

A ONE-STEP CONVERSION OF ESTERS TO SECONDARY ALCOHOLS WITH $\text{LiBH}_4\text{-RMgX}$

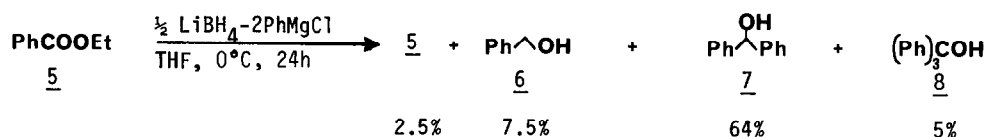
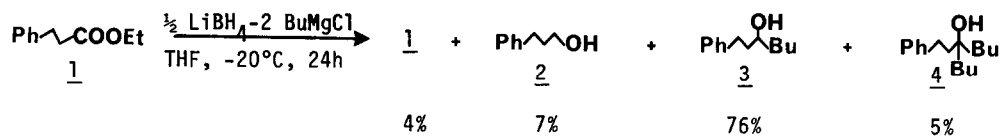
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Summary: A one-pot synthesis of secondary alcohols from esters and $\text{LiBH}_4\text{-RMgX}$ is described.

The classical preparation of secondary alcohols from esters involves two or three synthetic steps. First the ester is converted to an aldehyde either by reduction using diisobutylaluminum hydride,¹ or by over-reduction (e.g., LAH) to the alcohol and subsequent oxidation. The aldehyde is then treated with a Grignard or lithium reagent to give the desired secondary alcohol. An alternative route could involve converting the ester to a ketone followed by reduction of the ketone to a secondary alcohol. Unfortunately, a general method for the one-step conversion of an ester to a ketone is not available.² The addition of Grignard or lithium reagents to esters gives mainly tertiary alcohols. This is due to preferential attack on the ketone intermediate, which is generally more reactive than esters toward organometallics.³ We were curious about what effect a hydride reducing reagent would have on the ester-Grignard reaction. It seemed possible that an *in situ* reduction of the ketone intermediate might occur faster than addition of Grignard reagent. If this happens, then a one-pot conversion of esters to secondary alcohols is feasible. The hydride reagent must be chemoselective, able to rapidly reduce ketones but not esters, and soluble in ethereal solvents. Lithium borohydride appeared to be the reagent of choice for it is soluble in tetrahydrofuran (THF), reduces ketones rapidly, and reduces esters only very slowly below room temperature.⁴

The initial reactions were performed by adding ethyl 3-phenylpropionate to various mixtures of LiBH_4 and butylmagnesium chloride. In these experiments a 1/2/½ ratio of ester/RMgX/ LiBH_4 and a reaction temperature of -20°C gave the best results by affecting a reasonable reaction rate while minimizing side reactions. The reagents were mixed at -20°C and the mixture was placed in a freezer (-20°C) for 24 h.⁵ After workup, the crude product was analyzed (GC)⁶ for starting material 1, primary alcohol 2, secondary alcohol 3, and tertiary alcohol 4, and the results are shown below. The analogous reaction using ethyl benzoate and phenylmagnesium chloride was also performed and analyzed (GC)⁶ for starting material 5 and products 6-8.

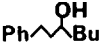



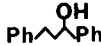





The success of the above experiments prompted us to investigate more examples and the results are given in the table. The yields (34-74%) of secondary alcohols by this method are comparable to the overall yields one would obtain from the classical two- or three-step procedure. A typical experimental is given below:

4-Phenyl-2-butanol - A solution of methylmagnesium chloride (6 mmol) in THF was added to LiBH_4 (1.5 mmol) in 6 ml of THF under nitrogen. The stirred mixture was cooled to -23°C (CCl_4 -dry ice) and ethyl 3-phenylpropionate (3 mmol) was added dropwise via a syringe. The reaction flask was placed in a freezer (-20°C) for 24 h. The mixture was poured slowly through a funnel into stirred cold 10% aqueous HCl (Caution! Fire hazard). After stirring at room temperature for 15 min, the mixture was extracted with ether (3 x 20 ml). The organic phase was washed with brine, dried (MgSO_4) and concentrated to give the crude product. Purification by preparative layer chromatography (10% acetone-hexanes) gave 310 mg (69%) of 4-phenyl-2-butanol as a clear oil.

The mechanism of this reaction appears to be a slow addition⁵ of Grignard reagent to the ester to provide a ketone intermediate, followed by rapid reduction of the ketone to the secondary alcohol. The reaction of 1-phenyl-3-pentanone (3 mmol) with a $\frac{1}{2} \text{LiBH}_4\text{-2 EtMgCl}$ mixture under the usual conditions (-20°C , 24 h) gave secondary and tertiary alcohols in a ratio of 2.5/1. This result supports the proposed mechanism by demonstrating that under the standard reaction conditions reduction of this ketone is faster than Grignard addition. Although the possibility exists that a tetrahedral intermediate, formed by addition of the Grignard reagent to the ester carbonyl, is reduced by LiBH_4 , we feel this is not likely. A ketone intermediate is strongly supported by the result of the experiment shown below using LiBH_4 -vinylmagnesium bromide.

Table I. Synthesis of Secondary Alcohols from Esters and LiBH₄-RMgX

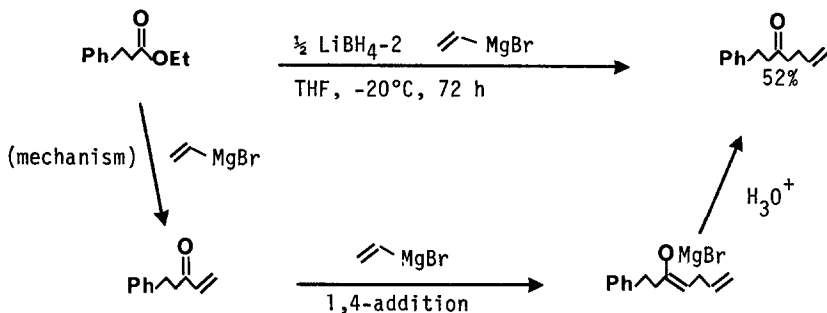
Ester	RMgX	Reaction Conditions ^a	Product ^b	Yield % ^c
1	<u>n</u> -BuMgCl	-20°C, 24 h		74
1	MeMgCl	-20°C, 24 h		69
1	EtMgCl	-20°C, 24 h		61 ^d
1	EtMgBr	-20°C, 24 h	"	66 ^d
1	EtMgI	-20°C, 24 h	"	34 ^d
1	<u>i</u> -PrMgCl	-20°C, 24 h		50
1	PhMgCl	-20°C, 72 h		65
5	<u>n</u> -BuMgCl	0°C, 24 h		61
5	<u>i</u> -PrMgCl	0°C, 24 h		67
5	PhMgCl	0°C, 24 h		64 ^d

^aReactions were performed on a 3 mmol scale. The ester was added to a mixture of LiBH₄ (1.5 mmol) and RMgX (6 mol) in THF. LiBH₄ was purchased as a 2M solution in THF from Aldrich Chemical Co.

^bAll products were known compounds and gave the expected IR and ¹H NMR spectra.

^cYields are for isolated, pure, material obtained from preparative layer chromatography (silica gel, acetone-hexanes).

^dGC yield.



Attempts to prepare a secondary alcohol from an ester and $\text{LiBH}_4\text{-RLi}$ failed. When ethyl 3-phenylpropanoate was added to $\frac{1}{2} \text{LiBH}_4\text{-2 } n\text{-BuLi}$ in THF (-20°C), or if $n\text{-BuLi}$ (1 equiv) was added slowly dropwise to $\text{LiBH}_4\text{-ethyl 3-phenylpropanoate}$ (1:1)(THF, -20°C), tertiary alcohol was the main product.

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References and Notes.

1. Review: E. Winterfeldt, *Synthesis*, 617 (1975). For other hydride reagents which reduce esters to aldehydes, see: M. Muraki and T. Mukaiyama, *Chem. Lett.*, 215 (1975) T. Tokoroyama and R. Kanazawa, *Synthesis*, 526 (1976).
2. C. A. Buehler and D. E. Pearson, "Survey of Organic Synthesis," volume 2, Wiley, New York, N.Y., 1977, p. 614.
3. J. March, "Advanced Organic Chemistry," 2nd ed., McGraw-Hill, Inc., New York, N.Y., 1977, p. 440.
4. H. C. Brown, "Hydroboration," Benjamin, New York, 1962, p. 245. H. C. Brown, S. Narasimhan, and Yong Moon Choi, *J. Org. Chem.*, **47**, 4702 (1982).
5. In the presence of lithium borohydride, the rate of addition of Grignard reagent to the ester carbonyl is slow.
6. Gas-liquid chromatography (GC) was performed with a Hewlett-Packard Model 5830 A gas chromatograph equipped with a 30 m x 0.25 mm FSOT column packed with OV-101. Ethyl 3-phenylpropanoate or ethyl benzoate were used as internal standards.

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