Electrochemical Oxidation

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Electrochemical Aerobic Oxidation of Aminocyclopropanes to Endoperoxides**

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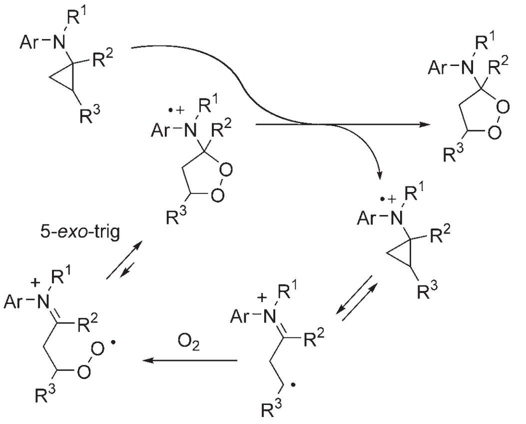
Dedicated to Professor William B. Motherwell on the occasion of his 60th birthday

The oxidation of cyclopropanes to 1,2-dioxolanes has been documented for almost 40 years and has been performed on many substrates under various conditions.[1–3] Among these, very few examples involve aminocyclopropanes. The transformation of secondary cyclopropylamines into α-amino endoperoxides by autocatalytic aerobic oxidation was reported by Wimalasena et al. a few years ago.[4] It was found that a catalytic amount of tris(1,10-phenantroline)iron(III) hexafluorophosphate, or hydrogen-abstracting agents such as benzoyl peroxide or *tert*-butyl peroxide under UV irradiation, could increase the reaction rate. A similar transformation was observed in our laboratory, spontaneously occurring in the presence of air and silica gel from electron-rich tertiary arylcyclopropylamines.[5] In this case, as well as in the iron-catalyzed process, the mechanism probably involves a one-electron oxidation of the substrate to a cation radical intermediate. After cyclopropane ring opening, reaction with oxygen, and ring closure, the newly produced cation radical would be able to function as an oxidant itself and thus close the catalytic cycle (Scheme 1).[4,5]

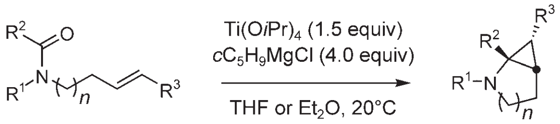
Although interesting, this reaction suffers from serious limitations: a) the transformation appears to be facile only in the special cases where the nitrogen atom bears a hydrogen atom or an electron-rich aromatic ring; b) the use of peroxides under UV irradiation is by nature limited to secondary amines because it involves hydrogen abstraction from the nitrogen atom; c) the iron(III) catalyst mentioned above is not commercially available; and d) occasionally experiencing problems in isolating the expected peroxides, we were led to suspect that some of them might be unstable.[6] We anticipated that electrochemical methods such as cyclic voltammetry and preparative electrolyses would be tools of choice to gain better insight in this reaction and could lead to the design of a more general and environmentally friendly experimental procedure.[7]



Scheme 1. Autocatalytic aerobic oxidation of aminocyclopropanes to α-amino endoperoxides.

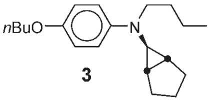
For the purpose of this study, aminocyclopropanes **1a–e**, **2a**,**b**, **3**, and **4** were prepared by using intra- or intermolecular Kulinkovich–de Meijere reactions,[8] following a modification

Table 1: Synthesis of aminocyclopropanes **1a–e**, **2a**,**b**, and **3** through intramolecular Kulinkovich–de Meijere reactions.[a]



R^1	R^2	R^3	*n*	**1**	Yield [%]
4-nBuOC$_6$H$_4$	H	H	1	**1a**[b]	42
4-nBuOC$_6$H$_4$	Me	H	1	**1b**	100
4-nBuOC$_6$H$_4$	Me	H	2	**1c**	44
Ph	Me	H	1	**1d**	90
Bn	Me	H	1	**1e**	75
Ph	Me	$(CH_2)_2$OTBS	1	**2a**	38
Ph	Me	$(CH_2)_2$OBn	1	**2b**	53

[a] Bn = benzyl, TBS = *tert*-butyldimethylsilyl. [b] By-product **3** isolated in 32% yield as the same time as compound **1a**.



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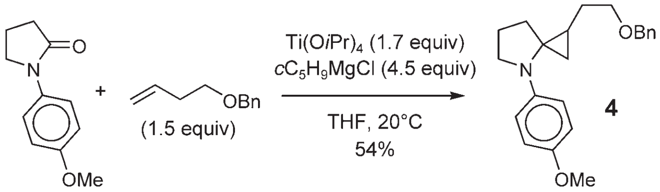
of the procedure reported by Cha and Lee[9] (Table 1, Scheme 2).



Scheme 2. Synthesis of aminocyclopropane **4** through an intermolecular Kulinkovich–de Meijere reaction.

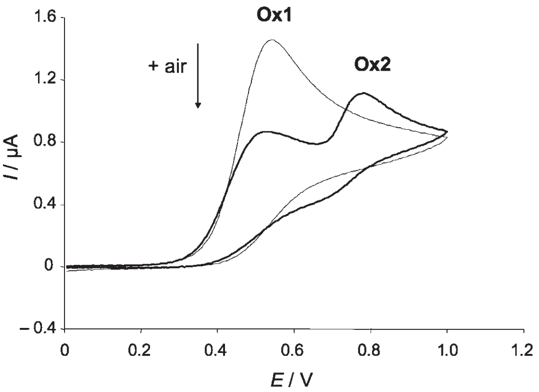


Figure 1. Cyclic voltammograms of **1b** (2.1 mM) in MeCN with TBABF$_4$ (0.1 M) recorded at a platinum electrode (0.5 mm diameter) at 0.2 V s^{-1} in the absence (Ox2) and in the presence of air (Ox1).

The study of their electrochemical behaviour was carried out by cyclic voltammetry, and a typical voltammogram is presented in Figure 1. Under argon, the aminocyclopropanes are oxidized in a single irreversible wave Ox$_1$ located between +0.5 and +1.1 V (versus the saturated calomel electrode (SCE)) depending on their chemical structures (Table 2). As expected, the presence of an electron-donating group either at the *para* position of the aromatic ring or on the cyclopropane moiety renders the oxidation process easier (compare **1b** vs **1d** and **1d** vs **2a**,**b**), while the *N*-benzyl derivative **1e** is more difficult to oxidize. In all cases, the process generates the corresponding aminium cation radicals, which are unstable at low scan rates in agreement with the irreversibility of Ox$_1$. In some cases (e.g. **1a** and **3**), however, the reduction of these intermediates can be observed if the potential range is swept sufficiently rapidly ($v > 20$ V s^{-1}), and the cyclic voltammograms become reversible.

Table 2: Oxidation wave peak potentials of cyclopropylamines **1a**–**e**, **2a**,**b**, **3**, and **4**.

Cyclopropylamine	E(Ox$_1$) [V][a]	E(Ox$_2$) [V][a]	E(Ox$_3$) [V][a]
1a	+0.54[b]	+0.88[b]	–
1b	+0.54	+0.78	–
1c	+0.52	+0.89	–
1d	+0.79	+1.17	–
1e	+1.10[b]	–	–
2a	+0.67	+1.08	+0.82
2b	+0.70	+1.10	+0.84
3	+0.55	+0.80	–
3	+0.63[b]	+0.84[b]	–
4	+0.50	+0.82	–

[a] Oxidation potential versus SCE, measured by cyclic voltammetry at 0.2 V s^{-1} in MeCN as the solvent unless otherwise stated. [b] Measured in *N*,*N*-dimethylformamide.

When the experiments are carried out under aerobic conditions, two main changes are observed in the voltammograms: 1) the intensity of Ox$_1$ decreases, and 2) a new oxidation wave Ox$_2$ appears at a higher potential value on the same timescale. The first point is characteristic of an electron catalytic process in which the starting compound is oxidized by an intermediate species but not by the electrode itself,[10] which supports the mechanism displayed in Scheme 1. The second point clearly indicates the formation of a new compound that can be assigned to the corresponding endoperoxide as verified with an authentic sample (see below). In the cases of **2a** and **2b**, a third oxidation wave Ox$_3$ appears to emerge between Ox$_1$ and Ox$_2$, probably owing to the presence of the OTBS and OBn groups. A structure–reactivity relationship is observed for the endoperoxides: although aminocyclopropanes **1b** and **1c** are oxidized at similar potential values, it is not the case for the corresponding peroxides **5b** and **5c**, the latter of which features a six-membered ring that is oxidized at a higher potential (0.89 vs 0.78 V). In the special case of **1d**, the wave Ox$_2$ is only observed on the timescale of a preparative electrolysis (see below), indicating a very slow formation of the endoperoxide product. Importantly, the higher potential of Ox$_2$ as compared to Ox$_1$ in all cases fully supports the hypothesis of an autocatalytic cycle where the cation radical of the product can oxidize the cyclopropylamine starting material (Scheme 1).

The results obtained on the cyclic voltammetry timescale led us to attempt the electrosynthesis of the endoperoxides. Preparative-scale electrolyses were carried out in a divided cell at constant potential values corresponding roughly to the peak potential of Ox$_1$. The aminium cation radicals could thus be generated cleanly and selectively to react with oxygen which was introduced by bubbling air through the anodic compartment. The electrolyses were followed by in situ cyclic voltammetry to ascertain the consumption of the aminocyclopropane along with the formation of the product, and to verify its stability on this timescale. Figure 2 shows typical voltammograms obtained before and after the experiment. Interestingly, a very ill-defined wave Ox$_2$ was observed in the cyclic voltammogram recorded before running the electrolysis. Under these conditions, the amount of dissolved oxygen is small compared to the amount of aminocyclopropane initially introduced in the cell. However, and as expected, the intensity ratio I(Ox$_2$)/I(Ox$_1$) increased as the electrolysis proceeded.

The experiments were stopped after the quasi-total consumption of the aminocyclopropanes. In all cases (**1b**–**d**, **2a**, **3**, and **4**), the last voltammograms showed the formation of the corresponding endoperoxides (wave Ox$_2$) and demonstrated their relative stability on the timescale of the reactions (about 1 h depending on the amount of starting material and

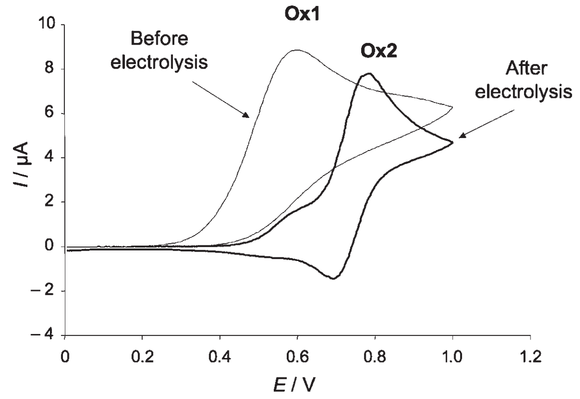
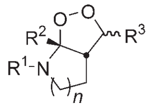
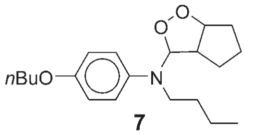


Figure 2. Cyclic voltammograms of **1b** (17.2 mM) in MeCN with TBABF$_4$ (0.1 M) recorded at a platinum electrode (0.5 mm diameter) at 0.2 V s^{-1}, under aerobic conditions, before (Ox1) and after the preparative electrolysis (Ox2).

the potential applied). Interestingly, in some cases Ox$_2$ is reversible, indicating the stability of the cation radicals obtained by oxidation of the endoperoxides.



5b: R^1 = 4-nBuOC$_6$H$_4$; R^2 = Me; R^3 = H; n = 1
5c: R^1 = 4-nBuOC$_6$H$_4$; R^2 = Me; R^3 = H; n = 2
5d: R^1 = Ph; R^2 = Me; R^3 = H; n = 1
6a: R^1 = Ph; R^2 = Me; R^3 = (CH$_2$)$_2$OTBS; n = 1



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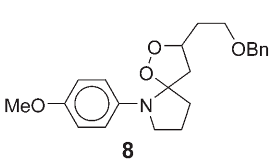

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After workup, the endoperoxide **5c** prepared from **1c** decomposed too rapidly to be analysed by NMR spectroscopy. The five-membered ring analogue **5b** (from **1b**) proved to be somewhat more stable, and ^{1}H and ^{13}C NMR spectra could be obtained. This compound had nevertheless totally decomposed the next day. Similar observations were made with **5d**, although its formation was slower compared to the other products, in agreement with the absence of Ox$_2$ on the timescale of the cyclic voltammetry performed on **1d**. This highlights the influence of an alkoxy group at the *para* position of the aromatic ring on the reactivity of the intermediates involved in the chemical reactions following the electron transfer. Endoperoxide **7** was easily obtained from **3** but decomposed slowly, while **8** (from **4**) was too unstable to be analysed even just after its preparation. Finally, **6a** (from **2a**) was the only truly stable endoperoxide obtained, showing that the additional substitution on the dioxolane ring plays a major role in its stabilization.[11] Another effect of the higher degree of substitution of the cyclopropane ring in **2a** is a faster conversion into the peroxide **6a** as compared to the reaction of **1d**. This can be rationalized by invoking the equilibrium between the cyclopropyl aminyl cation radical and the ring-opened iminium radical shown in Scheme 1, with the latter species being stabilized when the carbon-centered radical is secondary rather than primary. Besides this, the complete regioselectivity of the cyclopropane ring-opening of **1** and **2**, leading exclusively to [3.3.0] rather than [3.2.1] systems, is noteworthy. This can be accounted for by the geometrical alignment of the bond being broken with the orbital of the aminyl cation radical.

Finally, the analogy of the stable endoperoxide **6a** with some antimalarial drugs led us to examine its antiplasmodial activity.[12] Indeed, the endoperoxide moiety of antimalarial trioxanes such as artemisinin has been shown to be directly involved in the mechanism leading to the destruction of the parasite.[13] The two diastereoisomers of **6a** were thus separated by preparative HPLC, and their in vitro antimalarial activities were evaluated against the chloroquine-resistant FcB1 strain of *Plasmodium falciparum*. Both diastereoisomers exhibited moderate but interesting antiplasmodial activities, with $IC_{50} = 13\ \mu M$ for the *cis* diastereoisomer and $IC_{50} = 4.4\ \mu M$ for the *trans* diastereoisomer.[14,15]

In summary, cyclic voltammetry performed on bicyclic aminocyclopropanes **1a**–**e**, **2a**,**b**, **3**, and **4** provides new insight on the influence of the substitution pattern of these compounds on their aerobic oxidation, and is fully consistent with the currently accepted autocatalytic mechanism. A simple, environmentally friendly, and efficient procedure for the electrosynthesis of the corresponding endoperoxides was also developed. The instability of some of these molecules was confirmed, and conditions were found for the preparation of stable compounds. We believe that these findings could open the route to the design of similar oxidation methods starting from a broader range of cyclopropane derivatives. Moreover, reaction partners other than molecular oxygen could be envisaged, which will be the subject of our future work in this area, as well as the quest for new antimalarial compounds.

Experimental Section

Typically, the procedure for preparative electrolysis was as follows: Aminocyclopropane **2a** (65.4 mg; 197 μmol) was introduced in the anodic compartment of a divided cell containing the solvent MeCN (22 mL) and the supporting electrolyte TBABF$_4$ (0.1 mol L^{-1}). A potential value of +0.60 V/SCE was then applied between the reference and the working electrodes while bubbling air into the cell. After 1.5 h, the crude solution contained in the anodic compartment was concentrated under vacuum, extracted with diethyl ether, filtered, and concentrated under reduced pressure to afford an orange oil, which was analysed by NMR spectroscopy. Purification by flash column chromatography on silica gel (ethyl acetate/heptane 10%) led to a 50:50 mixture of the two possible diastereoisomers of pure compound **6a** (33.0 mg, 90.7 μmol, 46%) as a yellow oil.

For further experimental details, see the Supporting Information.

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[14] Chloroquine: $IC_{50} = 0.11\ \mu\text{M}$; $IC_{90} = 0.21\ \mu\text{M}$.

[15] The *cis* and *trans* diastereoisomers are defined according to the relative configurations of the amine and the 2-(*tert*-butyldimethylsilyloxy)ethyl substituents of the dioxolane ring.