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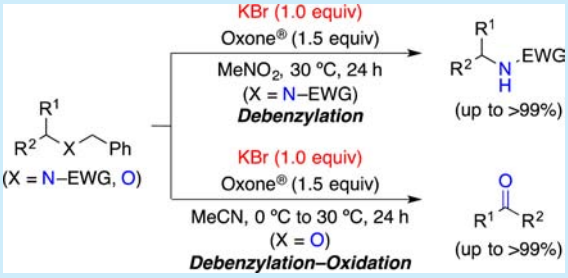
# Oxidative Debenzylation of *N*-Benzyl Amides and *O*-Benzyl Ethers Using Alkali Metal Bromide

Katsuhiko Moriyama,* Yu Nakamura, and Hideo Togo*

Department of Chemistry, Graduate School of Science, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

Supporting Information

**ABSTRACT:** The oxidative debenzylation of *N*-benzyl amides and *O*-benzyl ethers was promoted with high efficiency by a bromo radical formed through the oxidation of bromide from alkali metal bromide under mild conditions. This reaction provided the corresponding amides from *N*-benzyl amides and carbonyl compounds from *O*-benzyl ethers in high yields.




The benzyl group is one of the most frequently used protecting groups for amino and hydroxy functionalities in organic synthesis. The debenzylation of *N*-benzyl amines and *O*-benzyl ethers is classified into three types: (i) reductive cleavage by hydrogenolysis or single-electron transfer; (ii) acid-based cleavage with Lewis acids; (iii) oxidative cleavage with oxidants.[1] The debenzylation of *N*-benzyl amines proceeds sluggishly compared with that of *O*-benzyl ethers and thus requires harsh conditions. Moreover, the debenzylation of *N*-benzyl amides is problematic and challenging in terms of deprotection.[2] In previous works on the debenzylation of *O*- and *N*-benzyl derivatives, a catalytic amount of transition metals ($Pd/H_2$[3] and Ni[4]) and a stoichiometric amount of simple metals (Li[5] and Na[6]), Lewis acids (boron reagents,[7] silyl reagents,[8] and transition metal salt[9]), and oxidants (CAN,[10] DDQ,[4a,b,11] and NIS[12]) were generally required as a reaction activator. On the other hand, we have developed various oxidative transformations that involve the oxidation of bromide ion from alkali metal bromides, which are one of the most abundant natural resources on earth and feature stability in air and ease of handling, neutrality, nontoxicity, and non-elaborating products polluting the environment.[13] We report herein the oxidative debenzylation of *N*-benzyl amides and *O*-benzyl ethers using an alkali metal halide with an oxidant under mild conditions as a novel and green-sustainable method (Figure 1).

First, we screened a series of alkali or alkaline metal bromides, oxidants, and solvents for the oxidative debenzylation of *N*-benzyl-*N*-methylbenzenesulfonamide (**1a**) and cyclododecyl benzyl ether (**3a**) (Tables S1 and S2, Suporting Information). The optimum conditions for the reaction were **1a**, KBr (1.0 equiv), and Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) (1.5 equiv) in $MeNO_2$ at 30 °C, which provided *N*-methylbenzenesulfonamide (**2a**) in a quantitative yield (Scheme 1, eq 1), and **3a**, KBr (1.0 equiv), and Oxone (1.5 equiv) in MeCN at 0 to 30 °C, which provided cyclododecanone (**4a**) in 95% yield but not alcohol (Scheme 1, eq 2).

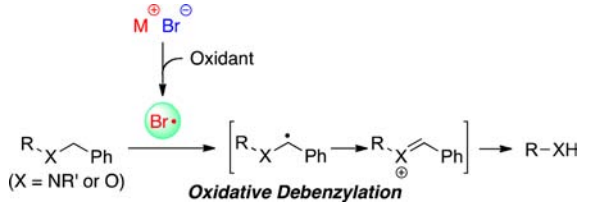
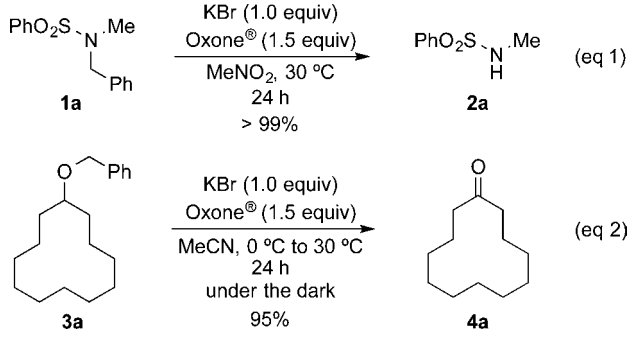



**Figure 1.** Debenzylation of benzyl-protected compounds using alkali metal bromide.

It is noteworthy that the use of NBS or $Br_2$, the absence of KBr, and the reaction under the dark conditions were much less effective than the optimum conditions for the transformation of **1a** into **2a** (Table S1, Supporting Information).

**Scheme 1. Oxidative Debenzylation of *N*-Benzyl Amide Derivative 1a and *O*-Benzyl Ether Derivative 3a**

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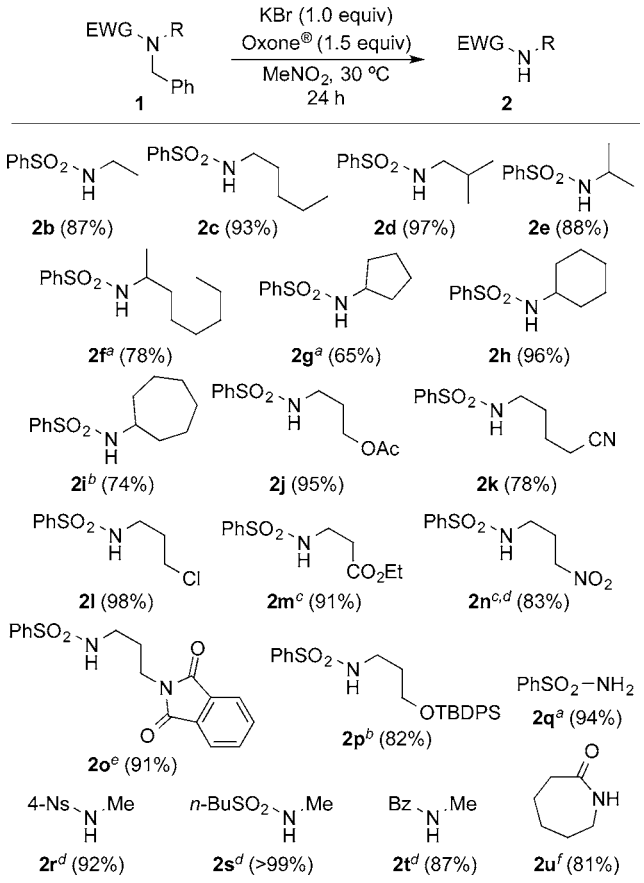
To explore the scope of the oxidative debenzylation, various *N*-benzyl amides **1** were examined using alkali metal bromide under the optimum conditions (Scheme 2). The reactions of

**Scheme 2. Oxidative Debenzylation of *N*-Benzyl Amides 1 Using Alkali Metal Bromide**



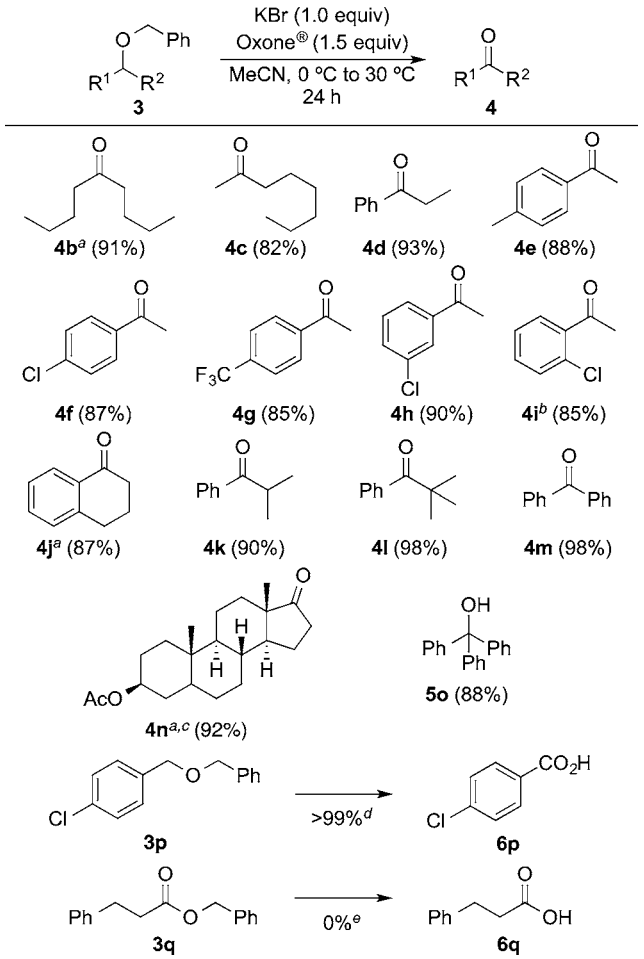

[a]The reaction was carried out at room temperature. [b]KBr (1.2 equiv), Oxone (1.2 equiv), and $Na_2CO_3$ (0.5 equiv) were used in $CH_2Cl_2$ at room temperature. [c]KBr (1.2 equiv) and Oxone (1.8 equiv) were used. [d]The reaction was carried out at 50 °C. [e]KBr (1.2 equiv) and Oxone (2.0 equiv) were used. [f]The reaction was carried out in a mixture of $CH_2Cl_2/H_2O$ (9:1).

*N*-alkyl-*N*-benzyl benzenesulfonamides bearing Et (**1b**), *n*-pentyl (**1c**), *i*-Bu (**1d**), *i*-Pr (**1e**), and *sec*-octyl (**1f**) groups gave the corresponding debenzylation products (**2b**–**2f**), respectively, in high yields (78–97%). *N*-Cycloalkyl-*N*-benzyl benzenesulfonamides bearing *c*-pentyl (**1g**), *c*-hexyl (**1h**), and *c*-heptyl (**1i**) groups were also converted into the desired products (**2g**–**2i**), respectively, in good yields (62–96%). Furthermore, various benzenesulfonamides bearing such functional groups as OAc (**1j**), CN (**1k**), Cl (**1l**), $CO_2Et$ (**1m**), $NO_2$ (**1n**), and phthalimide (**1o**) provided the corresponding products (**2j**–**2o**), respectively, in high yields (78–98%) without degrading the functional group. The reaction of *N*-benzyl benzenesulfonamide bearing silyl ether as an orthogonal protecting group effectively converted into the desired product (**2p**) in 82% yield.

Secondary *N*-benzyl benzenesulfonamide (**1q**) was also converted into benzenesulfonamide (**2q**) in 94% yield. Other amides bearing 4-$NO_2$-$C_6H_4SO_2$ (**1r**), *n*-$BuSO_2$ (**1s**), PhCO (**1t**), and cyclic caproyl (**1u**) groups instead of a $PhSO_2$ group were also efficiently debenzylated to form the corresponding amides (**2r**–**2u**) in high yields (72–>99%).

Next, we investigated a direct oxidation involving the debenzylation of *O*-benzyl ethers **3** using alkali metal bromide (Scheme 3). A direct oxidation of ethers into ketones with

**Scheme 3. Oxidation Involved Debenzylation of *O*-Benzyl Ethers 3 Using Alkali Metal Bromide**




[a]The reaction was carried out under dark conditions. [b]Oxone (1.8 equiv) was used. [c]The reaction was carried out for 28 h. [d]KBr (2.0 equiv) and Oxone (3.0 equiv) were used. [e]Benzyl ester **3q** was recovered in 98% yield.

transition metal[14] and organic oxidants has been reported.[15] The present debenzylation of aliphatic *O*-benzyl ethers, such as benzyl 5-nonyl ether (**3b**) and benzyl 2-octyl ether (**3c**), produced the corresponding ketones (**4b** and **4c**) in 91 and 82% yields, respectively. When a number of benzyl ethers, such as benzyl α-ethylbenzyl ether (**3d**), α-methylbenzyl ethers bearing 4-Me (**3e**), 4-Cl (**3f**), 4-$CF_3$ (**3g**), 3-Cl (**3h**), and 2-Cl (**3i**) on the aromatic ring, 1-benzyloxy-1,2,3,4-tetrahydronaphthalene (**3j**), and other benzyl ethers bearing *i*-Pr (**3k**), *t*-Bu (**3l**), and Ph (**3m**) at the α-position were used, the corresponding ketones (**4d**–**4m**) were also obtained in high yields (82–98%), respectively. 17β-Benzyloxy-5α-androstan-3β-ol acetate (**3n**), which has a tetracyclic skeleton with an ester group, was oxidized into 3β-acetoxy-5α-androstan-17-one (**4n**) in 92% yield. Furthermore, triphenylmethyl benzyl ether (**3o**) classified as 3°-benzyl ether and benzyl 4-chlorobenzyl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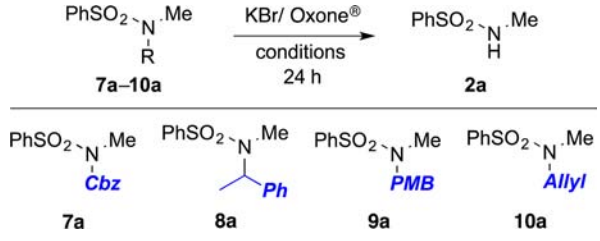
ether (**3p**) classified as 1°-benzyl ether were also converted into 3°-alcohol **5o** and carboxylic acid **6p** in high yields, respectively. Interestingly, benzyl ester **3q** was not effective for the present oxidative debenzylation using alkali metal bromide. It was noticed that the reactions under the dark conditions for the oxidation of **3a**, **3b**, and **3j** inhibited the $\alpha$-bromination of the corresponding products to give the desired ketones in high yields (Scheme S1, Supporting Information). We supeculate that the effect of light for the reaction of **3** is the promotion for generation of a bromo radical to accelerate the debenzylation.

Moreover, to expand the limitation of the protecting group for the present reaction, the oxidative deprotection of *N*-protected benzenesulfonamides bearing various benzyl and allyl protecting groups (**7a**–**10a**) was examined using alkali metal bromide (Table 1). In particular, the use of the substrates

**Table 1. Deprotection of *N*-Sulfonamides Bearing Various Protecting Groups**

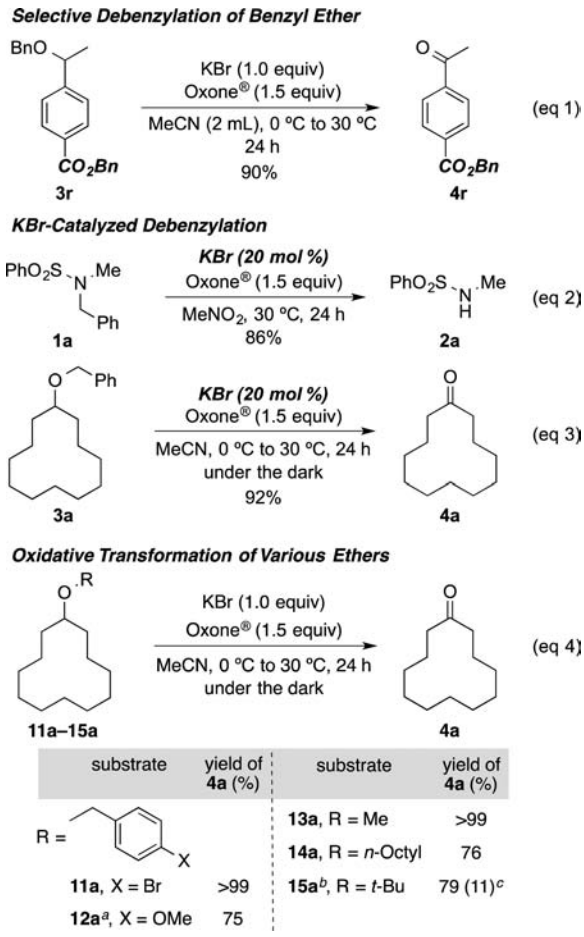



| substrate | KBr (equiv) | Oxone (equiv) | conditions | yield of **2a** (%) |
|---|---|---|---|---|
| **7a** | 1.0 | 1.5 | $MeNO_2$, 30 °C | 93 |
| **8a** | 1.2 | 1.3 | $MeNO_2$, 30 °C | 88 |
| **9a** | 1.2 | 1.5 | $CH_2Cl_2$, rt | 88 |
| **10a** | 3.0 | 2.0 | $CH_2Cl_2/H_2O$ (9:1), rt | 81 |

bearing *p*-methoxy benzyl (**9a**) and allyl group (**10a**) proceeded efficiently by the improvement of reaction conditions to give the desired product **2a** in high yields (88 and 81%), respectively.

On the other hand, with regard to the functional group selectivity of the debenzylation, the selective *N*-debenzylation of *N*,*N*′-dibenzylamino *O*-benzyl esters bearing two kinds of benzyl groups has been reported.[10,16] However, to the best of our knowledge, the selective *O*-debenzylation of benzyloxy benzyl ester bearing two kinds of *O*-benzyl groups has not been established. In this study, we found that the debenzylation of benzyl *p*-(*α*-benzyloxy)ethylbenzoate **3r** proceeded selectively to give benzyl *p*-acetylbenzoate **4r** in 90% yield (Scheme 4, eq 1). Furthermore, the alkali metal bromide-catalyzed debenzylation of **1a** and **3a** efficiently occurred to provide desired products **2a** and **4a** in 86 and 92% yields, respectively (Scheme 4, eqs 2 and 3). The present methodology with KBr/Oxone can be used for the conversion of various ethers into carbonyl compound. Indeed, not only benzyl ethers (**11a** and **12a**) but also methyl ether **13a**, *n*-octyl ether **14a**, and *t*-butyl ether **15a** were oxidized to obtain the desired ketone **4a** in high yields (75 to >99%) (Scheme 4, eq 4). We propose a reaction mechanism for the oxidative debenzylation of *N*-benzyl amides and *O*-benzyl ethers, as depicted in Scheme 5. When the oxidative debenzylation of **1a** and **3a** was carried out using alkali metal bromide, benzoic acid and/or benzaldehyde were obtained as co-products, together with the corresponding products (Scheme S2, Supporting Information). First, the bromo radical

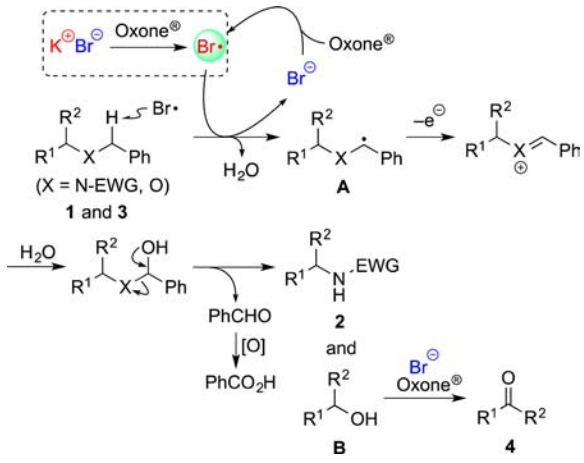
**Scheme 4. Application of Oxidative Debenzylation Using Alkali Metal Bromide**




| substrate | yield of **4a** (%) | substrate | yield of **4a** (%) |
|---|---|---|---|
| R = X | | **13a**, R = Me | >99 |
| | | **14a**, R = *n*-Octyl | 76 |
| **11a**, X = Br | >99 | **15a**[b], R = *t*-Bu | 79 (11)[c] |
| **12a**[a], X = OMe | 75 | | |

[a]The reaction was carried out with KBr (1.2 equiv) and Oxone (1.2 equiv) in $ClCH_2CH_2Cl$ at 0 °C to room temperature. [b]The reaction was carried out with KBr (1.2 equiv) and Oxone (1.8 equiv) for 36 h. [c]Number in parentheses indicates the recovery of **15a**.

**Scheme 5. Plausible Reaction Mechanism for the Debenzylation of Benzyl Amides and Ethers**




is generated via the oxidation of bromide by Oxone in situ. The bromo radical abstracts a hydrogen atom at the benzyl position of the substrates to form benzyl radical intermediates **A**. Once **A** are formed, they are smoothly oxidized to iminium and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oxonium cations via one-electron oxidation and then hydrolyzed to produce amides **2** and alcohols **B**, respectively. In the debenzylation of *O*-benzyl ethers, the formed debenzylated alcohols **B** are further oxidized to carbonyl compounds **4** through the $\alpha$-hydrogen atom abstraction by the bromo radical.[17] For the deprotection of alkyl ethers (**13a**−**15a**), a bromo radical dominantly abstracts a hydrogen atom at a tertiary $\alpha$-carbon atom on the substrate to proceed with alkylation.

In conclusion, we have developed an oxidative debenzylation of *N*-benzyl amides and *O*-benzyl ethers under mild conditions by an alkali metal bromide/oxidant system. The oxidized bromo radical can be utilized in the reaction with a broad range of substrates to obtain the corresponding debenzylated amides and carbonyl compounds in high yields. This reaction is transition-metal- and organic-reagent-free, and these reagents are stable and much less toxic. Therefore, the present method is green-sustainable as it does not yield any products that would pollute the environment. We have high hopes that the transformation via the oxidation of halides using alkali metal halides would be applicable to fine organic synthesis.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, spectral data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION


### Corresponding Authors

*E-mail: moriyama@faculty.chiba-u.jp.
*E-mail: togo@faculty.chiba-u.jp.


### Notes

The authors declare no competing financial interest.

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