



Aerobic oxidative deprotection of benzyl-type ethers under atmospheric pressure catalyzed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)/*tert*-butyl nitrite

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ABSTRACT

A facile and efficient protocol for the oxidative deprotection of benzyl-type ethers has been developed. The reaction was performed with catalytic amounts of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and *tert*-butyl nitrite (TBN) under atmospheric pressure of O₂. Under the optimal reaction conditions, a variety of *p*-methoxybenzyl (PMB), *p*-phenylbenzyl (PPB), and benzyl (Bn) ethers can be deprotected to their corresponding alcohols in excellent conversions and selectivities.

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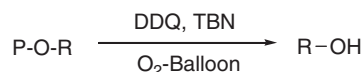
The selective and efficient protection and deprotection of hydroxyl groups play a crucial role in organic synthesis, as these methods have been extensively utilized in different areas of complex syntheses of natural products, pharmaceutical chemicals, and materials.¹ Protection of hydroxyl groups as benzyl-type ethers has long been developed as a valuable reaction,² which is mainly due to that benzyl-type protecting groups provide a number of significant advantages such as ease of introduction, stability toward both acidic and basic reaction conditions, and relative insensitivity to various oxidizing and reducing agents. These benzyl-type protecting groups include benzyl (Bn), diphenylmethyl, trityl, *p*-methoxybenzyl (PMB), *m*-methoxybenzyl, *p*-phenylbenzyl (PPB), *p*-halobenzyl, 3,5-dimethoxybenzyl, and 2-naphthylmethyl, etc.³ There are various methods for the removal of benzyl-type protecting groups. Lewis acids, including SnCl₄-PhSH,⁴ AlCl₃-EtSH,⁵ CeCl₃·7H₂O-NaI,⁶ NaCNBH₃-BF₃·Et₂O,⁷ ZrCl₄-CH₃CN,⁸ or Ce(OTf)₃-CH₃NO₂,⁹ etc, have been introduced to facilitate the cleavage of benzyl-type ethers. TfOH, a Bronsted acid, also can mediate *p*-methoxybenzyl group demasking.¹⁰ The use of stoichiometric oxidants, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),¹¹ ceric ammonium nitrate (CAN),¹² or phenyliodine bis(trifluoroacetate) (PIFA),¹³ for the oxidative

cleavage of benzyl-type ethers remains a popular protocol. Among these oxidants, DDQ is used most frequently. An example of oxidative deprotection of PMB ethers with DDQ in large-scale can be found in the synthesis of discodermolide by Novartis.¹⁴ However, the use of stoichiometric DDQ results in the isolation problem because of the concomitant by-product 2,3-dichloro-5,6-dicyano-hydroquinone (DDHQ). To avoid this inherent disadvantage, a combination of catalytic amount of DDQ and a less-expensive co-oxidant is an interesting alternative. Several inorganic oxidants can be acted as the co-oxidant to regenerate DDHQ, and the combination of DDQ-FeCl₃,¹⁵ DDQ-Mn(OAc)₃,¹⁶ or DDQ-MnO₂¹⁷ can be effectively used for the removal of PMB or 3,4-dimethoxybenzyl group. However, using of a great amount of these inorganic oxidants brings new environmental effluents.

In the recent years, using the catalytic oxidation systems employing catalytic amounts of DDQ and a co-catalyst with molecular oxygen serving as the terminal oxidant to replace the stoichiometric DDQ has received interests. These catalytic oxidation systems have remarkable environmental and economic benefits, and have been successfully applied in oxidative dehydrogenation,¹⁸ alcohol oxidation,¹⁹ and oxidative cross-dehydrogenative coupling reactions.²⁰ With our previous TEMPO-catalyzed aerobic oxidation,²¹ we recently reported DDQ/*tert*-butyl nitrite (TBN) catalyst system for the aerobic oxidation of alcohols and oxidative deprotection of PMB ethers in autoclave.²² For the purpose of simplifying the

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P: benzyl-type protecting group,
PMB, PPB or Bn

Scheme 1. Oxidative deprotection of benzyl-type ethers with DDQ/TBN/O₂.

equipment and extending the substrate scope, we investigated the aerobic oxidative deprotection of several benzyl-type ethers at atmospheric pressure of O₂ in the presence of DDQ/TBN (Scheme 1). The successful results are described in this Letter.

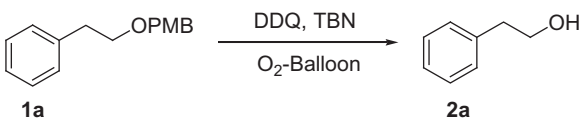
In our initial screening experiments, oxidative deprotection of PMB ether **1a** with DDQ/TBN/O₂ was selected as the model reaction. The optimized results of the influence of various parameters including solvent, the amounts of DDQ and TBN, reaction time, and reaction temperature are summarized in Table 1. Firstly, the reaction was carried out in different solvents with 5 mol % DDQ and 5 mol % TBN under atmospheric pressure of O₂ in balloon at 100 °C. Results in Table 1 showed the solvent can greatly affect the oxidative deprotection of PMB ether. It was found that chlorobenzene, ethylene glycol diethyl ether, and 1,1,2,2-tetrachloroethane led to excellent conversion of **1a** and selectivity to 2-phenylethanol (entries 1, 2, 5). Chlorobenzene might be the most suitable solvent, in which oxidative deprotection of **1a** could be completed in 1.5 h. In ethylene glycol monoethyl ether, moderate conversion of **1a** was obtained in 3 h (entry 3). Other solvents such as ethylene glycol, xylenes, DMF, and *n*-BuOH, resulted in poor conversions (entries 4, 6–8). Further study indicated that decreasing the load of DDQ and TBN from 5 to 3 mol %, a longer reaction time was needed and the selectivity to 2-phenylethanol was slightly decreased. Afterward, the effect of reaction time was investigated. At 80 °C, the reaction rate was slowed down, and a 96% conversion of **1a** was obtained in 3.5 h. When the reaction temperature was increased to 120 °C, the reaction time could be shortened to 1 h, while the selectivity to 2-phenylethanol was decreased to 95% (entry 11). On the basis of these experimental data, we concluded that 5 mol % of DDQ and 5 mol % TBN in chlorobenzene at 100 °C were suitable for oxidative deprotection of PMB ether under atmospheric pressure of O₂.²³

PMB is almost the most frequently used alcohol protecting group in the type of benzyl series, and the results of oxidative deprotection of a variety of PMB ethers with the optimized

reaction conditions are summarized in Table 2. PMB ethers of 1-octanol, 2-octanol, and cyclohexanol (**1b–d**) underwent a complete deprotection of PMB group to furnish the corresponding alcohols in excellent selectivity (entries 2–4). When PMB ethers **1e** and **1f** with high steric hindrance were subjected to deprotection, increasing the catalyst loading was needed (entries 5 and 6). PMB ethers containing a heterocyclic moiety (**1g–i**) could also be fully deprotected. The successful deprotection of **1g** showed that the oxidative deprotection can endure the Boc group (entry 7). Diacetone-*D*-glucose **2j**, bounding two acid-sensitive isopropylidene group as well as a glycosidic ring, could be obtained from its PMB ether **1j** in 94% isolated yield (entry 10). The substrates with two different hydroxyl protecting groups (**1l–o**) were also submitted to the oxidative deprotection reactions. The results showed that using this procedure the PMB ethers were selectively cleaved, giving the corresponding alcohols without affecting the other functional groups (entries 12–15). In case of entry 16, the PMB ether of *p*-chlorophenol (**1p**) gave very poor conversion (<5%) in deprotection under our reaction condition. Similar result was obtained when the PMB ether of phenol was used as the substrate. Thus, we thought that this method might be proposed to selectively deprotect alkyl PMB ether in the presence of aryl PMB ether, and PMB ether of 4-(2-hydroxyethyl)phenol (**1q**) with two PMB groups was subjected to the oxidative deprotection. The desired product **2q** was obtained in 81% isolated yield (entry 17).

Comparing with PMB group, the PPB group is more compatible under acidic conditions.^{11c} Thus, the oxidative deprotection of a series of PPB ethers catalyzed with DDQ/TBN under dioxygen atmosphere (balloon) at 100 °C was studied. The results are listed in Table 3. It was found that all the PPB ethers (**3a–n**) could be completely deprotected in an appropriate reaction time with excellent selectivities (entries 1–14). It should be noted that a longer reaction time was needed to complete deprotection of a PPB ether than that of a PMB ether. For example, for the cleavage of 1-octyl PPB ether and 1-octyl PMB ether, the reactions were complete in 5 h (Table 2, entry 2) and 3 h (Table 1, entry 2), respectively. When PPB ether **3j** was used as the substrate, dosage of DDQ and TBN should be increased to 12 mol % to shorten the reaction time and maintain the selectivity to **2j**. Relatively low isolated yield of **2j** (80%) was due to the hydrolysis of isopropylidene groups in the weak acidic reaction system. Then, the cleavage of benzyl protecting group of alcohols was performed in the same way. Bn ethers of 2-phenylethanol (**4a**) and 1-octanol (**4b**) were successfully deprotected to give the desired alcohols (entries 15 and 16). Thus, we believe that other benzyl-type

Table 1
Optimization of reaction conditions for the oxidative deprotection of **1a**^a

							
Entry	Solvent	DDQ (mol %)	TBN (mol %)	T (°C)	Time (h)	Conv. (%)	Select. (%)
1	PhCl	5	5	100	1.5	100	>99
2	EtO(CH ₂) ₂ OEt	5	5	100	3	99	>99
3	EtO(CH ₂) ₂ OH	5	5	100	3	67	90
4	HOCH ₂ CH ₂ OH	5	5	100	3	11	90
5	CHCl ₂ CHCl ₂	5	5	100	3	92	94
6	Xylenes	5	5	100	6	10	74
7	DMF	5	5	100	6	29	85
8	<i>n</i> -BuOH	5	5	100	6	28	94
9	PhCl	3	3	100	3	100	98
10	PhCl	5	5	80	3.5	96	98
11	PhCl	5	5	120	1	100	95

^a Reaction conditions: **1a** (2 mmol), solvent (5 mL), DDQ (5 mol %), TBN (5 mol %), O₂ (balloon, 1 atm). The conversion and selectivity were determined by GC with area normalization.

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