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INDIRECT ELECTROOXIDATION OF N-PROTECTED AMINES TO AMIDES WITH A DOUBLE MEDIATORY SYSTEM CONSISTING OF RuO_4 AND Cl^+

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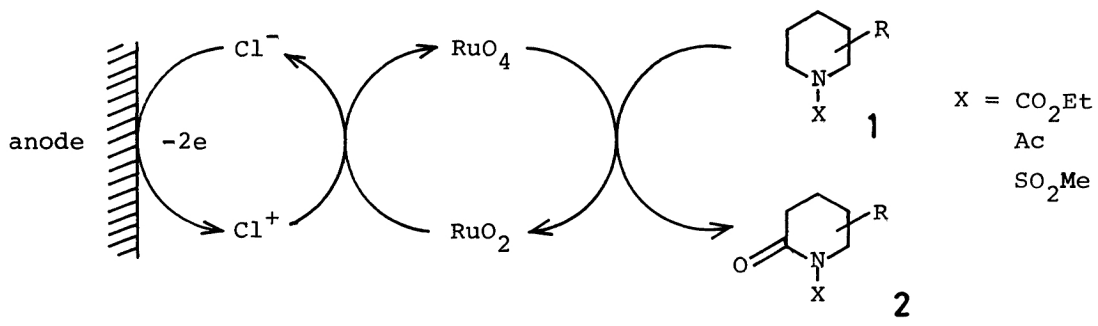
Indirect electrooxidative conversion of N-protected aliphatic amines into the corresponding amides with RuO_4 in a saturated NaCl-acetone system proceeds in excellent yields.

Although a variety of procedures have been explored for the oxidation of nitrogen containing compounds,[1] little attention has been paid to the direct oxidation of a methylene group at the α-position of amines to afford the corresponding carbonyl function. Ruthenium tetroxide (RuO_4) is recognized as a potential oxidizing agent to convert amines to amides.[2] In the course of an investigation of an indirect electrooxidation of organic compounds with a metal oxidant as a possible mediator, we have observed that RuO_4 can be easily generated from $RuO_2.2H_2O$ or $RuCl_3$ by the electrolysis in a mixed solution consisted of an aqueous sodium chloride and appropriate organic solvent. We report here an application of this electrolytic technique for the generation of RuO_4 to oxidation of methylene group linked to nitrogen atom, leading to the corresponding amides. As depicted in schematic picture 1, the present process includes three reaction steps which involves (1) oxidation of amine by RuO_4 in an organic solution, (2)



Scheme 1.

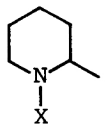
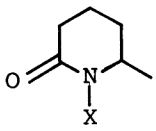
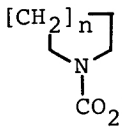
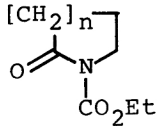
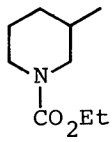
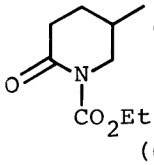
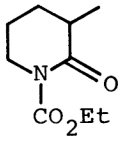
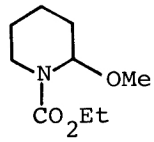
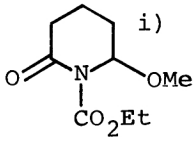
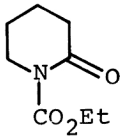
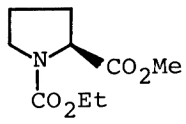
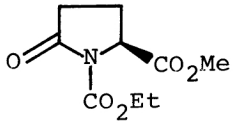
regeneration of RuO_4 by the oxidation of RuO_2 with oxidizing chlorine species, and (3) electrooxidative regeneration of oxidizing chlorine species.

Following is the typical electrooxidation procedure. A mixture of N-ethoxycarbonyl-2-methylpiperidine (1, 0.6 mmol) and $RuO_2.2H_2O$ (3 mg, 0.02 mmol) in an aqueous saturated NaCl (5 ml) and acetone (2.5 ml) was placed in an undivided cell. To this solution was immersed two platinum foil electrodes (3 cm^2) and the entire mixture was electrolyzed at room temperature under a constant current of 10 mA/cm^2 with changing the current direction every 30 s. After passage of 7.0 F/mol of electricity, the mixture was filtered off and the filtrate was subjected to extractive workup and chromatography (SiO_2, hexane-AcOEt 4:1) to give N-ethoxycarbonyl-6-methyl-2-piperidone 2 in 92% yield.

In a similar manner as described above, various cyclic and acyclic carbamates, acetamide, and sulfonamide were subjected to the electrooxidation and the results are summarized in Table 1. Oxidation occurred exclusively at the methylene groups linked to nitrogen atom, giving the corresponding amides, and no reaction had been observed at the branched carbon atom α to nitrogen atom. The formation of N-ethoxycarbonyl-2-piperidone 2 (X = CO_2Et) from N-ethoxycarbonyl-2-methoxypiperidine 1 (X = CO_2Et, R = MeO) may be explained by assuming the oxidation of the ether function[3] (entry 8). According to the amount of consumed electricity required for the complete conversion of substrates, cyclic structures are much more reactive toward RuO_4 than linear ones. Thus, the oxidation of most cyclic amines completed within 7 F/mol of electricity, whereas acyclic ones required about 15 F/mol of electricity. In the case of electrooxidation of α,α'-bismethyleneamines (entries 4-7), only amides were obtained independently on the passed electricity and no detectable amount of imides arising from further oxidation of the initially formed amides were produced by the prolonged electrolysis.

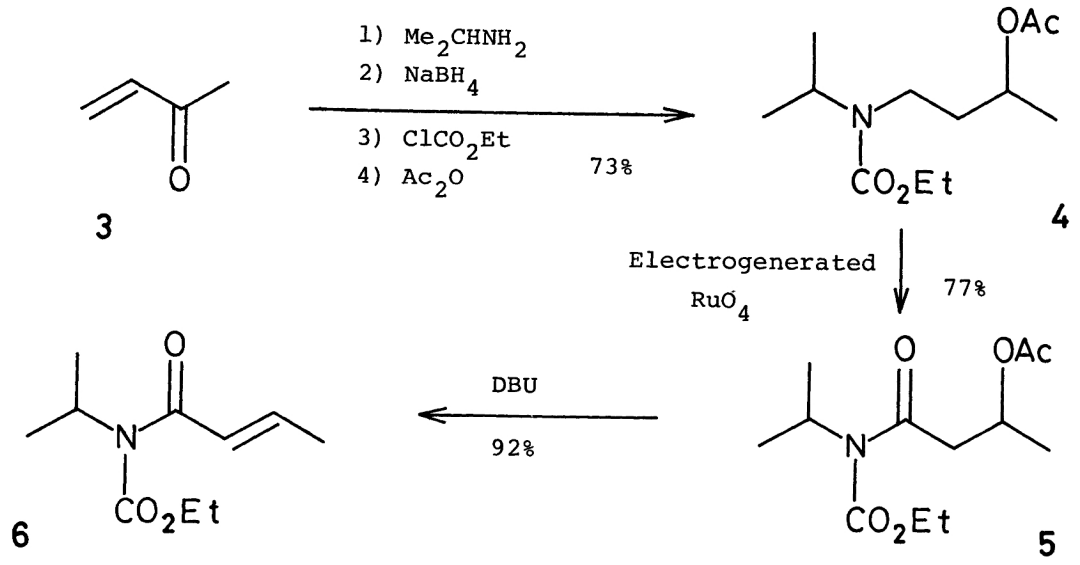
As an extention of the present studies on selective oxidation of nitrogen containing compounds, the transformation of the enone 3 into 6 was investigated. Thus, the structure of the starting 3 was reversed to α,β-unsaturated amide 6 by the transposition of carbonyl function into β-position of the molecule. Amination of 3 by the 1,4-addition of isopropylamine at room temperature and subsequent reduction with sodium borohydride in methanol was followed by successive treatment with ethyl chloroformate in 50% sodium hydroxide and acetic

Table 1. Indirect Electrooxidation of N-Protected Amines with RuO_4[a]

Entry	Substrate	F/mol[b]	Yield/%[c]	Product	Bp/°C (Torr)[d]
					
1	X = CO_2Et	7.0	92	X = CO_2Et	117(1)
2	X = Ac	7.0	93	X = Ac	76(1)
3	X = SO_2Me	10.0	50[e]	X = SO_2Me	132(0.8)
					
4	n = 1	7.0	90	n = 1	115(0.8)
5	n = 2	7.0	89	n = 2	122(1)
6	n = 3	7.0	92	n = 3	126(1)
7		7.0	91	 g)  h) (63:37)	
8		10.0	88	 i)  (68:32)	
9		7.0	66[f]		146(0.8)
10	$C_3H_7NC_3H_7$ | CO_2Et	15.0	96	$C_3H_7NCOC_2H_5$ | CO_2Et	74(1)
11	$C_6H_{13}NC_6H_{13}$ | CO_2Et	15.0	95	$C_6H_{13}NCOC_5H_{11}$ | CO_2Et	120(0.8)

[a] Carried out using 1 (0.6-1.0 mmol) and $RuO_2.2H_2O$ or $RuCl_3$ (2-3 mg) in a mixed solution of saturated NaCl (5 ml) and acetone (2.5 ml) under a constant current of 10 mA/cm^2 at room temperature. [b] Electricity based on 1. [c] Isolated yield. [d] Indicated by an air-bath temperature. [e] Starting 1 was recovered in 42% yield. [f] Starting 1 was recovered in 30% yield. [g] Bp 138 °C(2.5 Torr). [h] Bp 95 °C (1.5 Torr). [i] Bp 86 °C (1 Torr).

anhydride in pyridine to give 4 in 73% yield. In a similar manner as described for the preparation of 2, the urethane 4 was electrooxidized in a saturated NaCl-acetone (2/1 V/V) in the presence of a catalytic amount of $RuO_2.2H_2O$ to give the amide 5[4] in 77% yield. Finally, on heating with diazabicyclo[5.4.0]undec-8-ene (DBU) in benzene at 50-60 °C, 5 was converted into 6 in 92% yield, whose IR and NMR spectral data were consistent with the assigned structure.[5]



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2) J. C. Sheehan and R.W. Tulis, J. Org. Chem., 39, 2264 (1974); N. Tangari and and V. Tortorella, J. Chem. Soc., Chem. Commun., 1975, 71; S. Yoshifuji, H. Matsumoto, K. Tanaka, and Y. Nitta, Tetrahedron Lett., 21, 2963 (1980).

3) A. B. Smith, III and R. M. Scarborough, Jr., Synth. Commun., 10, 205 (1980).

4) Bp 138 °C (0.8 Torr); IR (neat) 1739, 1727, 1682 cm^{-1}; NMR (60 MHz) δ 1.31 (d, J = 7 Hz, 9H), 1.37 (t, J = 7 Hz, 3H), 2.01 (s, 3H), 3.03 (d, J = 6 Hz, 2H), 4.30 (q, 2H), 4.80 (m, 1H), 5.33 (m, 1H).

5) IR (neat)1732, 1680, 1641 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 1.29 (d, J = 7 Hz, 6H), 1.36 (t, J = 7 Hz, 3H), 1.88 (d, J = 6 Hz, 3H), 4.22 (q, 2H), 4.69 (m, 1H), 6.25-7.12 (m, 2H).

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