Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Transformation of ethers into aldehydes or ketones: a catalytic aerobic deprotection/oxidation pathway

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ARTICLE INFO

Article history:
Received 20 February 2015
Revised 6 April 2015
Accepted 8 April 2015
Available online xxxx

Keywords:
Functional group interconversion
PMB ethers
Carbonyl compounds
Oxidation
Oxygen

ABSTRACT

A facile and efficient protocol for direct transformation of *p*-methoxybenzyl (PMB) ethers to aldehydes or ketones via a catalytic aerobic oxidation process has been developed. The reaction was performed with the combination of catalytic amounts of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), 2,2,6,6-tetramethylpiperidine N-oxy (TEMPO), and *tert*-butyl nitrite (TBN), with molecular oxygen as terminal oxidant. A variety of PMB ether substrates derived from benzylic alcohols, heteroaromatic alcohols, and aliphatic alcohols, were converted to their corresponding carbonyl compounds in good conversions and selectivities.

Functional group interconversion is the process of the transformation of one functional group to another and is part of the basic toolkit of organic chemistry.[1] Aldehydes and ketones, two kinds of carbonyl compounds, are valuable intermediates for further elaboration into complex organic molecules. Normally, they are obtained from alcohols via conversion of hydroxyl groups to carbonyl groups.[2] As we know, hydroxyl groups are usually protected in advance during the multi-step syntheses.[3] There are many types of protecting groups for the hydroxyl, while ether groups are the most common ones owing to the high chemical stability of ethers under a wide variety of synthetic procedures and reaction conditions.[4,5] In many cases, the hydroxyl groups need to be further oxidized into carbonyl groups after removal of protecting groups, especially in the syntheses of those complicated natural products. Typically, a two-step process, sequential deprotection and selective oxidation of alcohols, is required to realize such a chemical transformation.[6] On these considerations, the direct transformation of ether groups to carbonyl groups is a potentially important and useful transformation in organic synthesis. Because of the stability of ethers, it is not easy to directly convert ethers to carbonyl compounds. Up to now, only a few reports showed the direct transformation of ethers to carbonyl compounds.[7] However, these reported methods have some drawbacks: (1) the oxidants were somewhat dangerous and expensive; (2) limited substrates could be used. Recently, a catalytic oxidation of ethers to carbonyl compounds using Mn complex as catalyst and *m*CPBA as oxidant has been reported.[8] The reagent system *m*CPBA/CCl_3CN/MeCN was also developed to the direct oxidation of ethers.[9] Very recently, Oxone/KBr system was successfully applied to oxidation of benzyl ethers.[10] It should be noted that oxidants *m*CPBA and Oxone were used in stoichiometric amounts, and ethers derived from primary alcohols were oxidized to carboxylic acid rather than aldehydes (Scheme 1). The direct transformation of ethers to corresponding aldehydes or ketones using molecular oxygen as the environmentally benign terminal oxidant has not been reported.*p*-Methoxybenzyl (PMB) ethers are one of the most widely used hydroxyl protecting groups due to their deprotection conditions being orthogonal to other protecting and functional groups, and due to their stability under acidic and/or basic reaction condition, feasibility of introduction.[5,11] We recently reported 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)/*tert*-butyl nitrite (TBN)/O_2 catalytic oxidation system to replace the stoichiometric amount of DDQ for the oxidative deprotection of benzyl-type ethers (including PMB, *p*-phenylbenzyl, and benzyl ethers), in which DDQ was employed as a catalyst, TBN as a co-catalyst, and molecular oxygen as the terminal oxidant.[12] In this transition metal-free

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http://dx.doi.org/10.1016/j.tetlet.2015.04.033
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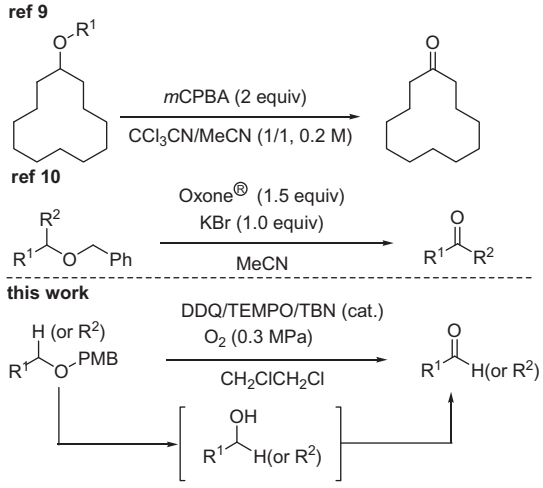

Scheme 1. Transformation of ethers into carbonyl compounds.

system, the key point is that TBN was served as the NO equivalent to activate molecular oxygen. Very recently, a similar oxidation system, DDQ/$NaNO_2$/O_2, was also applied to PMB ether deprotection.[13] In fact, the DDQ/TBN/O_2 catalytic oxidation system was expanded from our previous catalytic oxidation systems, such as 2,2,6,6-tetramethylpiperidin-*N*-oxyl (TEMPO)/TBN/O_2,[14] TEMPO/HBr/TBN/O_2,[15] TEMPO/1,3-dibromo-5,5-dimethylhydantoin/$NaNO_2$/O_2,[16] and TEMPO/Br_2/$NaNO_2$/O_2.[17] These oxidation systems have been successfully applied to selective oxidation of alcohols into corresponding carbonyl compounds with their unique advantages.

Based on our understandings of both oxidations, we envisioned that a three-component catalyst system, DDQ/TEMPO/TBN, can fulfill the direct transformation of PMB ethers into carbonyl compounds via aerobic deprotection/oxidation (Scheme 1). Herein, we reported our research results of this potential tandem reaction, that is, PMB ethers were deprotected into alcohols, which were sequentially oxidized into carbonyl compounds. Although deprotection of PMB ethers and aerobic oxidation of alcohols have been extensively studied,[11,18] to the best of our knowledge, this work is the first example of direct transformation of PMB ethers to aldehydes or ketones via deprotection/oxidation reaction catalyzed by DDQ/TEMPO/TBN with molecular oxygen as the oxidant.

To find a reliable and robust condition for the deprotection/oxidation of PMB ethers into carbonyl compounds, PMB ether of benzyl alcohol (**1a**) was selected as the model substrate. Our initial experiment of transformation **1a** to benzaldehyde was carried out with 10 mol % of DDQ, 5 mol % of TEMPO, and 10 mol % of TBN in 1,2-dichloroethane at 100 °C under 0.3 MPa of oxygen. It was found that **1a** was completely converted into benzaldehyde with a certain amount of benzoic acid due to over-oxidation. This preliminary result showed that DDQ/TEMPO/TBN/O_2 system for deprotection/oxidation of PMB ethers into carbonyl compounds designed in the Scheme 1 was feasible, and inspired us to further search the suitable reaction conditions. After optimization of oxygen pressure, reaction temperature, and the amounts of DDQ, TEMPO, and TBN, we finally concluded that 3 mol % of DDQ, 3 mol % of TEMPO, and 3 mol % of TBN at 100 °C under 0.3 MPa of oxygen in 2.5 h were suitable for the ideal transformation of **1a** to benzaldehyde.[18] Under such a condition, **1a** underwent a complete deprotection/oxidation to furnish benzaldehyde in excellent selectivity (high than 99%). Several solvents, such as ethylene glycol diethyl ether (EGDE), PhCl, toluene, $PhCF_3$, *t*-BuOH, 1,4-dioxane, and DMF were also examined, the conversions of **1a** were 100%, 45%, 29%, 18%, 27%, 6%, and 4%, respectively.[19] Although **1a** could be fully converted in EGDE, which was a good solvent for the DDQ/TBN-catalyzed aerobic oxidative deprotection of PMB ethers,[12a] the selectivity to benzaldehyde was only 76%, the intermediate benzyl alcohol could not be oxidized completely into benzaldehyde.

On the basis of these results, we then focused our studies on the application DDQ/TEMPO/TBN/O_2 system to a variety of PMB ethers. The results of PMB ethers derived from benzylic alcohols and their heteroaromatic analogs are summarized in Table 1. PMB ethers of methylbenzyl alcohol (**1b**–**1d**), 4-methoxybenzyl alcohol (**1e**), and 4-chlorobenzyl alcohol (**1f**) readily reacted, quantitatively afforded their corresponding benzaldehydes in 2.5–4 h (entries 1–6), and the isolated yields of **2b**–**2f** were all higher than 90%. The reaction of PMB ether of 3-chlorobenzyl alcohol (**1g**) required a longer reaction time, and 3-chlorobenzaldehyde (**2g**) could be obtained in 96% selectivity along with 4% of 3-chlorobenzyl alcohol in 6 h (entry 7). However, PMB ether **1h**, containing a 2-Cl on phenyl ring, needed an increased catalysts loading and extended reaction time. A full conversion of **1h** with 96% selectivity and 89% isolated yield of 2-chlorobenzaldehyde (**2h**) was achieved in 24 h by increasing the dosage of DDQ, TEMPO, and TBN to 12 mol % (entry 8). The slow rate of oxidation could be ascribed to the steric hinderance and electron-withdrawing properties. For PMB ether of 4-methylthiobenzyl alcohol (**1i**), this catalytic oxidation system could provide clean 4-methylthiobenzaldehyde (**2i**) without any observable oxidation of the methylthio group, and the isolated yield of 4-(methylthio)benzaldehyde (**2i**) was 91% (entry 9). When PMB ethers of heteroaromatic analogs (**1j** and **1k**) were submitted to the deprotection/oxidation reactions, the selectivities to furan-2-carbaldehyde (**2j**) and thiophene-2-carbaldehyde (**2k**) were also higher than 99% (entries 10 and 11). Then PMB ethers of secondary benzylic alcohols (**1l**–**1o**) were subject to the deprotection/oxidation, a longer reaction time or increased catalyst loading was needed, comparing with PMB ethers of primary benzylic alcohols (entries 12–15). When PMB ether of diphenylmethanol (**1p**) was used as the substrate, it could be converted to benzophenone (**2p**) in 93% isolated yield (entry 16).[20] A 90% selectivity of 2-chloro-5,6-dihydrocyclopenta[*b*]pyridin-7-one (**2q**), along with 10% of 2-chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-ol, could be obtained in the 10:20:20 molar ratio of DDQ/TEMPO/TBN (entry 17). 2-Chloro-6,7-dihydroquinolin-8(5*H*)-one (**2r**), a useful intermediate for organic synthesis, was achieved from PMB ether of 2-chloro-5,6,7,8-tetrahydroquinolin-8-ol (**1r**) in 90% isolated yield (entry 18).

With these results in hand, we tried the newly established DDQ/TEMPO/TBN/O_2 system for transformation of PMB ethers derived from aliphatic alcohols into their corresponding aldehydes or ketones. The representative results summarized in Table 2 demonstrate the effectiveness of this catalytic oxidation system for direct transformation of PMB ethers of aliphatic alcohols to aldehydes or ketones via deprotection/oxidation reaction. PMB ethers of primary aliphatic alcohols **3a** and **3b** could be smoothly converted into their corresponding aldehydes **4a** and **4b** in excellent selectivities (entries 1 and 2). PMB octan-2-yl ether (**3c**), a PMB ether derived from secondary aliphatic alcohol, was also successfully converted to the desired octan-2-one (**4c**) in 93% isolated yield (entry 3). When PMB ether of cyclohexanol (**3d**) was subjected to the deprotection/oxidation reaction, cyclohexanone (**4d**) was obtained in 95% selectivity, accompanying 5% of cyclohexanol (entry 4). The successful conversion of PMB ether of *N*-Boc-piperidin-4-yl-methanol (**3f**) to *N*-Boc-piperidine-4-carbaldehyde (**4f**) showed that this reaction could tolerate the Boc group (entry 6), and the isolated yield of **4f** was 87%. The tolerance of the DDQ/TEMPO/TBN/O_2 system toward other protecting groups was also explored. A series of hexane-1,6-diol derivatives were prepared and submitted to the deprotection/oxidation reactions (entries 7–