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# New selective *O*-debenzylation of phenol with Mg/MeOH

Wei Huang,[a] Xu Zhang,[a,b] Hong Liu,[a,*] Jianhua Shen[a] and Hualiang Jiang[a,c,*]

[a]*The Center for Drug Discovery and Design, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Shanghai Institutes for Biological Sciences, and Graduate School, Chinese Academy of Sciences, Shanghai 201203, PR China*
[b]*School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang, Liaoning, 110016, PR China*
[c]*School of Pharmacy, East China University of Science and Technology, Shanghai 200237, PR China*

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**Abstract**—Carboxylate-benzyl and nitro-benzyl groups used in phenols protection were selectively debenzylated with 3–25 equiv of Mg in methanol at room temperature. Good yields of the desired phenols were obtained within 3–10 h from a wide variety of *O*-(carboxylate-benzyl)- or *O*-(nitro-benzyl)-phenols. Selective *O*-debenzylation was possible in the presence of *O*-(carboxylate-benzyl)- or *O*-(nitro-benzyl)-phenols with Mg/MeOH.

*O*-Benzyl and *N*-benzyl groups are widely used in protecting many functional groups such as alcohols, phenols, acids, amines and amides. The commonly employed deprotecting methods include hydrogenolysis with catalytic Pd/C,[1] acid hydrolysis in refluxing trifluoroacetic acid (TFA),[2] $FeCl_3$,[3] lithium naphthalenide.[4] However, in many cases, clean benzyl group is not proper for those chemicals with labile groups under these debenzylation methods. Furthermore, in a lot of complex syntheses, diversiform and selective deprotection methods are required for more than two functional groups. Therefore, the specific debenzylation methods of various substituted benzyl groups have been reported in order to develop milder debenzylation conditions.[5–8] For example, 4-methoxylbenzyl (MB), 2,4-dimethoxylbenzyl (DMB) and 2,4,6-trimethylbenzyl groups with increased acid sensitivity have been used in the selective N-debenzylation with *p*-TsOH.[5]

Here we report a novel, convenient and selective debenzylation method with Mg/MeOH, an electron transfer reagent, for *O*-(carboxylate-benzyl)- or *O*-(nitro-benzyl)-phenols. To date, there is no debenzylation agent for these compounds. The application of this reagent is summarized in Table 1. The *O*-(carboxylate-benzyl)- or *O*-(nitro-benzyl)-phenols were synthesized by the reaction of the corresponding phenols with $CO_2$-Me(Et)-benzyl bromide or *p*-$NO_2$-benzyl bromide in the presence of potassium carbonate at rt in excellent yields. *O*-Debenzylation of compounds **1a**–**k** occurred smoothly with good yields of the isolated phenols. Even with the 2-(benzothiazole-2-yl)-*O*-(*p*-$CO_2$Me-benzyl)-phenol (**1k**), a 77% yield of the desired product was isolated in spite of steric hindrance.

Using *O*-(*p*-$CO_2$Me-benzyl)-phenol (**1a**) as a model compound, we optimized the reaction conditions by testing several parameters, such as different amounts of Mg and MeOH, as well as reaction time. Compound **1a** was separately debenzylated with 3, 6, 9 and 12 equiv of Mg and different reaction times. After 4 and 3 h, the conversion rate of **1a** achieved 100% (yields 90% and 91%) using 9 and 12 equiv of Mg at room temperature. But after 10 h, the reactions with lower amount of 3 or 6 equiv of Mg were incomplete with corresponding conversion rate of 68% and 82% (yields 52% and 70%). This indicates that optimization of the debenzylation conditions by increasing the amount of Mg may be useful than extending the reaction time. The optimum results were usually obtained when 0.1 M of the starting material was allowed to react with 3–25 equiv of Mg turning in 0.5–5 mL of anhydrous methanol at room temperature for 3–10 h (Table 1). The products were obtained by column chromatography with silica gel.

When we applied this reagent to debenzylation of *p*-$CO_2$Me-benzyl, *m*-$CO_2$Me(Et)-benzyl and *p*-$NO_2$-benzyl as protecting groups, good to excellent yields of

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*Keywords*: Substituted benzyl; Phenol protecting group; Selective *O*-debenzylation; Mg/MeOH.

* Corresponding authors. Tel.: +86 21 5080 6600x1210; fax: +86 21 5080 7088; e-mail: hljiang@mail.shcnc.ac.cn

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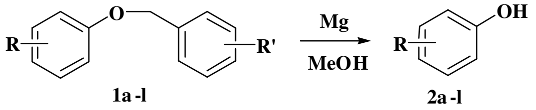
**Table 1.** Examples of *O*-debenzylation with Mg/MeOH



| Entry | R | R′ | Mg (equiv) | Time (h) | Product (yield, %) |
|---|---|---|---|---|---|
| **a** | H | *p*-$CO_2Me$ | 9 | 4 | 90 |
| **b** | 4-Me | *p*-$CO_2Me$ | 12 | 5 | 86 |
| **c** | 4-*tert*-Butyl | *p*-$NO_2$ | 12 | 10 | 88 |
| **d** | 4-$CH_2CH_2OH$ | *p*-$NO_2$ | 20 | 10 | 83 |
| **e** | 4-Cl | *m*-$CO_2Me$ | 10 | 5 | 87 |
| **f** | 2,4,6-Tribromo | *m*-$CO_2Me$ | 10 | 5 | 91 |
| **g** | 4-$CO_2Et$ | *m*-$CO_2Et$ | 3 | 3 | 86 |
| **h** | 3-$CO_2Et$,6-BnO[a] | *m*-$CO_2Me$ | 6 | 5 | 93 |
| **i** | 3-$CO_2Et$,6-BnO | *p*-$CO_2Me$ | 6 | 5 | 93 |
| **j** | 3-$CO_2Et$,6-BnO | *p*-$NO_2$ | 6 | 5 | 90 |
| **k** | 2-(Benzothiazole-2-yl) | *p*-$CO_2Me$ | 25 | 10 | 77 |
| **l** | H | H | 40 | 24 | 0 |

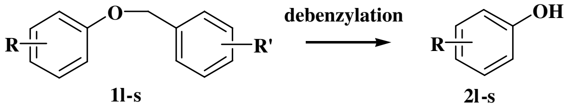
[a] This material was prepared according to Ref. 9.

the desired phenols were isolated as shown in Table 1. The results indicate that benzyls substituted with strong electron-attracting groups are easy to be reductively cleaved by Mg/MeOH, but clean benzyl group is stable under the same condition (**1l**, in Table 1). At the same time, with strong electron-attracting group substituted phenols such as 3-, or 4-$CO_2Et$-phenols are much easily debenzylated, while alkyl or halogen substituted phenols need more Mg for debenzylation cleavage. Thus, 93% yield of the desired phenol **2h** was isolated using 6 equiv of Mg at room temperature for 5 h, while 87% and 91% yields of the desired phenols **2e** and **2f** were isolated using 10 equiv of Mg at room temperature for 5 h. Compounds **1a–c**, **1f** and **1h–k** need to add THF to help dissolution.

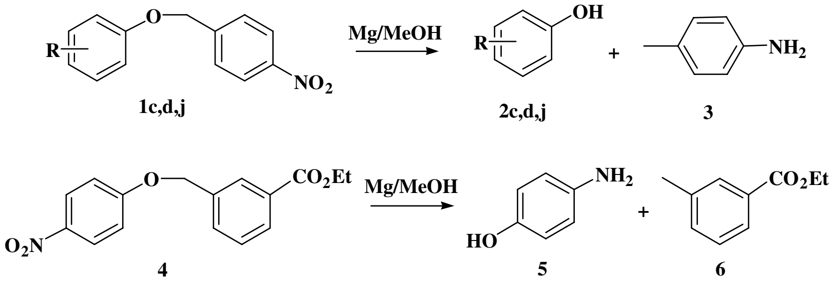
Since Mg/MeOH could also reduce nitro group,[10] *p*-$NH_2$-toluene (**3**) was given as the debenzylation product of *O*-(*p*-$NO_2$-benzyl)-phenol (Scheme 1). Similarly, the *O*-(*m*-$CO_2Et$-benzyl)-4-$NO_2$-phenol (**4**) was debenzylated and reduced to be *p*-$NH_2$-phenol (**5**) by 3 equiv of Mg in 5 h with 87% yield.

We then compared this method with two of the commonly used *O*-debenzylation methods, that is, hydrogenolysis in catalytic Pd/C, and cleavage in $FeCl_3$/$CH_2Cl_2$, using compound **1l–s** as starting materials. The results are summarized in Table 2. Under the condition of catalytic hydrogenation, clean benzyl or substituted benzyls of **1l–s** were all cleaved, but $FeCl_3$/$CH_2Cl_2$ displayed high selectivity against clean benzyl group and Mg/MeOH selectively debenzylated the substituted benzyl groups. Compounds **1l** and **1n** were very labile in $FeCl_3$/$CH_2Cl_2$, and were completely debenzylated by 1 equiv of $FeCl_3$/$CH_2Cl_2$ in 5 min. Mg/MeOH as a mild condition showed its specific cleavage capability against *O*-(carboxylate-benzyl)- or *O*-(nitro-benzyl)-phenols in **1m**, **1o**, **1q** and **1s**.

**Table 2.** Examples of selective *O*-debenzylation product

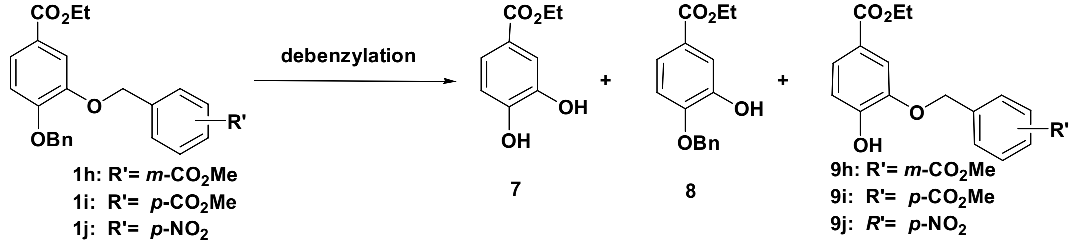


| | R | R′ | Product (yield, %) | | |
|---|---|---|---|---|---|
| | | | $H_2$ | $FeCl_3$ | Mg |
| **1l** | H | H | 90 | 79 | 0 |
| **1m** | H | *p*-$NO_2$ | 90 | 0 | 87 |
| **1n** | 4-Cl | H | 89 | 78 | 0 |
| **1o** | 4-Cl | *p*-$CO_2Me$ | 93 | 0 | 82 |
| **1p** | 4-$CO_2Et$ | H | 88 | 92 | 0 |
| **1q** | 4-$CO_2Et$ | *p*-$CO_2Me$ | 90 | 0 | 88 |
| **1r** | 4-Phthalimid-*N*-yl | H | 95 | 90 | 0 |
| **1s** | 4-Phthalimid-*N*-yl | *m*-$CO_2Me$ | 86 | 0 | 79 |



**Scheme 1.**

**Table 3.** Comparison of *O*-debenzylation methods



| S.M.[a] | Reagents (deprotection) | Temperature | Time (h) | Product (yield, %) | | |
|---|---|---|---|---|---|---|
| | | | | 7 | 8 | 9 |
| **1h** | $H_2$/5% Pd–C | Rt | 3 | 93 | — | — |
| **1i** | $H_2$/5% Pd–C | Rt | 3 | 96 | — | — |
| **1j** | $H_2$/5% Pd–C | Rt | 3 | 92 | — | — |
| **1h** | Mg (6 equiv)/MeOH–THF | Rt | 5 | — | 93 | — |
| **1i** | Mg (6 equiv)/MeOH–THF | Rt | 5 | — | 93 | — |
| **1j** | Mg (6 equiv)/MeOH–THF | Rt | 5 | — | 90 | — |
| **1h** | $FeCl_3$ (12 equiv)/$CH_2Cl_2$ | Rt | 0.5 | — | — | 89 |
| **1i** | $FeCl_3$ (12 equiv)/$CH_2Cl_2$ | Rt | 0.5 | — | — | 92 |
| **1j** | $FeCl_3$ (12 equiv)/$CH_2Cl_2$ | Rt | 0.5 | — | — | 90 |
| **1h** | TFA (20 equiv)/$CH_2Cl_2$ | Reflux | 24 | — | — | — |
| **1i** | TFA (20 equiv)/$CH_2Cl_2$ | Reflux | 24 | — | — | — |
| **1j** | TFA (20 equiv)/$CH_2Cl_2$ | Reflux | 24 | — | — | — |

[a] S.M., starting material.

Using compounds **1h–j** as model compounds, we further compared Mg/MeOH against debenzylation cleavage in $FeCl_3/CH_2Cl_2$, or in $TFA/CH_2Cl_2$ and hydrogenolysis in catalytic Pd/C (Table 3). The benzylation product **7** was given by catalytic hydrogenation, in which, the clean benzyl and $CO_2Me$(Et)-benzyl (or *p*-$NO_2$-benzyl) were totally hydrogenated. On the other hand, Mg/MeOH afforded 93%, 93% and 90% of **8** from **1h–j** after 5 h at room temperature, respectively, and the substituted benzyls were selectively cleaved. In the case of $FeCl_3/CH_2Cl_2$, the debenzylation products **9h–j** were given, respectively, while clean benzyl was solely debenzylated. No debenzylation product was observed with $TFA/CH_2Cl_2$, even after refluxing for 24 h. These results demonstrated our debenzylation conditions are selective and may distinguish different benzyl protecting groups for phenols. Apparently, they are valuable for multiple protections in complex syntheses.

In summary, a new, selective *O*-debenzylation method with Mg/MeOH is described. This method is featured with high specificity against $CO_2Me$(Et)-benzyl and *p*-$NO_2$-benzyl, high yields, mild conditions and wide application in various phenols. It provides a new choice for specific protection and deprotection of phenol hydroxyls and is of value in the protection of multiple functional groups.

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