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A Mild Method for Electrochemical Reduction of Heterocyclic *N*-Oxides.

Yasuaki Fukazawa,^[a] Aleksandr E. Rubtsov,^[b] and Andrei V. Malkov*^[a]

 [a] Prof. A. M. Malkov, Y. Fukazawa Department of Chemistry, School of Science, Loughborough University, Loughborough, Leicestershire, LE11 3TU, UK Department Loughborough, Leicestershire, LE11 3TU, UK E-mail: <u>a.malkov@lboro.ac.uk</u>; URL: <u>https://www.lboro.ac.uk/departments/chemistry/staff/academic-research/andrei-malkov/</u>
 [b] Dr A. E. Rubtsov, Department of Chemistry

Perm State University Bukireva 15, Perm 614990, Russia

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Abstract: Deoxygenation of heteroaromatic *N*-oxides is commonly accomplished using chemical or enzymatic methods. In this work, we report on an expedient protocol for electrochemical reduction of pyridine *N*-oxide derivatives under mild conditions. A diverse range of mono- and bis-*N*-oxides were converted into the corresponding nitrogen bases in good yields. Importantly, the method is highly selective towards *N*-oxides and tolerates challenging halo and nitro substituents in the heteroaromatic ring.

In the chemistry of pyridines and related heterocyclic compounds, N-oxides occupy an important niche. First, they represent a separate class of compounds with distinct biological activity;^[1] and secondly, N-oxidation dramatically alters reactivity of the parent base by activating the heteroaromatic ring towards both nucleophilic and electrophilic reagents.^[2] Depending on the transformation, the oxygen is either removed during the process or remain in the molecule. For the removal of oxygen without further functionalization plethora of methods have been developed over the years.^[3] The most recent protocols include photocatalytic reduction of N-oxides,[4] catalytic hydrogenation using water as a source of hydrogen,[5] metal-catalyzed,[6] and metal-free^[7] oxygen transfer methods. Despite the great number of chemical and biochemical methods for deoxygenation of aromatic N-oxides, there is still room for protocols that are operationally simple, atom-economical, easily scalable and applicable to a wide range of substrates. Our attention turned towards electrochemical methods. A few examples of electrochemical reduction of pyridine N-oxides at the dropping mercury electrodes were published nearly three decades ago^[8] but they were of limited scope and practicality. While our work was in progress, an electrochemical reduction of heteroaromatic Noxides was reported by Xu,^[9] though in their protocol, halosubstituted hetarenes were not tolerated. Herein, we present a mild method for the reduction of N-oxides with a wide scope, including challenging derivatives with halo and nitro substituents present in the heterocyclic ring.

Earlier, while developing an electrochemical coupling of deprotonated chiral pyridine *N*-oxide derivatives, we optimized the reaction conditions to retain the *N*-oxide functionality in the resulting bis-*N*-oxides by suppressing possible electrochemical reduction of the N-O functionality.^[10] In contrast, this work is

focused on developing the deoxygenation process to reveal free bases.

For optimization of the reaction conditions, 2-phenylpyridine Noxide 1a was chosen as a model substrate (Table 1). The most efficient protocol was identified as follows: the reaction was carried out in an undivided electrochemical cell with two carbon electrodes at a constant current of 10 mA at rt in a 1:1 acetonitrile/water mixture using LiBF₄ (0.04 M) as a supporting electrolyte. The reaction was complete in just under 4 h to furnish the reduced pyridine 2a in an 89% isolated yield. Earlier,^[10] we observed that the addition of Ph₃PO to the electrochemical cell seemed to suppress the reduction of N-oxide. Indeed, this has been now confirmed by running the model reaction under the standard conditions in the presence of 1.5 equiv of Ph₃PO. The yield dropped to just 28% (Table 1, entry 2). The reduction also proceeded sluggishly in dry acetonitrile (Table 1, entry 3), however, the yield gradually improved with the addition of triethanolamine (TEOA), which may serve as both a sacrificial reducing agent, by providing a paired oxidation reaction on anode, and also a proton source (Table 1, entries 4-6).[11]

The influence of pH on the reaction efficiency was investigated using buffer solutions, however no much difference was observed between acidic (pH 4), neutral (pH 7) and basic (pH 10) media (Table 1, entries 7-9). Variation of the anode material was assessed briefly. Sacrificial Zn electrode furnished the result similar to carbon (Table 1, entry 10), whereas with Fe anode the reaction slowed down and with Cu it hardly proceeded at all (Table 1, entries 11 and 12, respectively). An investigation into the role of the electrolyte revealed that guaternary ammonium salts with an inert anion, like bisulfate, can also be used in the reaction, however salts with a halide as a counterion, particularly iodide, inhibited reduction (entry 14). The reaction can be scaled up with little or no effect of the yield either by increasing the substrate concentration from 0.022 M to 0.18 M (entry 15) or by using a larger reaction vessel and keeping the same proportions of the reaction components (entry 16).

Having established the optimal conditions, we next embarked on an investigation into the reaction scope (Table 2). Alkyl and aryl (**1b**, **1c**, **1n**), as well as heteroaromatic substituents (**1p**, **1q**) around the pyridine ring are tolerated well. Fused heterocycles, isoquinoline (**1i**) and quinoline (**1j**) derivatives, as well as aliphatic *N*-oxide **1o** followed the trend. On the other hand, pyridine *N*-

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Ph

Ph

 NO_2

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oxides with donor (OMe, 1e) or acceptor (CN, 1f) groups showed slightly reduced reactivity. Importantly, the developed electrochemical conditions are compatible with N-oxides having halides (1g, 1h, 1k) or nitro group (1l) in the heterocyclic ring, resulting in a clean reduction of the N-O bond without affecting the substituents. Quinoline N-oxide 1m with free hydroxyl also proved to be a competent substrate.

Table 1. Optimization of reductive deoxygenation of pyridine N-oxide 1a^[a]



to axially chiral bipyridines via bis-N-oxides are more advantageous compared to other approaches in terms of stepeconomy and stereoselectivity, therefore the reduction of the N-O bond is an integral part of such methods. Table 3 illustrates the application of the electrochemical methods to the deoxygenation of bipyridine-N,N'-dioxides. Formation of bipyridines 2p-2s proceeded uneventfully under the standard conditions. Both N-O bonds are reduced simultaneously.[8a] It is worth noting that the

deoxygenation of axially chiral 1t furnished the respective

[a] Standard conditions: the reaction was carried out at a 0.15 mmol scale (22 mM solution of 1a) at rt for 4 h (constant current 10 mA, current density 1.5 mA/cm², immersed electrode surface area 6.5 cm²), unless stated otherwise. The yield is shown for isolated, chromatographically pure material.

Deoxygenation of bipyridine-N,N'-dioxides is of a particular interest for the synthesis of chiral bipyridines that find application as ligands in asymmetric catalysis.^[10, 12] In some instances, routes [a] Standard conditions: see footnote to Table 1

Electrochemical behaviour of pyridine N-oxides 1a, 1g, 1h and 1t' was briefly investigated by cyclic voltammetry (see Supporting Information for details). Compounds 1g and 1h showed two distinct irreversible reduction peaks, whereas only one clear peak

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was visible in the reduction of **1a** and **1t**'; the results generally agree with the published data for related compounds.^[8a, 13]

Table 3. Electrochemical reduction of bipyridine N,N-dioxides



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[a] Standard conditions: see footnote to Table 1

In summary, we have developed a convenient electrochemical method for the reduction of N–O bond in aromatic *N*-oxides. The method tolerates the presence in the aromatic ring of such challenging functional groups as nitro and halides. In the case of bipyridine derivatives, both oxidized nitrogens are deoxygenated simultaneously. Combined with an efficient synthesis of bipyridine *N*-oxides reported by us previously,¹⁰ this method can provide a facile access to axially chiral bipyridines.

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Keywords: nitrogen heterocycles • reduction• electrochemistry • N ligands • synthetic method

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Electrochemical reduction

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