CHEMISTRY LETTERS, pp. 1045-1048, 1994.

Oxidation of Ethers by $NO_3^\bullet$ Generated from NO_3^- with Anodic Oxidation[1)]

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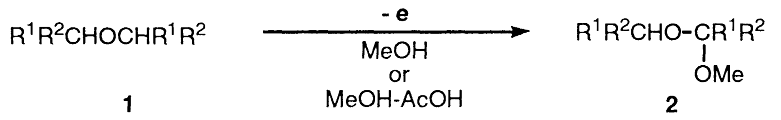
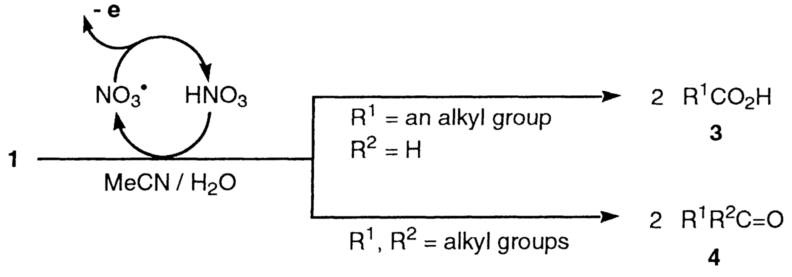
A radical $NO_3^\bullet$ generated by anodic oxidation of NO_3^- was found to be an effective species to the oxidation of ethers to the corresponding carboxylic acids and ketones, and this reaction was successfully applied to the synthesis of dihydrojasmone.

We have previously reported that the direct anodic oxidation of ethers (**1**) carried out in some non-aqueous solvents such as MeOH and MeOH-AcOH gave the corresponding acetals (**2**) (Scheme 1).[2,3)]



Scheme 1.

On the other hand, it has been found in this study that the indirect anodic oxidation of **1** could successfully be achieved in an aqueous solvent system ($MeCN\text{-}H_2O$) by carring out the reaction in the presence of NO_3^- as a precursor of a radical $NO_3^\bullet$[4)] and the products were the corresponding carboxylic acids (**3**) or ketones (**4**) (Scheme 2) depending on the structure of the starting compounds **1**.



Scheme 2.

In the first place, the anodic oxidation of **1** was examined in the presence of some types of electrolytes, since so far the indirect anodic oxidation of **1** had never been reported. As the results are shown in Table 1, the oxidation of dibutyl ether (**1a**; R^1 = *n*-Pr, R^2 = H) carried out in the presence of an electrolyte containing halide ion (LiCl; Run 1, LiBr; Run 2, LiI; Run 3) did not take place at all in an aqueous solvent ($MeCN : H_2O = 10 : 1$) and **1a** was recovered almost completely, while the oxidation of **1a** carried out in the presence of NH_4NO_3

(Run 4) or $LiNO_3$ (Runs 5-8) yielded the corresponding butyric acid (**3a**; R^1 = *n*-Pr) with a reasonable yield. These results clearly indicated that the halogen ion was not useful to the oxidation of **1**, whereas NO_3^- was remarkably effective to the oxidation of **1**. The fact that only 0.1 molar equivalent of the $LiNO_3$ was reasonably effective to the oxidation clearly indicated that NO_3^- behaved as a mediator in this oxidation.

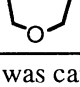
Table 1. Anodic Oxidation of Dibutyl Ether (**1a**)[a)]

Run	Supporting Electrolyte[b)]		Supplied Electricity F/mol[c)]	Yield / %[d)] **3a**
1	LiCl	(0.5)	7.5	trace[e)]
2	LiBr	(0.5)	7.5	trace[e)]
3	LiI	(0.5)	7.5	0[e)]
4	NH_4NO_3	(0.5)	7.5	59
5	$LiNO_3$	(0.5)	7.5	60
6	$LiNO_3$	(0.5)	10	70
7	$LiNO_3$	(0.25)	7.5	60
8	$LiNO_3$	(0.1)	7.5	57

a) The reaction was carried out in a mixed solvent (MeCN : H_2O = 10 : 1). b) The number in parenthesis shows the molar equivalent of supporting electrolyte based on **1a**. c) Based on **1a**. The theoretically required amount of electricity is 8F/mol. d) Isolated. e) **1a** was recovered.

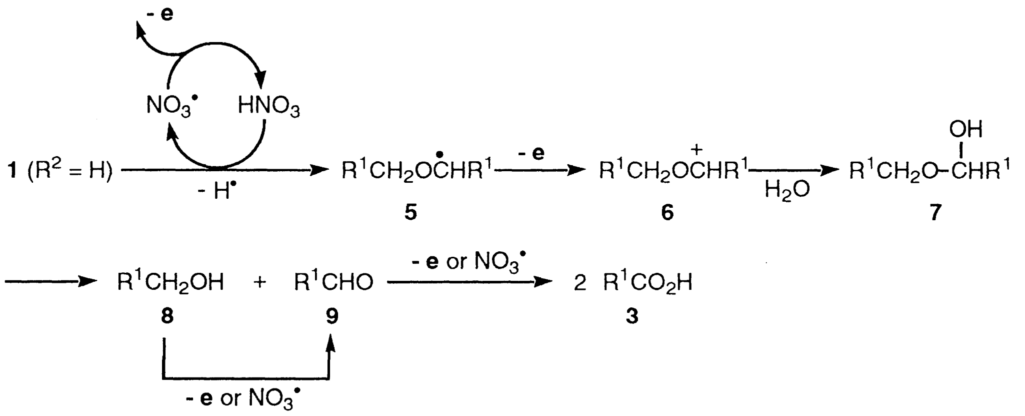
Hence, the anodic oxidation of a variety of **1** was studied by using the reaction procedure shown below, and the typical results are shown in Table 2. A solution of **1** (2.5 mmol) in MeCN : H_2O = 10 : 1 (20 mL) containing $LiNO_3$ (1.25 mmol) was put into an undivided electrolysis cell equipped with two platinum electrodes (2 x 2 cm), a thermometer, and a magnetic bar. The anodic oxidation was carried out under conditions of constant current (200 mA) with cooling by means of running water, and the temperature of the solution was maintained at 25°C. After 7.5 F/mol of electricity was passed, the reaction mixture was poured into a saturated solution of NaCl (100 mL). The organic solution was extracted with CH_2Cl_2 (4 x 20 mL) and the combined organic solution was dried over $MgSO_4$. The residue obtained by evaporation of the solvent was distilled to give the product (**3a-f**). The structure of the product (**3a-f**) was determined by the comparison of its spectroscopic values (^{1}H-NMR, IR, mass spectra) with those of the commercially available authentic sample.

Table 2. Anodic Oxidation of Ether (**1**)[a)]

Run	Ether (**1**)		Product (**3**)		Yield / %[b,c)]
1	$(C_6H_{13})_2O$	(**1b**)	$Me(CH_2)_4CO_2H$	(**3b**)	74
2	$C_8H_{17}OMe$	(**1c**)	$Me(CH_2)_6CO_2H$	(**3c**)	77
3	$MeO(CH_2)_{12}OMe$	(**1d**)	$HO_2C(CH_2)_{10}CO_2H$	(**3d**)	78
4		(**1e**)	$HO_2C(CH_2)_3CO_2H$	(**3e**)	66
5		(**1f**)	$HO_2C(CH_2)_4CO_2H$	(**3f**)	71

a) The reaction was carried out in a mixed solvent (MeCN : H_2O=10 : 1) using 0.5 eq. of $LiNO_3$ as a supporting electrolyte. b) Isolated yields based on **1**. c) 10 F/mol of electricity based on **1** was passed.

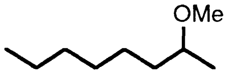
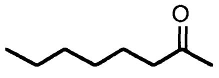
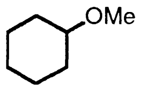
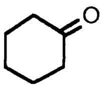
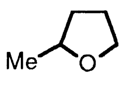
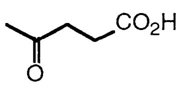
In the reaction, a radical $NO_3^\bullet$ is initially generated by the anodic oxidation of NO_3^- and it abstracts a hydrogen atom from **1** to form a radical intermediate **5** and it is further oxidized to a cationic intermediate **6**. The reaction of **6** with H_2O gives a half acetal (**7**) which collapses to an alcohol (**8**) and an aldehyde (**9**). Since further oxidation of **8** and **9** gives **3** (Scheme 3),5) the oxidation of one molecule of **1** gives two molecules of **3**. This pattern of the anodic oxidation is called the indirect anodic oxidation.



Scheme 3.

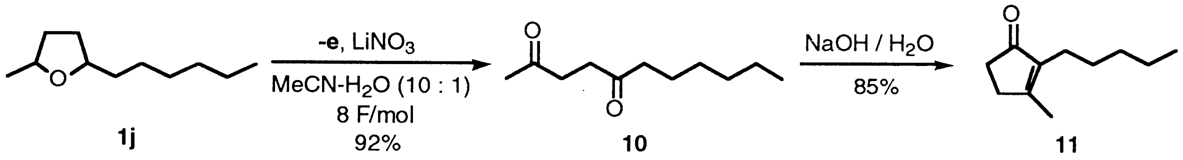
It was also found that in the presence of $LiNO_3$, the indirect anodic oxidation of ether (**1**) having a secondary alkyl group yielded ketone (**4**) with a reasonable yield (Table 3). This indirect anodic oxidation seems to be useful in organic synthesis due to its mild and simple reaction conditions, since the transformation of **1** to **4**, for instance, usually requires hazardous metal oxidizing agents such as chromic acid,9) Ce(IV),10,11) and silver oxide.12)

Table 3. Anodic Oxidation of Secondary Alkyl Ether **1**a)

Run	Ether (**1**)	Supplied Electricity F/mol	Product (**4**)	Yield / %b)
1	 (**1g**)	7.0		54
2	 (**1h**)	7.7		89
3	 (**1i**)	12.0		48

a) The reaction was carried out in a mixed solvent (MeCN : H_2O = 10 : 1) using 0.5 eq. of $LiNO_3$ as a supporting electrolyte. b) Isolated yields based on **1**.

This reaction led to a convenient synthesis of dihydrojasmone. As shown in Scheme 4, the anodic oxidation of ether (**1j**)13,14) carried out in the presence of $LiNO_3$ gave 1,4-diketone (**10**)15) with an excellent yield and it was easily transformed to dihydrojasmone (**11**)16) by the known method (Scheme 4).17)



Scheme 4.

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15) **10**; IR (neat) 1718 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.0 Hz), 1.10-1.80 (m, 8H), 2.18 (s, 3H), 2.47 (t, 2H, J = 7 Hz), 2.75 (s, 4H); MS, *m/e* 184 (M$^+$).

16) **11**; IR (neat) 1700, 1650 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (t, 3H, J = 6H), 1.17-1.07 (m, 6H), 2.10 (s, 3H), 2.10-2.50 (m, 6H); MS, *m/e* 166 (M$^+$).

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(Received February 28, 1994)