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Efficient *N*-*p*-Methoxyphenyl Amine Deprotection through Anodic Oxidation

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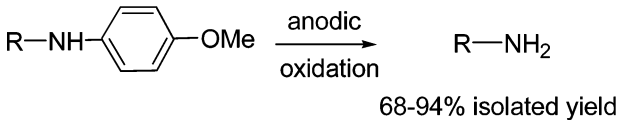
Received September 6, 2005

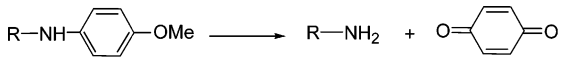


A new method of deprotection of *N*-*p*-methoxyphenylamines using anodic oxidation in acidic medium is presented. The process furnishes a high yield of amine and is compatible with several oxidable functional groups.

In recent years, *p*-anisidine has emerged as a very attractive reagent in several synthetic processes and particularly in the development of new powerful asymmetric strategies. Its enhanced nucleophilicity and its effectiveness to form imines with carbonyl compounds render this reagent quite useful and versatile.[1] It was also proven that the addition of several nucleophiles to the imines under the control of asymmetric catalysts gave better stereoselectivity and yields compared to imines derived from other anilines or alkylamines.[2] This was recently applied to the asymmetric version of some very well-known reactions such as the Mannich reaction. For example, the asymmetric Mannich reaction with *p*-anisidine and using L-proline as catalyst was reported with ee's as high as 99%. Asymmetric synthesis of amino acids, β-lactams, and saturated N-heterocycles was also described via this strategy.[3]

Eventually the possibility to cleave the *p*-methoxyphenyl (PMP) group through oxidative process constitutes a further advantage contributing to the usefulness of *p*-anisidine. It thus constitutes a very good source of nitrogen if a clean and efficient deprotection method of the PMP group is available. The deprotection of the PMP group is crucial in many cases, and it is then quite important to have at hand an efficient, selective, and high-yielding deprotecting method. This is particularly important in the synthesis of enantiomerically pure amino acids.

SCHEME 1. Cleavage of the *N*-PMP Bond



1 2

The cleavage of the *N*-PMP bond is classically obtained by oxidation which occurs with formation of quinone and the corresponding amine (Scheme 1).

For this transformation, the most widely used reagent is cerium ammonium nitrate (CAN),[4] whereas few publications reported the use of other reagents such as hypervalent iodine.[2b,3b] In most cases, CAN gives the expected primary amines in good yield. Nevertheless, there have been some reports in the literature proving that, in some instances, CAN was poorly effective in removing the PMP group.[5] Modest yields (25−50%) have been reported, and modified procedures have been proposed. Tomioka, for example, suggested to first acetylate the NH-PMP group before cleavage or to perform a one-pot NH-PMP deprotection and N-acetylation to improve the yield of the oxidative reaction.[6] Additionally, it can be expected that some sensitive functions are not compatible with this very powerful oxidative reagent;[7] thus, polyfunctionalized compounds require more selective oxidation processes. Furthermore, massive quantities of CAN are needed due to high molecular weight and the use of several molecular equivalents of reagent.

We were also confronted with difficulties in the deprotection of *p*-methoxyphenyl with CAN. In the course of the optimization of the CAN oxidation, we decided to try

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10.1021/jo051867o CCC: $30.25
Published on Web 10/29/2005

to reproduce the deprotection of *N*-*p*-methoxyphenyl *N*-methylbenzylamine (**1a**) described in the literature with 81% yield:[8] in our hands, under the same reaction conditions, we could not detect the formation of **2a**. However, a tedious optimization of the reaction conditions by varying temperature, reagent equivalents, solvent, and acidic medium allowed us to attain an acceptable but hardly reproducible 70% yield.

According to these observations, we developed an alternative method based on anodic oxidation to achieve this goal. This method exhibits several advantages since electrochemical approaches permit us to adjust the oxidative potential to the exact value required for the deprotection and therefore are respectful of other oxidable functional groups.

To the best of our knowledge, no data are available in the literature concerning the electrochemical deprotection of *N*-PMP amines.[9]

Herein we report the first successful *N*-*p*-methoxyphenyl cleavage of amines (mainly secondary amines) using anodic oxidation and show that it represents an interesting alternative to oxidative reagents since high-yielding deprotection was observed in all cases we examined even in the presence of sensitive functional groups present on the structure.

Anodic α-oxidation of amines and particularly *N*-arylamines has been broadly described in the literature.[10] This latter reaction has to be circumvented to avoid possible side reactions. Furthermore, it is noteworthy that *N*-*p*-methoxyphenyl oxidative cleavage leads to primary amine **2**, which is at least as easily oxidable as the starting material **1**. This constitutes, a priori, a serious drawback. Nevertheless, we thought that we could take advantage of the difference in basicity between secondary *N*-*p*-methoxyphenylamine **1** and primary amine **2** resulting from the desired cleavage reaction. *N*-*p*-Methoxyphenylamines **1**, which are substituted anilines, are less basic than corresponding alkylamines formed during the reaction. The latter are therefore selectively protonated by addition of at least 1 equiv of acid and consequently protected against further oxidation by protonation.

After some trials, the anodic oxidation of several *N*-*p*-methoxyphenylamines **1** (Table 1) was found to be quite efficient, leading to the primary amines **2** in high yields. The reaction was conducted at a controlled potential (i.e., 0.85 V versus saturated calomel electrode, SCE) at a platinum electrode in CH_3CN/H_2O 9:1 mixture and in the presence of 2 equiv of $HClO_4$ to give a clean deprotection of the *p*-methoxyphenyl group in all examples shown in Table 1. The given yields are those of isolated products, while HPLC analysis of the crude reaction mixture showed the complete disappearance of the starting material and the formation of only two new products: the quinone and the expected amine **2**, which was easy to separate from the quinone by simple acid/base extraction and to isolate. The regioselectivity of this oxidation is complete since no product resulting from oxidation at the α-position of nitrogen was detected. We also compared our results with deprotection with CAN: the yields were generally found to be lower with this chemical reagent and are those obtained after optimization (Table 1).

Several functional groups are compatible with the electrochemical process: olefin (**1b**), ester (**1e**,**f**), ketone (**1e**), and phenol (**1f**) are not affected. The method is respectful of chiral centers if present: the anodic oxidation of **1e** led to the corresponding primary amine **2e** isolated in a good 87% yield without loss of enantiomeric purity.

The *N*-*p*-methoxyphenyl cleavage was also found to be efficient in the case of tertiary amines: *N*-methyl methylbenzylamine **2d** was obtained from its *N*-*p*-methoxyphenyl parent **1d** in 76% isolated yield.

As shown in entry 7, the 2,4-dimethoxyphenyl group of compound **1g** is also easily removed by this procedure. In our hands, CAN was found totally ineffective in this case.

Deprotection of the phenylglycine derivative **1f** was performed in an excellent 94% yield by the electrochemical process without oxidation of the phenol group and in sharp contrast with the CAN method that gave a low conversion (entry 6).

To emphasize the interest of controlled oxidation potentials, we investigated the behavior of 1,3-dithiane and *p*-methoxybenzyl groups in anodic oxidative conditions. A mixture of **1a** and a thioketal **3** was electrolyzed at 0.85 V versus SCE (Scheme 2). The latter was recovered unchanged, while a clean deprotection of *p*-methoxyphenyl was observed. This result is noteworthy since thioketals are classically cleaved by CAN or under anodic oxidation using upper potential values.[11] A complete disappearance of the thioketal compound **3** was noticed in the presence of the strong oxidant CAN.

Since no oxidation α to nitrogen was observed even at benzylic position (entries 1, 4, and 7), we anticipated that *N*-*p*-methoxybenzyl groups (-*N*-PMB) should be resistant to the anodic oxidation conditions we used. Indeed, under these conditions, amine **1h** was recovered totally unchanged, whereas this classical protecting group was cleaved using CAN oxidation.[12] To demonstrate that this selectivity could be quite useful to perform orthogonal deprotection, we studied the selective electrochemical *N*-PMP deprotection of two compounds, **1i** and **1j**, bearing both the PMP and the PMB groups. As shown in Table 1 (entries 10 and 11), the PMP groups of secondary amine **1i** and amide **1j** were easily cleaved via that anodic oxidation without altering the PMB group.

In summary, we have shown in a series of various examples that anodic oxidation realized at fixed potential constitutes an alternative method to the CAN procedure for removal of *N*-*p*-methoxyphenyl group. The method is

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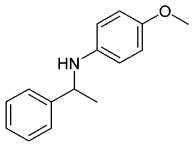
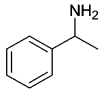
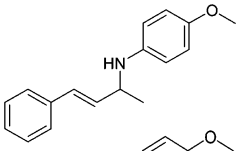
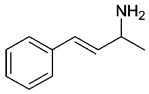
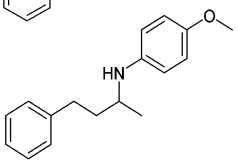
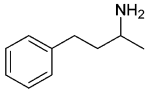
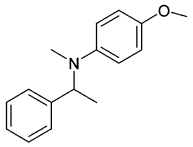
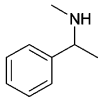
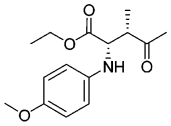
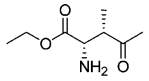
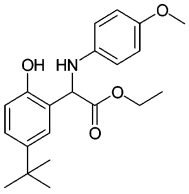
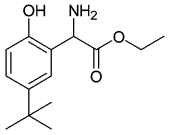
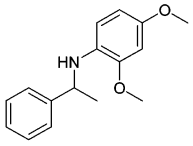
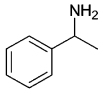
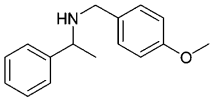
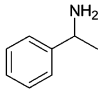
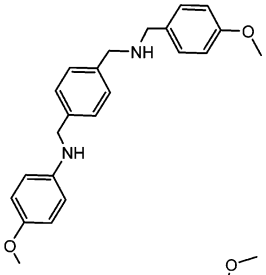
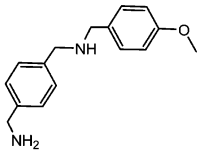
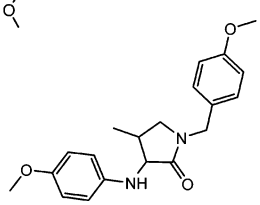
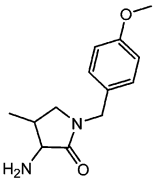
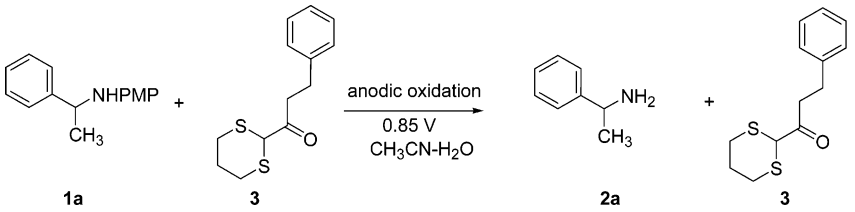
TABLE 1. Deprotection of the PMP Group by Anodic and CAN Oxidation

Entry	*N*-PMP amine		Deprotected amine		standard Anodic oxidation[a] yield (%)[c]	optimized CAN oxidation[b] yield (%)[c]
1	**1a**		**2a**		89	70
2	**1b**		**2b**		90	67
3	**1c**		**2c**		83	70
4	**1d**		**2d**		76	65
5	**1e**		**2e**		87	85
6	**1f**		**2f**		94	26
7	**1g**		**2a**		76	0
8	**1h**		**2a**		0	-[d]
10	**1i**		**2i**		72	-
11	**1j**		**2j**		68	-

[a] At 0.85 V in the presence of 2 equiv of $HClO_4$ (see General Anodic Oxidation Method). [b] Optimized conditions with CAN at controlled temperature (°C). [c] Isolated yields. [d] 100% conversion, cleavage products (anisaldehyde) as well as imine were found to be formed.

SCHEME 2. Selective Deprotection of the PMP Group in the Presence of the 1,3-Dithiane



highly selective, allowing the presence of several sensitive functional groups. The experimental procedure is very simple, and a clean reaction allows the isolation of deprotected amines in high yield.

Furthermore, this method is applicable to large amounts of material with cheap and environmentally friendly reagents and conditions. It is noticeable that this process is very easy to perform with basic electrochemical equipment.

Experimental Section

General Anodic Oxidation Method. Protected amine **1** (0.5 mmol) was dissolved in a mixture of CH_3CN (90 mL) and water (10 mL) that contained $NaClO_4$ (5 mmol) and $HClO_4$ (1 mmol). The electrolysis was conducted at 0 °C, under nitrogen, in a divided glass cell equipped with two platinum electrodes. The potential was maintained at a constant value of 0.85 V. The electrolysis was stopped when the current was lowered to residual value (about 1−5 mA compared to an initial value of 40−50 mA) classically after 2 or 3 h. Most of the organic solvent was then evaporated under vacuum, and a 0.1 N HCl solution (50 mL) was added before the solution to be extracted with diethyl ether to remove the quinone. The aqueous mixture was made alkaline (0.1 N NaOH) and then extracted with diethyl ether. The ethereal solution was dried (Na_2SO_4), and the solvent was removed in vacuo to furnish amine **2**.

Supporting Information Available: Preparation of starting materials and copies of ^1H and ^{13}C NMR spectra of unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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