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A practical and efficient procedure for reduction of carboxylic acids and their derivatives: use of KBH_4–$MgCl_2$

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Abstract—The use of KBH_4–$MgCl_2$ to reduce carboxylic acids and their derivatives to the corresponding alcohols or the respective reduced products is described. Methyl (*S*)-3,4-*O*-isopropylidene-3,4-dihydroxy butanoate **2** used as a reference substrate was reduced with KBH_4 and $MgCl_2$ in 1:1 mol ratio to (*S*)-1,2-*O*-isopropylidene-1,2,4-butanetriol **1**.
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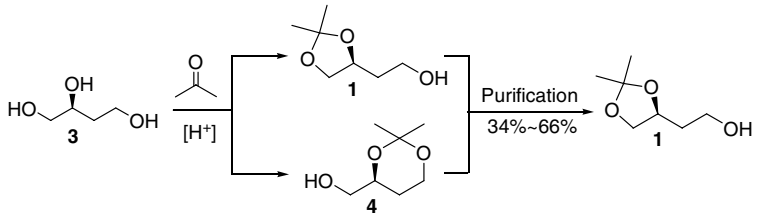
Since Brown[1] reported that some carboxylic acids and their derivatives can be reduced to alcohols by using a combination of $NaBH_4$ and Lewis acid (such as LiBr, $MgCl_2$, $MgBr_2$, $AlCl_3$, and $CaCl_2$) by heating in diglyme or THF/toluene, there have been many complex borohydrides [such as $NaBH_4$–MX (MX = LiCl, $ZnCl_2$),[2] $NaBH_4$–CF_3CO_2H,[3] $NaBH_4$–H_2SO_4,[4] $NaBH_4$–I_2,[5] BH_3·Me_2S,[6] KBH_4–MX (MX = $ZnCl_2$, $AlCl_3$)[7]] reported for the similar reactions. To our surprise, KBH_4 combined with $MgCl_2$ used as a reductant has not been properly explored.

In continuation of our work[7d] to develop practical preparative methods of pharmaceutical intermediate, (*S*)-1,2-*O*-isopropylidene-1,2,4-butanetriol **1** from methyl (*S*)-3,4-*O*-isopropylidene-3,4-dihydroxybutanoate **2**, we developed a practical and efficient procedure for reduction of carboxylic acids and their derivatives to the corresponding reduced products with KBH_4–$MgCl_2$ combination (KBH_4:$MgCl_2$ = 1:1).

(*S*)-1,2-*O*-Isopropylidene-1,2,4-butanetriol **1** is an important synthon, used as the chiral resources for the total synthesis of many natural products.[8] There are two methods for its preparation based on starting materials.

The first method used (*S*)-1,2,4-butanetriol **3** as the starting material, which was selectively protected by acetone[9] to give a mixture of 5-membered acetonide **1** and its corresponding regioisomeric 6-membered acetonide **4** in the ratio of 9:1. When cyclohexanone[10] or 3,3-dimethoxypentane[11] was used instead of acetone, the ratio of 5-membered ketal to its isomeric 6-membered ketal was 19:1 and 45:1, respectively. Because of the similarity of the physical and chemical characters, **1** and **4** cannot be successfully separated by conventional techniques. In order to remove **4**, the mixture was converted into the corresponding esters and purified by recrystallization[9] or column chromatography,[12] followed by hydrolyzation to give pure **1** in a low yield of 34–66% (Scheme 1).



Scheme 1.

Keywords: (*S*)-1,2-*O*-Isopropylidene-1,2,4-butanetriol; Acid derivatives; KBH_4–$MgCl_2$; Reduction.
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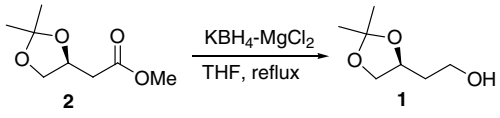
The second method used methyl (*S*)-3,4-*O*-isopropylidene-3,4-dihydroxybutanoate **2** as the starting material by reduction with $LiAlH_4$[13] to give **1** in 72% yield or with 6.0 mol equiv $NaBH_4$ in methanol[14] in 96.4% yield. By these methods, the reducing agent became expensive or was consumed in abundance.

In order to find a suitable reductive method, a series of experiments were undertaken to use a combination of KBH_4 and several Lewis acids (LiCl, $AlCl_3$, $ZnCl_2$, $CaCl_2$, $MgCl_2$) as reductant to prepare **1** from **2** (prepared from lactose,[15] and refined by fractional distillation; GC purity >98%, bp = 70 °C/4 mmHg). It was found that KBH_4–$MgCl_2$ system worked well to reduce **2** in THF to give a yield comparable with the above cited reactions (Scheme 2).

The results of the parallel experiments showed that **2** was partially decomposed and no **1** was detected when using KBH_4 combined with $AlCl_3$ or $ZnCl_2$ and no **2** was converted when using $CaCl_2$. Among the metallic chlorides, LiCl and $MgCl_2$ could enhance the reductive activity of KBH_4 obviously with conversion rates of **2** as 98.1% and 55.6%, respectively, and the yields of **1** as 88.3% and 50.4%, respectively (by procedure A: under N_2 atmosphere, all materials were added in dry THF at one time and heated under reflux for 3 h). But considering the cost of LiCl, we chose the cheaper $MgCl_2$ combined with KBH_4 (**2**:KBH_4:$MgCl_2$ = 1:1:0.5) as a reducing agent and the experimental conditions were optimized (by procedure B: under N_2 atmosphere, KBH_4 and $MgCl_2$ were added in dry THF, refluxed for 2 h, then **2** was added and refluxed for another 1 h) and the conversion rate of **2** increased from 55.6% to 89.4% with the yield of **1** from 50.4% to 80.2%. The first refluxing stage of KBH_4 with $MgCl_2$ in THF for 2 h is critical. When the refluxing time is shortened too much, the reducing activity would be weakened but there is no improvement for prolonged time. The suitable reaction temperature is the refluxing temperature in THF (65–67 °C) and the reaction rate would be slowed down obviously if the temperature is lowered to 50 °C.

The remarkable effect of the $MgCl_2$ ratio on the reaction rate is shown in Figure 1. When the mol ratio of **2** to KBH_4 is 1:1, the reaction rate increased sharply with the mol equiv of $MgCl_2$ changing from 0.50 to 1.0 (Fig. 1, curves a–d). On the other hand, KBH_4 also played a key role and its effect on the reaction rate is shown in Figure 2. When the mol ratio of **2** to $MgCl_2$ is 1:1, the reaction rate decreased obviously with the mol equiv of KBH_4 changing from 1.0 to 0.50. It is noticeable that the reaction could not be completed with 0.65 mol equiv of KBH_4 even for prolonged reaction time (Fig. 2, curves d–g).



Scheme 2.

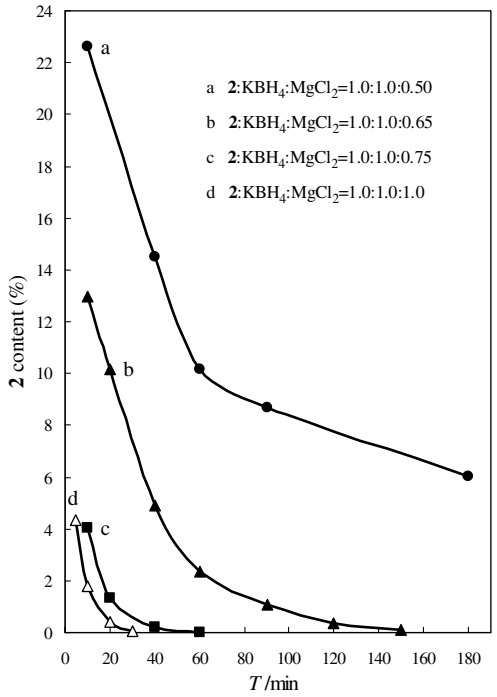


Figure 1. Effect of $MgCl_2$ mol ratio on reaction rate (procedure B).

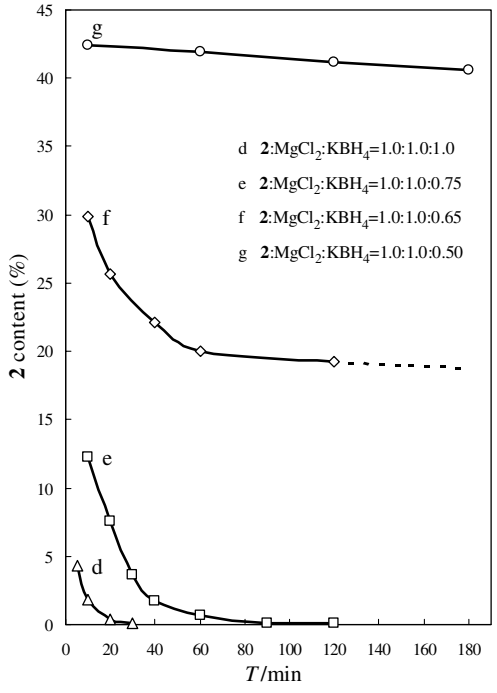
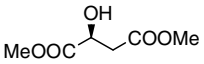
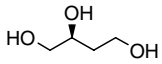
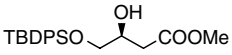
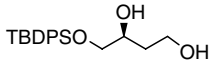
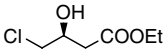
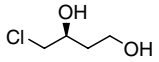
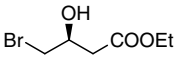
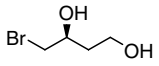
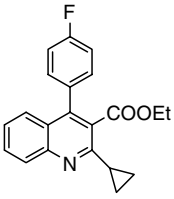
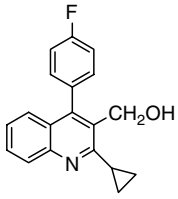
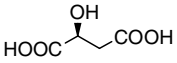
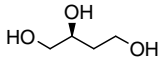
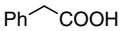
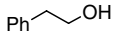
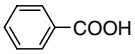
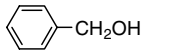
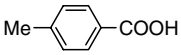
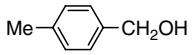
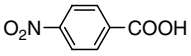
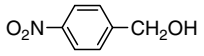
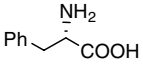
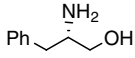
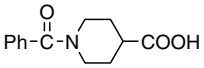
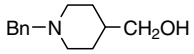
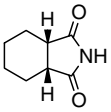
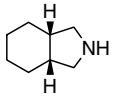
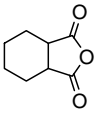
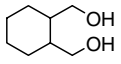
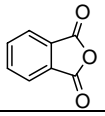
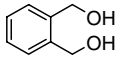


Figure 2. Effect of KBH_4 mol ratio on reaction rate (procedure B).

The optimum experimental condition is as follows: the mol ratio of **2**:KBH_4:$MgCl_2$ = 1:1:1, and the latter two were added in THF and heated under reflux for 2 h, then **2** was added and the resulting reaction mixture was under reflux for an additional 40 min to give crude **1** (yield >90%, GC purity >97%),[16] which can be used in the next step.

Table 1. Reduction of carboxylic acids and their derivatives with KBH_4–$MgCl_2$

Entry	Substrate (1 mol equiv)	Equimolecular KBH_4–$MgCl_2$ (mol equiv)	Conditions[a]	Product	Yield[b] (%)
1		2.3	25 °C, 0.5 h		67.1[c]
2		1.2	25 °C, 1 h		98.2
3		1.2	25 °C, 1 h		79.5
4		1.2	25 °C, 1 h		92.4
5		1.0	66 °C, 10 h		13.8; 98.3[d]
6		2.5	66 °C, 2 h		49.8[c]
7	$CH_3(CH_2)_{10}COOH$	1.5	66 °C, 10 h	$CH_3(CH_2)_{10}CH_2OH$	52.6
8		1.5	66 °C, 24 h		81.5
9		2.0	66 °C, 24 h		67.7
10		2.0	66 °C, 24 h		71.4
11		2.0	66 °C, 24 h		65.5
12		1.2	66 °C, 24 h		59.0
13		3.0	66 °C, 2 h		59.3; 81.7[d]
14		2.5	66 °C, 24 h		6.2; 78.6[d]
15		2.5	66 °C, 24 h		61.8; 84.3[d]
16		2.5	66 °C, 24 h		40.2; 72.4[d]

[a] Reaction condition: equimolecular $MgCl_2$ and KBH_4 were added in THF and heated under reflux for 2 h, then the substrate or its mixture with toluene was added.
[b] Isolated yield and all products were identified by ^1H NMR and mass spectrometry or by comparison with authentic samples.
[c] Isolated as acetonide.
[d] Carried out in the indicated time at 100 °C after addition of substrate in toluene.

This facile KBH_4–$MgCl_2$ reduction method provides a practical and efficient preparation of alcohol **1** from ester **2**, and avoids not only the removal of isomeric 6-membered acetonide **4**[9] but also the expensive $LiAlH_4$[13] or great excess of $NaBH_4$.[14]

The KBH_4–$MgCl_2$ (1:1) combination as a reducing agent is extended to the reduction of carboxylic acids and their derivatives to the corresponding reduced products. The results[17] are shown in Table 1. In this method a variety of functional groups such as halogen, Si–O

bond and nitro can be tolerated. Esters with β-hydroxy were reduced more easily (entries 1–4). When the reduction products contained an amino group, an additional treatment was necessary to hydrolyze the B–N adducts or borate esters by 20% aqueous sodium hydroxide at reflux for 2 h to afford the corresponding products (entries 12–14). Addition of substrate in toluene to raise the reaction temperature enhanced the reducing power of KBH_4–$MgCl_2$ (entries 5 and 13–16).

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16. *Procedure for the reduction of ester* **2** *to alcohol* **1**: A dry, 250-mL three-neck flask with $CaCl_2$ drying tube and magnetic stirrer was charged with 100 mL of THF, 3.27 g (purity: 95%, 57.47 mmol) of KBH_4, and 5.46 g (57.47 mmol) of $MgCl_2$. The reaction mixture was heated under reflux for 2 h, then 10.0 g (57.47 mmol) of **2** was added dropwise over 5 min and maintained at reflux for an additional 40 min. After cooling to 5–10 °C, methanol (15 mL) was carefully added dropwise to quench the reaction and the white inorganic solid was filtrated and washed with 80 mL of THF/MeOH (v/v = 10:1). The combined filtrate was concentrated to dryness, MeOH (40 mL) was added to the residue and concentrated to dryness again. The resulting residue was dissolved in 300 mL of ethyl acetate and washed with brine, dried over $MgSO_4$ and concentrated to dryness to provide 7.58 g (yield 90.3%) of **1** as colorless oil: GC 97.8%; bp 75–76 °C/2 mmHg (lit.[8a] 55–61 °C/0.05 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.42 (s, 3H), 1.79–1.84 (m, 2H), 2.39 (br s, 1H), 3.58 (dd, 1H, $J = 8.4$, 6.0 Hz), 3.78 (t, 2H, $J = 5.0$ Hz), 4.08 (dd, 1H, $J = 8.4$, 6.0 Hz), 4.23–4.29 (m, 1H); ESI-MS *m*/*z*: $[M+Na]^+$ 169. GC condition: HP5890; column: INNOWAX (30 m × 0.53 mm × 1 μm); oven: 150 °C (hold 4.5 min) to 200 °C (hold 6 min) at 70 °C/min; carrier gas: nitrogen; detector: FID; 2.2 min: starting material (**2**); 3.3 min: 6-membered acetonide (**4**); 3.9 min: product (**1**).
17. *General method* 1: $MgCl_2$ and KBH_4 were added in THF and heated under reflux for 2 h, then the substrate or its mixture with toluene was added. After the reaction was completed, methanol was added dropwise at room temperature to quench the reaction. After filtration, the solvent was removed in vacuo and the residue was purified via conventional techniques to afford the corresponding product. *General method* 2 (product with amine group): Same as *method* 1, but used brine to quench the reaction. After filtration and extraction, the resulting organic layer was isolated and concentrated to dryness, 20% aqueous sodium hydroxide was added to the residue and refluxed for 2 h. After cooling to room temperature, the resulting mixture was extracted with dichloromethane. The combined organic layer was dried over Na_2SO_4 and concentrated to dryness. The residue was purified via conventional techniques to afford the corresponding product.