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A novel and efficient procedure for the preparation of allylic alcohols from α,β-unsaturated carboxylic esters using $LiAlH_4$/BnCl

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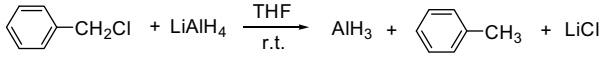
ABSTRACT

A new and efficient method for the reduction of α,β-unsaturated carboxylic esters to allylic alcohols utilizing $LiAlH_4$/BnCl is described. Various α,β-unsaturated esters, including the coumarins bearing α,β-unsaturated lactone skeleton, can be converted smoothly into their corresponding allylic alcohols in high yields under mild conditions with short reaction times.

Allylic alcohols are found as structural motifs in a wide range of naturally occurring compounds.[1] They have also been used as valuable synthetic intermediates in the total synthesis of many natural products and biologically active compounds.[2] Among the various methods for accessing allylic alcohols, the reduction of α,β-unsaturated carboxylic esters is often used, since they are easily prepared from aldehydes through reactions such as the Wittig reaction, the Homer-Wadsworth-Emmons reaction and the Knoevenagel reaction.[3] However, reduction of conjugated carbonyl compounds with various reducing agents including $LiAlH_4$ and $NaBH_4$ is generally complicated by the competing 1,4- and 1,2-processes.[4,5] Presumably for this reason, AlH_3, mostly generated in situ from $LiAlH_4$ and $AlCl_3$,[6] and diisobutylaluminium hydride (DIBAL-H)[7] practically act as the most popularly used reductants for the conversion of α,β-unsaturated esters into unsaturated alcohols. However, despite the potential utility of these two reducing agents, the methodologies for the reduction are associated with several disadvantages such as expensive reagents, harsh reaction conditions, low temperature, long reaction time and much excessive use of reducing agents. Consequently, there is still a need to develop practical and convenient methods for preparation of allylic alcohols from α,β-unsaturated carboxylic esters.

In our previous work, using a ratio of α,β-unsaturated carboxylic esters/$LiAlH_4$/$AlCl_3$ of 1:3:1 equiv, we have successfully prepared allylic alcohols as vital intermediates in the total synthesis of natural products.[8] Though efficient, this procedure requires 3 equiv of $LiAlH_4$ at least, which eventually poses the cumbersome separation from the generated large quantity of solid. As a result, the disposal of the excess solid waste would lead to more environmental pollution. Moreover, this protocol requires the addition of solid $AlCl_3$ in batches to the moisture sensitive suspension of $LiAlH_4$ in dry ether,[6c] which also renders somewhat inconvenience in practice. This prompted us to develop a convenient, economical and environmentally benign method for the title reaction.

As a part of our continual efforts to utilize AlH_3 as a reductant, previously generated by reaction of $LiAlH_4$ and $AlCl_3$, we are keen to develop a more efficient method for accessing allylic alcohols. A literature survey then revealed that, although exclusively used for the reduction of alkyl halides to the corresponding hydrocarbons, reaction of $LiAlH_4$ and alkyl halide could lead to the formation of AlH_3 as a by-product.[9] Nonetheless, to the best of our knowledge, applications of $LiAlH_4$/alkyl halide methodology for generating AlH_3 as reducing agent have never been reported so far. Furthermore, in terms of $LiAlH_4$ reduction of various commercially available alkyl halides, benzyl chloride seems to be much superior to others since it has several advantages such as cost efficiency, high reactivity,[9a] lower irritating to the eyes than benzyl bromide and convenience for TLC monitoring. Encouraged by these, herein we report the use of AlH_3 derived from $LiAlH_4$ and BnCl (Scheme 1) for the efficient and practical conversion of α,β-unsaturated carboxylic esters into allylic alcohols.



Scheme 1. Preparation of AlH_3 by reaction of $LiAlH_4$ and BnCl.

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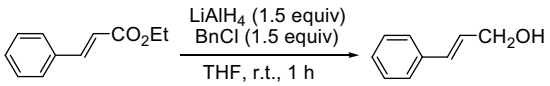


Scheme 2. Reduction of ethyl cinnamate to cinnamyl alcohol using $LiAlH_4$/BnCl.

Initially, we tested the reduction of ethyl cinnamate in anhydrous THF at ambient temperature using molar ratios of α,β-unsaturated ester/$LiAlH_4$/BnCl of 1:1.5:1.5, 1:2:2 and 1:3:3 equiv, respectively. It was found that the first ratio is sufficient to carry out the reduction successfully to afford the desired product cinnamyl alcohol in 88% yield in a short time (Scheme 2). An increase in the amount of reducing agent from 1.5 to 2 and 3 equiv showed no substantial improvement in the yield. It is worth noticing that, in comparison with the addition of solid $AlCl_3$ in prior $LiAlH_4$/$AlCl_3$ procedure, the addition of liquid BnCl through dropping funnel in our present method is more convenient and can drastically reduce the contact of reaction mixture with moisture.

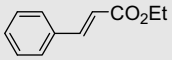
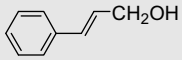
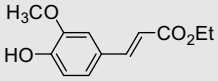
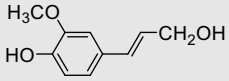
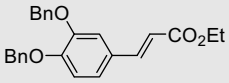
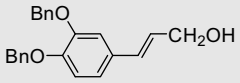
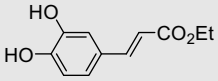
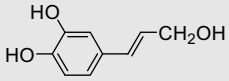
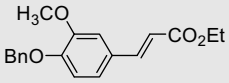
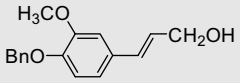
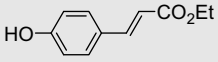
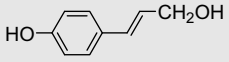
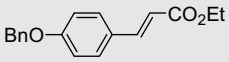
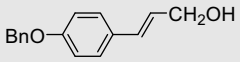
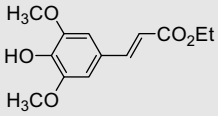
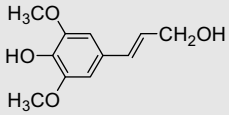
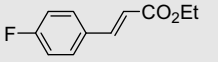
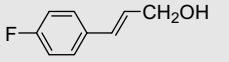
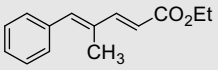
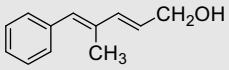
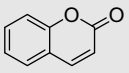
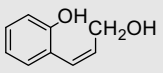
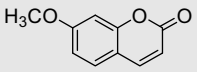
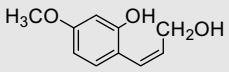
Under this optimized cost-effective reaction condition, the scope of the utility of $LiAlH_4$/BnCl was then explored to prepare a variety of unsaturated allylic alcohols. The results are summarized in Table 1. A wide range of structurally diverse α,β-unsaturated esters (Table 1), including dienylic ester (entry 10) and coumarins bearing α,β-unsaturated lactone skeleton (entries 11 and 12), were subjected under this protocol using 1.5 equiv of $LiAlH_4$ and 1.5 equiv of BnCl. The acyclic α,β-unsaturated esters and the dienylic ester (Table 1, entries 1–10) were readily prepared by the standard Knoevenagel reaction and Wittig reaction.[8,10] The two coumarins (Table 1, entries 11 and 12) are commercially available (Aldrich).

As the results in Table 1 indicate, allylic alcohols were obtained exclusively in all cases in a high yield of 81–94% without the further reduction products, namely the saturated alcohols that are reportedly hard to separate even by recrystallization.[11] A variety of functional groups on the benzene ring were tolerated under the reaction condition. For most of the substrates (Table 1, entries 1–10), the conversion proceeded smoothly with a short time within 1–2 h at room temperature. The somewhat prolonged reaction time for coumarins (Table 1, entries 11 and 12) is probably because of their poor solubility in the solvent. Most of the products (Table 1, entries 1–8, 10, 11) have been reported in the literatures.[2a,4,8,12] Thus, all the products in our reactions listed in Table 1 were easily characterized on the basis of physical and spectral data[13] and also by comparison with authentic samples. It should be noted that reduction of coumarin with $LiAlH_4$ itself to the corresponding *Z*-allylic alcohol has been widely used in studies of coumarin-based prodrug system.[12f,g] Comparing to the low yields of the reduction product reported in these studies, our present method has proven to be more efficient and should be helpful for exploring further usages of coumarins in the preparation of prodrugs.

In conclusion, an extremely efficient and practical method for the conversion of α,β-unsaturated esters into the corresponding allylic alcohols has been developed. This method is bestowed with several unique merits, such as high conversions and yields, simplicity in operation and cost-effectiveness. Thus, we believe that this novel methodology will be a practical alternative to the existing procedures to cater the need of academia as well as industries. Further work is in progress to broaden the scope of this reduction process.

General procedure for the preparation of allylic alcohols from α,β-unsaturated esters using LiAlH₄/BnCl: To a stirred suspension of $LiAlH_4$ (0.015 mol) in dry THF (40 ml), a solution of BnCl (0.015 mol) in dry THF (10 ml) was added dropwise through dropping funnel at room temperature. After the suspension was stirred for 15 min, a solution of α,β-unsaturated ester (0.01 mol) in dry THF was added dropwise to the suspension. The reaction mixture was stirred at room temperature for the appropriate time (see Table 1). Then the reaction was quenched with water, filtered and the filtrate was dried with Na_2SO_4. The solvent was evaporated under vacuum and the crude product was purified by column chromatography on silica gel eluting with a mixture of petroleum ether and ethyl acetate.[13]

Table 1
Reduction of α,β-unsaturated carboxylic esters to allylic alcohols using $LiAlH_4$/BnCl

Entry	Substrate	Time (h)	Product	Yield[a] (%)
1		1		88
2		1.5		83
3		2		92
4		1.5		81
5		2		93
6		1.5		83
7		2		90
8		1.5		85
9		1		94
10		1.5		86
11		5		87
12		5		84

[a] Isolated yield.

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13. The spectral data of some products. Product **9**: White crystals, mp 57–58 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 7.34 (m, 2H), 7.00 (m, 2H), 6.57 (d, 1H, J = 15.9 Hz), 6.28 (dt, 1H, J = 15.9, 5.4 Hz), 4.31 (d, 2H, J = 5.4 Hz), 1.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_{ppm} 162.32 (d, J = 245.5 Hz), 132.78, 129.91, 128.18, 127.92 (d, J = 8.0 Hz), 115.46 (d, J = 21.4 Hz), 63.54. IR (ν cm^{-1}): 3269, 1600, 1229, 970, 847. HRMS (ESI) Calcd for C_9H_9FONa $(M+Na)^+$: 175.0530. Found: 175.0538. Product **12**: White crystals, mp 89–90 °C. ^{1}H NMR (400 MHz, acetone-d_6): δ_{ppm} 7.04 (d, 1H, J = 8.4 Hz), 6.55 (d, 1H, J = 11.6 Hz), 6.46 (d, 1H, J = 2.4 Hz), 6.42 (dd, 1H, J = 8.4, 2.4 Hz), 5.74 (dt, 1H, J = 11.6, 6.4 Hz), 4.28 (d, 2H, J = 6.4 Hz), 3.74 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ_{ppm} 161.32, 156.80, 131.82, 131.53, 125.56, 117.83, 105.58, 102.30, 59.94, 55.53. IR (ν cm^{-1}): 3393, 1613, 1253, 954, 817, 696. HRMS (ESI) Calcd for $C_{10}H_{12}O_3Na$ $(M+Na)^+$: 203.0679. Found: 203.0676.