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Anodic Oxidation: An Attractive Alternative to CAN-Mediated Cleavage of *para*-Methoxyphenyl Ethers

Carine Vaxelaire,[a] Florence Souquet,[a] Marie-Isabelle Lannou,[a] Janick Ardisson,*[a] and Jacques Royer*[a]

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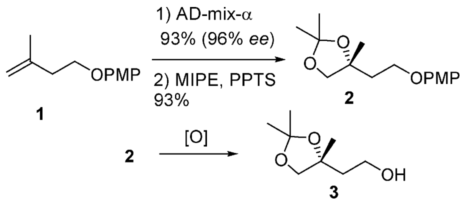
para-Methoxyphenyl (PMP) ether is a very convenient protecting group for the alcohol function; however, its cleavage requires strong oxidative conditions. In this field, the use of powerful ceric ammonium nitrate has been widely described, despite the fact that its strong nature results in the formation of degradation products in acid- or oxidation-sensitive substrates. In this paper, a new anodic oxidation method for the cleavage of *para*-methoxyphenyl ethers in weakly basic medium is reported. This process is an attractive alternative to circumvent the use of ceric ammonium nitrate.

Introduction

para-Methoxyphenyl (PMP) ether has emerged as a very interesting and useful protecting group for the alcohol function, as this ether is stable under strongly acidic or basic conditions and is specifically cleaved under oxidative conditions. Moreover, this ether possesses unique properties in inducing high stereoselectivities in enantioselective reactions. For instance, according to Corey et al.,[1] asymmetric dihydroxylation of homoallylic alcohols has been shown to provide enantiopure diols with good enantiomeric excesses (96 %*ee*) exclusively when the hydroxy group is protected as a PMP ether. When the PMP group was replaced by any other protecting group, for example, the *para*-methoxybenzoate group, a severe loss of enantioselectivity was observed. Thus, the PMP group is a powerful hydroxy protecting group; however, its synthetic usefulness relies on the availability of a general and efficient cleavage method. Although ceric ammonium nitrate (CAN) remains the most widely used reagent for this purpose,[2] in our case some difficulties were encountered.

In the course of our work, we have been interested in the preparation of alcohol **3** according to a procedure reported by Tietze (Scheme 1).[3] In our hands, the CAN cleavage step unfortunately failed to give alcohol **3** within the same yield as that reported (91 %). In fact, compound **3** was isolated in 20–80 % yield, the rest of the mass balance accounting mainly for degradation products.



Scheme 1. Procedure outlined by Tietze for the preparation of compound **3**.

Exploitation of the oxidizing properties of CAN for synthetic purposes remains limited due to a striking lack of selectivity in the cleavage of PMP ethers with regard to other hydroxy protecting groups. This drawback is particularly well evidenced in reactions involving acid-sensitive moieties, as the mechanism of CAN-induced removal of PMP ethers involves the liberation of hydronium ions in the reaction medium. This can be circumvented by the use of bases like pyridine or an aqueous solution of sodium hydrogen carbonate,[4] but even under these conditions, CAN still leads to partial decomposition of material. Finally, from an experimental point of view, purified compounds systematically reveal a red colour, which implies that trace amounts of cerium salts still remain.

However, despite the disadvantages mentioned above, to date only a few alternative methods have been reported and are anecdotally used, among these are: lithium in liquid

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[a] Laboratoire de Synthèse et Structure de Molécules d'Intérêt Pharmacologique UMR 8638-CNRS Université Paris Descartes
Faculté des Sciences Pharmaceutiques et Biologiques
4, av. de l'Observatoire, 75270 Paris cedex 06, France
Fax: +33-1-43291403
E-mail: janick.ardisson@parisdescartes.fr

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ethylamine,[5] silver oxide/nitric acid in dioxane[6] silver(II) dipicolinate–H_2O complex in a $MeCN/H_2O/MeOH$ mixture[7] and silver oxide/2,6-pyridine dicarboxylic acid in $MeCN/H_2O$.[8] Thus, in case of highly functionalized substrates and more particularly in the field of total synthesis, selective and efficient cleavage of PMP protecting groups has turned out to be of primary interest.

Electrochemical deprotection methods are scarcely reported[9] while generally providing mild conditions respective of many sensitive functional groups. In 2005, our group described the deprotection of *N-para*-methoxyphenylamines (N-PMP) by anodic oxidation.[10] To date, very few papers deal with the anodic cleavage of the carbon–oxygen bond in PMP ethers. The first example concerns diaryl ethers.[11] The reaction, conducted in methanol, provides bis(acetal)s. This method is directed by *p*-methoxy substitution.

The second example deals with the deprotection of *para*-methoxyphenyl pyranosides.[12] In this particular case, the removal of anomeric PMP groups was described without investigation of the scope of the reaction and, as such, cannot be extended to the standard regeneration of aliphatic alcohols. Noteworthy, experiments have only been carried out on analytical scale (0.006 to 0.139 mmol). Thus, the lack of preparative scale methods is obvious.

In this paper, a preparative anodic cleavage of primary and secondary alkyl *para*-methoxyphenyl ethers is reported.

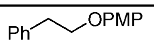
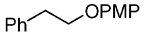
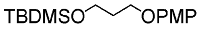
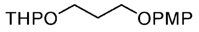
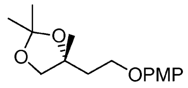
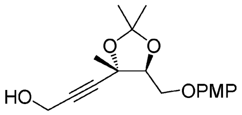
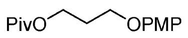
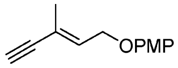
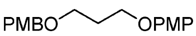
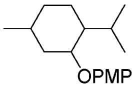
Results and Discussion

In order to establish a general method, the reaction was first carried out on PMP ether **4** derived from 2-phenylethanol. The results are presented in Table 1. All the experiments were conducted in a separated cell at a controlled potential (i.e, vs. saturated calomel electrode, SCE) at platinum electrodes. The very first assay was performed at a concentration of 1.5 mM in a 9:1 mixture of acetonitrile/water at room temperature, and the oxidation potential was fixed at a constant value of 1.55 V (Table 1, Entry 1).[13] Under these conditions, alcohol **5** was obtained with a satisfactory 77% yield within 1 h. It was then observed that the use of a saturated aqueous solution of sodium hydrogen carbonate instead of water had a beneficial effect, giving a cleaner reaction. In parallel, increasing the potential to 1.7 V resulted in an increased yield. Finally, it was found possible to work under more concentrated conditions (from 1.5 to 15 mM) without loss of yield, thus giving access to a preparative method. Finally, the combination of the three above-mentioned conditions led to excellent results (92% yield; Table 1, Entry 2) and was elected as a standard for the cleavage of a set of PMP ether compounds (Scheme 2).[14]

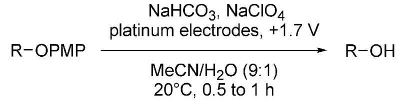
The course of the electrolysis can be monitored by TLC or by measurement of residual intensity (the reaction was stopped when the intensity reached less than 5% of its initial value).

In order to establish a comparison, most relevant substrates were submitted to both anodic oxidation (AO) and buffered CAN-mediated cleavage of PMP ethers.

Table 1. Oxidative cleavage of primary and secondary alkyl *para*-methoxyphenyl ethers.

Entry	R-OPMP		R-OH	Anodic oxidation yield [%][a,b]	CAN yield [%]
1		**4**	**5**	77[c]	nc
2		**4**	**5**	92	72
3		**6**	**7**	67	5
4		**8**	**9**	72	64
5		**2**	**3**	78	0–80
6		**10**	**11**	48	nc
7		**12**	**13**	79	54
8		**14**	**15**	66	30
9		**16**	**17**	65[d]	59
10		**18**	**19**	50	nc

[a] Reactions were conducted on 3.75 mmol at *C* = 15 mM. [b] Yields of isolated product. [c] Reaction was conducted at 1.55 V vs. SCE and at *C* = 1.5 mM. [d] Reaction conducted at *E* = 1.4 V.



$$\text{R−OPMP} \xrightarrow[\text{MeCN/H}_2\text{O (9:1)},\ 20^\circ\text{C, 0.5 to 1 h}]{\text{NaHCO}_3,\ \text{NaClO}_4,\ \text{platinum electrodes, +1.7 V}} \text{R−OH}$$

Scheme 2. General procedure for the oxidative cleavage of alkyl *para*-methoxyphenyl ethers.

Compared to AO, model compound **4** was easily deprotected by using CAN, despite a lower yield,[15] showing that CAN-mediated cleavage is more degradative (Table 1, Entry 1).

Various diols bearing both a PMP and an acid-sensitive protecting group (*tert*-butyldimethylsilyl **6**, tetrahydropyran **8** and dimethylacetonide **2**, **10**) evidenced selective PMP ether cleavage under buffered-anodic oxidation conditions (Table 1, Entries 3–6). Interestingly, the protocol for AO was successfully applied to ether **2** and target alcohol **3** was easily regenerated in high yield (Table 1, Entry 5). In contrast, the CAN-mediated cleavage of ethers **2** and **6** (Table 1, Entry 5 and 3, respectively) resulted in degradation products, whereas **8** (Table 1, Entry 4) was cleanly cleaved. Finally, anodic oxidation gave the best yield in the selective removal of the PMP group of **12** bearing a base-sensitive pivaloate function (Table 1, Entry 7).

Anodic oxidation using $NaHCO_3$ as buffer is suitable to the cleavage of PMP ethers in the presence of acid- and base-sensitive substrates. Consequently, a wide range of hydroxy protecting groups is compatible with buffered-anodic oxidation method.

The reaction was further checked on oxidation sensitive substrates. Enyne **14** was successfully converted into alcohol **15** (Table 1, Entry 8), and neither decomposition nor allylic oxidation was observed. In the same manner, the PMP group of substrate **16** was cleanly cleaved in the presence of a *para*-methoxybenzyl (PMB) group (Table 1, Entry 9). However, in this latter case, the potential was fixed at 1.4 V to avoid PMB group oxidation. At the opposite, under CAN-mediated cleavage conditions, enynol **15** was isolated in low yields from **14**, whereas PMP ether function of **16** was selectively cleaved in the presence of PMB ether.

Finally, cleavage of the secondary *para*-methoxyphenyl ether group of **18** was also carried out, leading to menthol (**19**; Table 1, Entry 10) in satisfactory, although unoptimized, yield.

As a conclusion, in all cases studied, anodic oxidation provided the required alcohols in better yields than buffered CAN-mediated reaction. These examples have efficiently demonstrated that the anodic oxidation reaction was highly selective, contrary to CAN-induced cleavage of PMP ethers, which has exhibited side reactions such as cleavage of acid-labile functions. Moreover, contrary to the CAN-mediated reaction, the AO process is highly reproducible.

The mechanism of the anodic oxidation is similar to the one assumed for CAN-mediated cleavage of *para*-methoxyphenyl ethers. In both cases, stepwise oxidation of the *para*-methoxyphenyl function led to the formation of quinone together with the expected aliphatic alcohol. It is worth specifying that the reaction was complete when a quantity of electricity of 2.2 F mol^{-1} was delivered into the reaction medium; thus the coulometric yield is close to the theoretical amount of electricity (2 F/mol).

Conclusions

In summary, we have demonstrated that primary and secondary alkyl *para*-methoxyphenyl ethers can easily be cleaved by anodic oxidation. The reaction is rapid (0.5 to 1 h) and constitutes an attractive, nondegradative alternative to CAN-mediated cleavage, which provides desired alcohols in a cleaner manner and with more reproducible yields. Moreover, this is also an original orthogonal process for the selective deprotection of *para*-methoxyphenyl protecting groups, as a wide range of acid-, base- and even oxidation-sensitive functions are tolerated. Finally, this method can be easily carried out by using basic electrochemical equipment and on preparative scale.

Supporting Information (see footnote on the first page of this article): Detailed procedures and characterization data for ethers and alcohols illustrated in Table 1.

Acknowledgments

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[13] Voltammogram of the substrate revealed an oxidation wave around 1.4 V.

[14] The anodic oxidation of compound **4** was also done under constant current conditions (120 mA) and alcohol **5** was obtained with a good yield of 70%. The elaboration of a general method is currently under investigation in our laboratory.

[15] Two batches of commercial CAN were used for testing. Slight differences in yields were observed, depending on the batch used.

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