Electrochemical oxidative methoxylation of 4*H*-imidazole 1,3-dioxides to give α-methoxy substituted nitroxyl radicals

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Electrochemical methoxylation of substituted 4*H*-imidazole 1,3-dioxides has been carried out for the first time. Nitroxyl radicals of the 2- and 3-imidazoline series with methoxy groups at the α-carbon atom of the radical site were synthesized. The yields and ratios of the electrochemical methoxylation products are close to those observed in the chemical methoxylation carried out with PbO_2 and MnO_2 as oxidants.

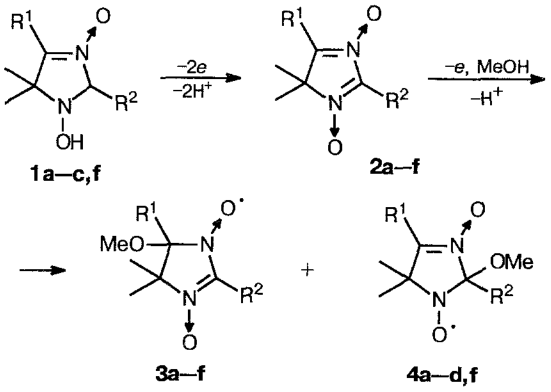
Key words: anodic methoxylation; 4*H*-imidazole 1,3-dioxides; electrochemical synthesis; nitroxyl radicals.

Oxidative methoxylation of 4*H*-imidazole *N*-oxides by the action of PbO_2 or MnO_2 in MeOH has been suggested as a method for preparing stable nitroxyl radicals (NR) of the 2- and 3-imidazoline series, containing a methoxy group at the α-carbon atom relative to the radical site.[1] The employment of electrochemical methods makes it possible to do away with using heavy metal oxides as oxidants and to conduct the synthesis at a controlled oxidation potential of the starting compound. The literature data on the electrochemical synthesis of NR known at this time are restricted to oxidation of α-tetramethyl-substituted cyclic hydroxylamines to form the corresponding NR or to oxidation and reduction of functional groups present in the molecule.[2] Previously we studied the electrochemical oxidation of 4*H*-imidazole *N*-oxides by cyclic voltammetry (CVA) and ESR spectroscopy and showed that the oxidative methoxylation of these compounds occurs according to a radical-cation mechanism.[3] It has been of interest to use these results for the electrochemical synthesis of α-methoxy-substituted NR.

We carried out the electrochemical oxidation (Scheme 1) of 2,5-disubstituted 4,4-dimethyl-4*H*-imidazole 1,3-dioxides (**2**) and their precursors, 1-hydroxy-3-imidazoline 3-oxides (**1**), at a platinum anode in a diaphragm cell under potentiostatic conditions at potentials of the oxidation of compounds **2** to give the corresponding radical cations (RC).[3] The process was carried out in a MeOH—MeCN (9:1) system (0.1 *M* Et_4NClO_4 as the supporting electrolyte). The course of the reaction was monitored by CVA at an indicator Pt electrode, by ESR spectroscopy, and by TLC with a reference spot.

Under these conditions, 1-hydroxy-3-imidazoline 3-oxides **1** undergo two-electron oxidation at the anode to afford 4*H*-imidazole 1,3-dioxides **2** which are further oxidized[3,4] to give RC and react with MeOH yielding methoxy-substituted nitroxyl radicals **3** and **4**.

Scheme 1



R^1 = Ph (**a**—**e**), 2-furyl (**f**), R^2 = Ph (**a**, **f**), *o*-FC_6H_4 (**b**), *m*-$NO_2C_6H_4$ (**c**), 2-furyl (**d**), 2-thienyl (**e**)

Yields and ratios of the products of the electrolysis of oxides **1** and **2** are given in Table 1. The yields of the methoxy-substituted NR **3a** and **4a** in the methoxylation of 2,5-diphenyl-substituted oxide **1a** are 53 and 25 %, respectively. The presence of 7 % of the intermediate oxidation product **2a** indicates that under these conditions (Q = 2.55 F mol^{-1}, where Q is the amount of electricity) the reaction does not proceed to completion. In fact, an increase in Q to 3.09 F mol^{-1} results in the exhaustive electrolysis of the starting compound and an increase in the yields of **3a** and **4a** to 67 and 31 %,

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Table 1. Yields of disubstituted 4,4-dimethyl-5-methoxy-2-imidazoline-1-oxyl 3-oxides (**3a—f**) and 5,5-dimethyl-2-methoxy-3-imidazoline-1-oxyl 3-oxides (**4a—d,f**) in the electrochemical methoxylation of oxides **1a—c,f** and dioxides **2c—e**

Compound	E^a/V	Q/F mol^{-1}	Yield[b] (%)		Yield (%)		
			3	4	2	3	4
1a	1.4	2.55	65	30	7	53	25
1a	1.4	3.09	—	—	0	67	31
1b	1.3	2.51	55	30	5	43	21
1c	1.4	2.49	60	35	25	30	14
2c	1.4	1.69	—	—	9	4	25
2c	1.4	1.89	—	—	4	45	26
2c	1.4	2.56	—	—	0	36	18
2d	1.35	1.59	65	15	15	34	10
2e	1.35	1.82	65	0	7	68	0
1f	1.25	3.36	25	50	0	18	37

[a] With respect to saturated calomel electrode. [b] Methoxylation in the presence of PbO_2 (see Ref. 1).

respectively, which provides support for the above-presented Scheme 1.

When 2.51 F mol^{-1} of electricity was passed through the reaction mixture, NR **3b** and **4b** were obtained in 43 and 21 % yields, respectively, along with dioxide **2b** formed in 5 % yield. Oxidation of oxide **1c** at Q = 2.49 F mol^{-1} affords 25 % dioxide **2c**, 30 % NR **3c**, and 14 % NR **4c**. The high content of intermediate product **2c** and low yields of NR **3c** and **4c** are probably due to the fact that the potential (1.4 V) maintained in the synthesis is not high enough and to the fact that part of the electricity is spent for oxidation of MeOH. An increase in the potential of the electrolysis did not lead to satisfactory results owing to the oxidation of MeOH and a drastic increase in the background current. Using **2c** as the starting compound and Q = 1.89 F mol^{-1} made it possible to increase the yield of products **3c** and **4c** to 45 and 26 %; the reaction mixture still contained 4 % of the starting compound. An increase in Q to 2.56 F mol^{-1} resulted in the complete consumption of the starting compound, but the yield of radicals **3c** and **4c** decreased to 36 and 18 %, respectively. This is apparently caused by further oxidation of the methoxy substituted NR, since the potentials for their oxidation are lower than that maintained in the synthesis (according to CVA, E_r^{1a}(**3a—f**) = 0.9÷1.1 V, E_r^{1a}(**4a—d,f**) = 1.35÷1.55 V). Oxidation of compound **2d** at Q = 1.59 F mol^{-1} afforded NR **3d** and **4d** in 34 and 10 % yields, respectively; 15 % of 4*H*-imidazole 1,3-dioxide remained unreacted. The low degree of conversion of compound **2d** and low yields of NR **3d** and **4d** may probably be explained by the reasons outlined above in the discussion of the methoxylation of compound **1c**. When 1.82 F mol^{-1} of electricity is passed through a solution of compound **2e**, 68 % radical **3e** and no isomer **4e** is formed.

Electrolysis of oxide **1f** at Q = 3.36 F mol^{-1} resulted in the complete conversion of the starting compound, however, the yields of radicals **3f** and **4f** were only 18 and 36 % respectively.

The results obtained show that the electrochemical methoxylation of dioxides **2** occurs with rather high yields and that in some cases the yields of the products are obviously not the maximum possible. At the same time, it should be taken into account that attempts to carry out the exhaustive electrolysis of dioxides **2** may result in oxidation of NR **3** and **4**.

A comparison of the results of electrochemical and chemical methoxylation indicates that the electrolysis of compounds **1a** and **2e** affords NR **3a**, **4a**, and **3e** in the same yields as in the case when PbO_2 is used. Electrochemical methoxylation of compounds **1b**, **2c**, and **1f** gives the corresponding methoxy substituted NR in overall yields which are 20—25 % (for **2d** 36 %) lower than those in chemical methoxylation, due to the occurrence of side reactions.

The ratio between the resulting methoxy substituted NR **3** and **4** is in agreement with the known data.[1] For example, electrolysis of compounds **1a—c**, **2c** gives methoxy substituted NR **3a—c**, **4a—c** in the 2:1 ratio; in the case of 2-furyl substituted compound **2d** the proportion of the radical, a derivative of 2-imidazoline, increases, and methoxylation of 2-thienyl substituted compound **2e** gives **3e** as the only reaction product. When a donor substituent, 2-furyl, is introduced to position 5 of the ring, the ratio between the methoxylation products is reversed (**3f** : **4f** ~ 1 : 2).

Thus, in the present work electrochemical methoxylation of substituted 4*H*-imidazole 1,3-dioxides **2** was carried out for the first time and nitroxyl radicals of 2- and 3-imidazolines having methoxy groups at the α-carbon atom of the radical site were prepared. The yields and the ratios of the products are close to those observed in the chemical methoxylation with PbO_2 and MnO_2 used as the oxidants.

Experimental

IR spectra were recorded on a Specord M-80 spectrometer ($CHCl_3$), the ESR spectra were measured on a Bruker ESR-300 instrument (MeOH). Electrochemical synthesis was carried out in a three-electrode cell with separated anode and cathode areas, V of the anode area was 20 mL. The potential was controlled by a P-5848 potentiostat. A platinum foil with a surface of 7 cm^2 was used as the working electrode, a wire helix of a nickel—chromium alloy was the auxiliary electrode. To obtain cyclic voltammograms, an indicator Pt electrode with a surface of 8 mm^2 was used. For electrochemical methoxylation, (1.75—2.5) · 10^{-2} M solutions of starting compounds in a 0.1 M solution of Et_4NClO_4 in a MeOH—MeCN (9:1) system were prepared. Cyclic voltammograms were recorded on a modified LP-7e polarograph. An aqueous saturated calomel reference electrode was used. MeOH was purified by distillation over magnesium methylate; MeCN was purified by distillation over $KMnO_4$ and P_2O_5. The characteristics of compounds **1a—c,f** (see Ref. 5) and **2c—e** (see Ref. 9) and the procedures for their preparation have been described previously.

General procedure for the preparation of 2,5-disubstituted 4,4-dimethyl-5-methoxy-2-imidazolin-1-oxyl 3-oxides (3a—f) and 2,4-disubstituted 5,5-dimethyl-2-methoxy-3-imidazolin-1-oxyl 3-oxides (4a—d,f). Compound **1a—c,f** or **2c—e** (0.25—0.5 mmol) was placed in an electrochemical cell with a solution of the electrolyte. The electrochemical synthesis was carried out at a controlled anode potential (see Table 1) at room temperature; the solution was stirred with a magnetic stirrer. The course of the reaction was monitored by cyclic voltammetry, TLC with a reference spot on Silufol UV-254 plates, and ESR spectroscopy. The completion of the reaction was detected either by the disappearance of compound **2** or by the attainment of the maximum amount of one of the methoxylation products. When the synthesis was completed, the mixture was extracted with ether, the extract was concentrated, and the residue was chromatographed on a column with silica gel (using chloroform as the eluent).

IR spectra of compounds **3a—f** and **4a—d,f** obtained are identical to those described previously[3] for the corresponding NR. The ESR spectra of compounds **3a—f** in MeOH are quintets with the HFC constants $a^{N(1)} = a^{N(3)} = 7.5 \div 7.5$ G; the ESR spectra of compounds **4a—d,f** exhibit triplets with the HFC constant $a^{N} = 12.5 \div 13.0$ G (see Refs. 7,8).

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