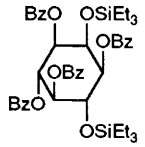
# A Novel Deacylation Method using Grignard Reagent without affecting the Neighbouring Base-sensitive Functional Groups

**Yutaka Watanabe,* Takahiro Fujimoto and Shoichiro Ozaki**

*Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama 790, Japan*

Methyl and ethyl Grignard reagents are shown to cleave ester functions such as benzoate and acetate without affecting the neighbouring base-sensitive functional groups.

A variety of acyl groups have been employed for protection of alcohols in organic synthesis. Acetate and benzoate which are common protected derivatives are usually deprotected by alkaline hydrolysis or by using nucleophiles such as ammonia, hydrazine and metal alkoxides.[1] Reductive cleavage of ester linkages using reducing reagents such as lithium aluminum hydride (LAH)[1] and lithium triethylborohydride[2] are also employed. However, such procedures sometimes encounter difficulties. For example, we could not remove benzoyl groups from 2,6-di-*O*-triethylsilyl-1,3,4,5-tetra-*O*-benzoyl-*myo*-inositol **1** without migration of the silyl functions by usual deprotecting procedures. In fact, 1,2- and 1,3-diol monosilyl




**1** (Bz = PhCO)

ethers are known to be prone to silyl migration under basic conditions.[3] In contrast, employment of the Grignard reagent with **1** was eventually found to be highly efficient to afford the corresponding 2,6-disilyl ether in high yield.[4] These facts prompted us to investigate the applicability of the procedure for removal of some common acyl groups from carboxylic ester derivatives, especially in the case where a base-sensitive functional group such as a silyl ether, halide or phosphate group exists adjacent to the ester. In this communication, we show that methyl and ethyl Grignard reagents can be utilized effectively for the purpose mentioned above.

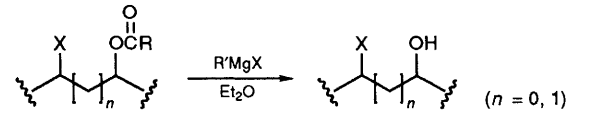
Treatment of 2-benzoyloxy-1-triethylsilyloxy-1-phenylethane **2a** with ethylmagnesium bromide (3 molar equiv.) in diethyl ether at room temperature for 1 h afforded the corresponding 1-*O*-silyl ether **3** quantitatively. No formation of the silyl migration product was confirmed by TLC and HPLC analysis. It should be noted that, when the same substrate **2a** was subjected to the reaction with NaOMe–MeOH, hydrazine or LAH, removal of the benzoyl group was accompanied by migration and emission of the triethylsilyl group. The regioisomeric benzoate **4b** was also deacylated without migration of triethylsilyl group at C-2. In the latter case, however, 14 molar equiv. of the Grignard reagent and longer reaction time (3 h) were necessary because of steric hindrance of the ester function. Deacylations of acetate **4a** and 4-oxopentanoate (levulinate) **4c** were quite smoothly achieved respectively on treatment with slight excess† of ethylmagnesium bromide. Furthermore, 2-*O*-2,2-dimethylpropionyl (pivaloyl) derivative **2b** was also smoothly deblocked with ethylmagnesium bromide to give the corresponding silyl ether in 90% yield. Methyllithium was utilized for removal of pivaloyl group.[5] Levulinic esters react with the Grignard reagent at the ketonic carbonyl whose reactivity is higher than the ester.[6] Based on this fact, 1-benzoyloxy-2-levulinyloxypropane **8** was treated with methylmagnesium iodide at 0 °C resulting in the chemoselective cleavage of the levulinyl without affecting the benzoate.

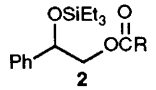
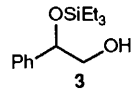
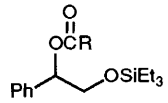
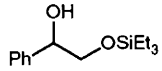
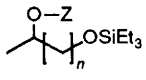
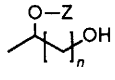
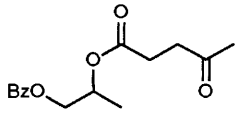
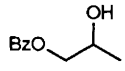
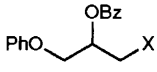
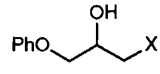
Inhibition of silyl migration is attributed mainly to the low nucleophilicity of magnesium alkoxides‡ which are formed by cleavage of ester linkage. This feature of the alkoxide was successfully applied to deacylation of phosphoryloxy and halo benzoates **6c** and **10** as shown in Table 1. In the latter case, bromohydrin especially tends to form epoxide under basic conditions. Expediently, the reaction of β-bromoethyl benzoate **10b** with ethylmagnesium chloride at −42 °C afforded the corresponding alcohol **11b** in 90% yield while the same reaction except for using ethylmagnesium bromide instead of the chloride gave the alcohol in 43% yield accompanied by 53% of the recovered starting material.

In summary, ethylmagnesium bromide as the Grignard reagent can be commonly used for removing acyl protecting groups in the presence of other sensitive functions. When the reactions (**6c** and **10b** to **7c** and **11b**, respectively) were carried out at low temperatures to avoid side reactions, ethylmagnesium chloride was more effective than the bromide which was less reactive than the former reagent.§ Debenzoylation of secondary alkyl esters required a considerable excess of Grignard reagent whereas the reaction for alkanoyl esters took place with a slight excess of the reagent. Grignard reagent has now been found to be useful for deacylation, particularly bearing a base-sensitive functional group around the ester.

This work was partially supported by a Grant-in-Aid for Scientific Research on Priority Areas (No. 501240114722)

**Table 1** Removal of acyl protecting groups in the presence of other sensitive groups by Grignard reagent[a,b]




| Substrate | R'MgX (equiv.) | Reaction conditions[c] | Product and isolated yield (%) |
|---|---|---|---|
|  **2** | | |  **3** |
| **a**; R = Ph | EtMgBr (3) | r.t., 1 h | (quant.) |
| **b**; R = Bu$^t$ | EtMgBr (10) | r.t., 3 h | (90) |
|  **4** | | |  **5** |
| **a**; R = Me | EtMgBr (4.0) | r.t., 4 h | (90) |
| **b**; R = Ph | EtMgBr (14) | r.t., 3 h | (94) |
| **c**; R = MeCO(CH$_2$)$_2$ | EtMgBr (1.4) | r.t., 15 min | (87) |
|  **6** | | |  **7** |
| **a**; Z = TBDMS ($n$ = 1) | MeMgI (3.0) | r.t., 1.25 h | (84) |
| **b**; Z = TBDMS ($n$ = 2) | EtMgBr (3.0) | r.t., 5 h | (87) |
| **c**; Z = (BnO)$_2$P(O) ($n$ = 2) | EtMgCl (30) | −42 °C, 2.5 h | (93) |
|  **8** | MeMgI (2.0) | 0 °C, 2 h |  **9** (93) |
|  **10** | | |  **11** |
| **a**; X = Cl | EtMgBr (30) | r.t., overnight | (quant.) |
| **b**; X = Br | EtMgCl (20) | −42 °C, 2 h | (90) |

[a] Bz = PhCO; TBDMS = SiBu$^t$Me$_2$; Bn = PhCH$_2$; Lev = MeCO(CH$_2$)$_2$CO. [b] Compounds employed here gave reasonable IR and $^1$H NMR spectra. New compounds were also characterized by elemental analysis. Each product was confirmed to be pure by HPLC analysis. [c] r.t. = room temp.

† In the former case, 2 molar equiv. of the Grignard reagent was stoichiometrically necessary to form 2-ethylbutan-2-ol, while equimolar amounts of **4c** and the reagent were necessary in the latter case for forming γ-butyrolactone.[6]

‡ We observed that magnesium methoxide did not react with compound **1** while sodium methoxide removed benzoyl groups in **1** smoothly.

§ There are some reports on the studies of the relative reactivities of Grignard reagents with compounds containing an acidic hydrogen such as hexy-1-ne or phenylacetate: J. H. Wotiz, C. A. Hollingsworth and R. Dessy, *J. Am. Chem. Soc.*, 1955, **77**, 103, and references cited therein.

from the Ministry of Education, Science and Culture, Japanese Government.

*Received, 23rd December 1991; Com. 1/06430D*

## References

1 T. W. Greene, *Protective Groups in Organic Synthesis*, Wiley, New York, 1981.
2 M. J. Ford, J. G. Knight, S. V. Ley and S. Vile, *Synlett.*, 1990, 331.
3 J. Mulzer and B. Schöllhorn, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 431, and references cited therein.
4 Y. Watanabe, T. Fujimoto, T. Shinohara and S. Ozaki, *J. Chem. Soc., Chem. Commun.*, 1991, 428.
5 B. M. Trost, S. A. Godleski and J. L. Belletire, *J. Org. Chem.*, 1979, **44**, 2052.
6 R. F. Frank, P. G. Arvan, J. W. Richter and C. R. Vanneman, *J. Am. Chem. Soc.*, 1944, **66**, 4.