	H	0
6	$PhCH_2$-	Me	Me	H	63
7	CH_2=CH$(CH_2)_2$-	Et	Ph	Me	38[b]

[a] 1.1 equiv TMS ether was used. 1.5 equiv TMS ether was used in other entries.
[b] Diastereomeric ratio = 1.4:1.

The proposed mechanism is shown in Scheme 1. The ester is first reduced by DIBALH to give the aluminated hemiacetal, which coordinates to boron trifluoride, producing a highly electrophilic aluminated intermediate. There are two possible routes from this complex: in the first possibility, the silyl enol ether attacks the complex to give the aluminated aldol, which is hydrolyzed to the corresponding aldol. In the other route, the initially produced complex is decomposed to give aluminated aldehyde, which is subsequently attacked by the silyl enol ether to give the aluminated aldol adduct, which is subsequently hydro-

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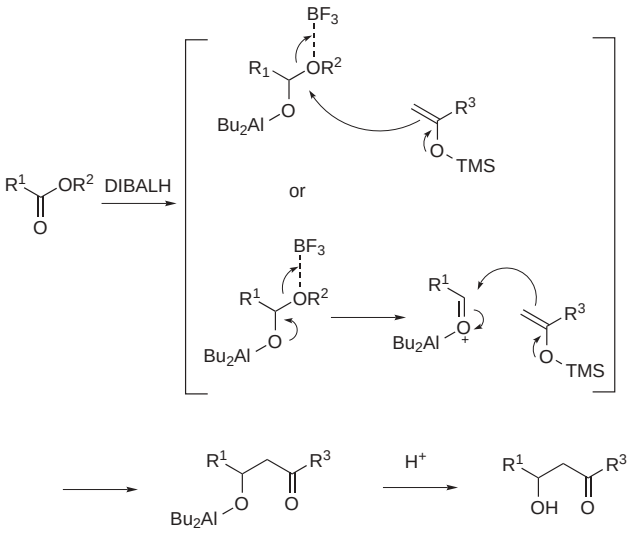
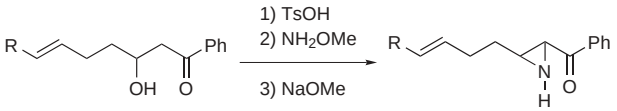
lyzed to the corresponding aldol. As a result, the aldol adduct is produced in a one-pot reaction from the corresponding ester without isolating the intermediate aldehyde.



Scheme 1 Proposed mechanism of the reduction–aldol reaction

The obtained aldols can be converted to the corresponding β-ketoaziridines (Equation 2), which have found a range of applications as important starting materials for various saturated nitrogen-containing heterocycles.[8]



Overall yield: 63% (R = H)
64% (R = Me)

Equation 2 Aldols as the starting materials to β-ketoaziridines

In conclusion, we have developed a new method to synthesize aldol adducts from esters in a one-pot reaction without isolating the corresponding aldehydes. Further studies such as asymmetric version of this reaction are in progress. Particularly exciting is the possibility of applying the highly reactive aluminated intermediates in other types of nucleophilic addition processes.

Representative Procedure of 3-Hydroxy-1-phenylhept-6-en-1-one (Table 1, Entry 1):

To a mixture of ethyl 4-pentenoate (10.0 g, 78 mmol) and toluene (100 mL), 1.5 M DIBALH in toluene (57 mL, 86 mmol) was slowly added at –78 °C, and the mixture was stirred for 1 h at –78 °C. To this reaction mixture THF (240 mL), $BF_3{\cdot}OEt_2$ (11 mL, 86 mmol), and 1-phenyl-1-trimethylsilyloxyethylene (16.5 g, 86 mmol) were successively added at –78 °C, and the reaction mixture was allowed to warm up to around 0 °C under stirring. After completion (judged by TLC), 1 N HCl (240 g), cooled in an ice bath, was added to the reaction mixture and separated to two layers and the water layer was extracted with toluene (50 mL). The combined organic layers were washed with H_2O (150 mL) and dried over $NaSO_4$. The solvent was removed in vacuo and 3-hydroxy-1-phenylhept-6-en-1-one was obtained as a crude yellow oil (16.2 g). The purity was 88% and containing 12% of acetophenone (yield: 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97–8.00 (m, 2 H), 7.59–7.64 (m, 1 H), 7.48–7.53 (m, 2 H), 5.83–5.96 (m, 1 H), 5.00–5.14 (m, 2 H), 4.24–4.32 (m, 1 H), 3.05–3.24 (m, 2 H), 2.20–2.34 (m, 2 H), 1.58–1.82 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.8, 138.3, 136.8, 133.6, 128.7, 128.1, 115.0, 67.2, 45.0, 35.6, 29.8 ppm.

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