INDIRECT ELECTROCHEMICAL OXIDATION OF 4-PICOLINE AND ITS *N*-OXIDE TO PYRIDINE-4-ALDEHYDE DIACETATE WITH ELECTROGENERATED COBALT(III) ACETATE IN AN IN-CELL PROCESS

Magdi Abdel Azzem[a] and Eberhard Steckhan[*]

Institut für Organische Chemie und Biochemie der Universität, Gerhard-Domagk-Str. 1, D-5300 Bonn, West Germany; [a] present address: Chemistry Department, Faculty of Science, El Monoufia University, Egypt

<u>Abstract</u> - The indirect electrooxidation of 4-picoline and its *N*-oxide with in situ electrogenerated Co(III) acetate has been studied. Pyridine-4-aldehyde diacetate was obtained in good yield (45 - 68%), if the electrolysis was performed in acetic anhydride at 80°C in an undivided cell under controlled current conditions.

INTRODUCTION

A large number of methods have been described for the oxidation of 4-picoline to pyridine-4-carboxylic acid using chemical oxidizing agents like nitric acid or transition metal compounds in high oxidation states like potassium permanganate or chromium trioxide.[1-6] The formation of the synthetically interesting pyridine-4-aldehyde by chemical oxidation of 4-picoline is only possible with low yields by selenium dioxide in dioxane.[7] In addition to that, the spent oxidizing agents are a hazard to the environment and therefore the waste treatment is getting more and more difficult and costly. A clean oxidation technique would be the electrochemical method, as it does not generate any waste. Direct electrochemical oxidation of picolines because of the electron-poor heteroaromatic ring is only possible at high oxidation potentials under acidic conditions yielding pyridine carboxylic acids. Thus, in a divided cell under application of a Pt, Pb, or PbO_2 anode and an acidic medium 4-picoline is transformed to pyridine-4-carboxylic acid.[8,9] The indirect electrochemical method could in principle solve these problems as strong inorganic oxidizing agents may be electrochemically activated and regenerated in situ in a continuous process. This is true, for example, in the case of manganese(III) and cobalt(III) acetates,[10] which are known for their selective sidechain oxidation of alkyl aromatic compounds. Electrochemically generated cobalt(III)

acetate in acetic acid was used to oxidize 2- and 3-picoline in a two-step ex-cell process in presence of oxygen to yield the corresponding pyridinecarboxylic acid.[11]

We are now presenting an indirect electrochemical process for the selective oxidation of 4-picoline to pyridine-4-aldehyde diacetate with in situ electrogenerated respectively regenerated cobalt(III) in an undivided cell using graphite electrodes.
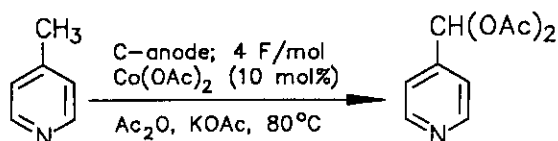
To our knowledge this acetylation was up to now only carried out chemically in a step by step reaction via treatment of 4-picoline N-oxide respectively the thus formed 4-pyridinemethanol acetate N-oxide with acetic anhydride by rearrangement of the intermediate N-acetoxypyridinium acetate. This tedious method, however, is unfavourable in particular because four steps are needed instead of one and therefore the overall yield of 16% is very low.[12]

RESULTS

Controlled Current Electrolysis of 4-Picoline

The selectivity and effectivity of the indirect electrochemical oxidation of 4-picoline in presence of $Co(OAc)_2$ were optimized towards the formation of pyridine-4-aldehyde diacetate by changing the optimum conditions.

(a) Effect of the solvent:

First attempts for an in situ indirect electrochemical oxidation of 4-picoline (10 mmol) using $Co(OAc)_2$ (1 mmol) as regenerable redox catalyst were performed in an undivided cell at a graphite anode at 2 mA/cm^2 using glacial acetic acid as solvent. The temperature was 80°C. However, only small amounts of the pyridine-4-aldehyde and pyridine-4-carboxylic acid could be isolated. Under the same conditions only changing the solvent from glacial acetic acid to acetic anhydride resulted in the formation of 43% of pyridine-4-aldehyde diacetate.

(b) Effect of the mediator concentration:

By changing the molar ratio between 4-picoline and $Co(OAc)_2$ from 20 to 2 it was found that the best results could be obtained by using a molar ratio 10 (43%) or 5 (46%).

(c) Effect of added supporting electrolyte:

The addition of potassium acetate to the solution led to an enhancement of the reaction rate. Addition of 10 mmol of KOAc to 10 mmol of 4-picoline and 1 mmol of $Co(OAc)_2$ in 150 ml of acetic anhydride resulted in an increase of the product yield to 55%.

(d) Effect of oxygen:

Passing oxygen through the electrolyte solution during electrolysis resulted in a dramatical decrease of the yield to 7% after the consumption of 1 F/mol and 20% after 4 F/mol.

(e) Effect of current density:

The current density was changed from 2 to 6 mA/cm^2 and it was found that the yield slowly dropped with increasing current density.

(f) Effect of charge consumption:

The maximum yield was obtained with 4 F/mol, the equimolar amount for the formation of the aldehyde,as shown in the Table. Lower as well as higher charge consumption resulted in a drastic decrease of the yield.

(g) Effect of the temperature:

The effect of the temperature on the yield was examined in the range of 20 to 80°C. It was observed that the yield was strongly influenced by the temperature giving best results with highest temperatures. This can be attributed to the donor property of the N-heterocycle towards cobalt(III) forming complexes.[13] These complexes dissociate at elevated temperatures giving free Co(III) ions able to oxidize picoline. The much smaller yield in the oxidation of 2-picoline may be attributed to a stronger complex formation.

(h) Effect of the addition of water and bromide ions:

It was described that bromide ions can act as co-catalyst for the allylic and benzylic oxidation of olefins and alkylarenes by Co(III) acetate.[14] Therefore we studied the reaction in presence of 1 mmol of KBr. However the yield decreased to 31%. The addition of 10% by volume of water also decreased the yield to 32%.

(i) Effect of added $Cu(OAc)_2$:

The addition of copper(II) acetate as excellent oxidizing agent for carbon radicals should result in better yields of the product, if the reaction takes place via the side-chain radical.[21] However, the addition of $Cu(OAc)_2$ in a ratio of 1 to 10 respectively 1 to 5 compared with $Co(OAc)_2$ reduced the yield to one half (28%).

Table: Results of the Indirect Electrochemical Oxidation of 4-Picoline Using $Co(OAc)_2$ as Mediator in Acetic Anhydride as Solvent

Exp. No.	Ratio of 4-Picoline to $Co(OAc)_2$[a]	Current Density [mA/cm^2]	Charge Consump [F/mol]	Temp [^{o}C]	KOAc [mmol]	O_2 insertion	$Cu(OAc)_2$ [mmol]	Yield[b] [%]
1	20	2	4	80	0	-	0	35
2	10	2	4	80	0	-	0	43
3	5	2	4	80	0	-	0	46
4	2	2	4	80	0	-	0	21
5	10	2	4	80	10	-	0	55
6	10	2	4	80	20	-	0	47
7	10	4	4	80	10	-	0	53
8	10	6	4	80	10	-	0	46
9	10	6	2	80	10	-	0	21
10	10	6	6	80	10	-	0	28
11	10	6	4	20	10	-	0	5
12	10	6	4	40	10	-	0	7
13	10	6	4	60	10	-	0	14
14	10	2	4	80	10	+	0	20
15	10	2	4	80	10	-	0.1	28

[a] 10 mmol of 4-picoline always in 150 ml of acetic anhydride.

[b] for 4 F/mol: chemical yield = current yield.

Controlled Current Electrolysis of 4-Picoline *N*-oxide

The nitrogen oxide group in 4-picoline *N*-oxide should enhance the reactivity as compared with 4-picoline towards the indirect electrochemical oxidation. This was in fact found. Under standard conditions (substrate to $Co(OAc)_2$ ratio = 10:1; 80°C; 2 mA/cm^2; 4 F/mol; no KOAc; no oxygen; no $Cu(OAc)_2$) the chemical yield of pyridine-4-aldehyde diacetate was 68 % (34% current yield).
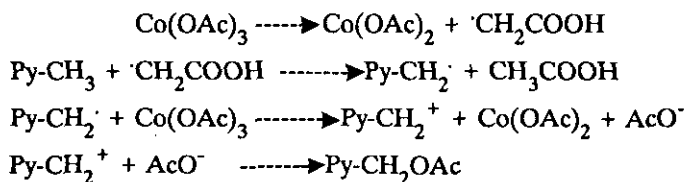
DISCUSSION

Oxidations with Co(III) acetate have been extensively investigated and most of the results[15-17] have been interpreted in terms of an electron transfer mechanism including a radical cation as intermediate:

$$RCH_3 + Co^{3+} \longrightarrow RCH_3^{\cdot +} + Co^{2+}$$
$$RCH_3^{\cdot +} \longrightarrow RCH_2^{\cdot} + H^+$$
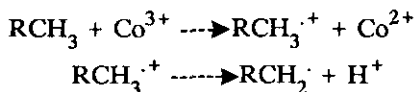
On the other hand, the hydrogen atom transfer process leading directly to the free radical has also been suggested in which the rate determining step involves the abstraction of the hydrogen atom from the organic molecule by the Co(III) ion.[18-20]

$$RCH_3 + Co^{3+} \longrightarrow RCH_2^{\cdot} + H^+ + Co^{2+}$$
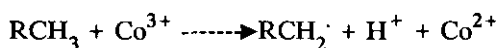
From the observation that oxygen very negatively influences the oxidation of 4-picoline it can be concluded that the *N*-oxide is not an intermediate on the way to the product because the *N*-oxide has to be formed by an oxygen derived intermediate. Oxygen also usually does not influence electrochemical oxidations via cation radicals very much. On the other hand oxygen can act as radical trap. This might point to a reaction driven by a radical. This radical could be the carboxymethyl radical ($^{\cdot}CH_2COOH$) as described for the reaction between toluene derivatives and $Mn(OAc)_3$.[21] Acetic anhydride and the presence of KOAc are reported to suppress the electron transfer relative to the carboxymethyl radical pathway.[21,22] This is in agreement with our observations. The presence of Cu^{2+} as a good oxidizing agent for benzylic radicals to the benzylic cations should favor the electron transfer reaction and hinder the reaction via the carboxymethyl radical. Our results again point to the radical pathway. The electrophilicity of the carboxymethyl radical obviously prevents its addition to 4-picoline. Thus the following mechanism would explain the effect of the solvent, electrolyte, presence of Cu^{2+}, and oxygen.

$$Co(OAc)_3 \longrightarrow Co(OAc)_2 + {^{\cdot}CH_2COOH}$$
$$Py\text{-}CH_3 + {^{\cdot}CH_2COOH} \longrightarrow Py\text{-}CH_2^{\cdot} + CH_3COOH$$
$$Py\text{-}CH_2^{\cdot} + Co(OAc)_3 \longrightarrow Py\text{-}CH_2^{+} + Co(OAc)_2 + AcO^{-}$$
$$Py\text{-}CH_2^{+} + AcO^{-} \longrightarrow Py\text{-}CH_2OAc$$

The acetoxy substituent would then lead to an easier side-chain oxidation by electron transfer by $Co(OAc)_3$ giving the end product. As benzaldehyde   acetals have much higher oxidation potentials than the corresponding benzyl ethers and even the corresponding toluene derivatives,[23] it can be expected that the pyridine-4-aldehyde diacetate behaves similarly having an oxidation potential so high that further oxidation can not occur. Starting from 4-picoline *N*-oxide is a totally different

reaction, as in acetic anhydride the intermediate *N*-acetoxypyridinium acetate rearranges under formation of the benzylic acetate[24] which subsequently is further oxidized as mentioned above.

EXPERIMENTAL

Materials. 4-Picoline was purified by distillation. Co(II) acetate, KOAc, acetic anhydride (Riedel de Haen) and 4-picoline *N*-oxide (Janssen Chimica) were used without further purification.

Equipment for Preparative Electrolysis. Preparative electrolyses were carried out using a stabilized current source, model NTN 700 M-200 (FuG, Rosenheim), together with a digital coulometer. An undivided beaker type cell (200 ml) with a cooling mantle equipped with two parallel graphite plate electrodes (24 cm^2) and a magnetic stirrer was used.

General Procedure for the Constant Current Electrolysis. 10 mmol of 4-picoline were dissolved in 150 ml of acetic anhydride containing the appropriate amount of Co(II) acetate as mediator and sometimes KOAc as supporting electrolyte (see Table). The electrolyses were performed at a constant current under thermostatization.

General Method for the Separation and Identification of the Product. After the passage of 4 F/mol, the electrolysis was stopped. The solvent was evaporated, the residue was dissolved in chloroform, filtrated, and evaporated. The residue was chromatographed on column (silica gel) using chloroform/methanol (100:1) as eluent. The separated product gave satisfactory ir, nmr and ms spectra. Moreover, the hydrolysis of the product in refluxing concentrated HCl for 3 h gave the corresponding pyridine-4-aldehyde as proven by gc/ms analysis (Hewlett Packard HP 5970 B MSD) and comparison with an authentic sample.

REFERENCES

1. A. W. Singer and S. M. McElvain, Org. Synth., Coll. Vol., 1955, III, 740; N. Rabjohn, Org. Reactions, 1949, 5, 331.

2. E. B. Bengtsson, Acta Chem. Scand., 1955, 9, 832.

3. B. Hughes and H. Suschitzky, J. Chem. Soc., 1965, 875.

4. H. Stopsak, M. Schmidt, H. Teubner, H. Titze, E. Schroetter, and H. Schick, Ger. (East) Patent **DD 248,119** (15.6.1984) (Chem. Abstr., 1988, **108**, 150322u).

5. D. Jerchel, E. Bauer, and H. Hippchen, Chem. Ber., 1955, **88**, 156; D. Jerchel, J. Heider, and H. Wagner, Ann., 1958, **613**, 153.

6. S. Paraskewas, Synthesis, **1974**, 819.

7. H. R. Henze and M. B. Knowles, J. Org. Chem., 1954, **19**, 1127.

8. A. Ito and K. Kawada, Ann. Rep. Takamine Lab., 1953, **5**, 14 (Chem. Abstr., 1955, **49**, 14516); M. Yokoyama, Bull. Chem. Soc. Japan, 1932, **7**, 69.

9. H. V. Udupa, M. S. Venkatachalapathy, S. Mysore, S. Chidambaram, K. S. S. Lalitha, and A. Hamamoorthy, **Indian** Patent 144 132 (9.10.1975) (Chem. Abstr., 1980, **92**, 31033s); J. Alamelu, K. S. Lalitha, K. Radhakrishnamurthi, S. Chidambaram, M. S. V. Pathy, and H. V. K. Udupa, Trans. Soc. Advan. Electrochem. Sci. Technol. , 1971, **6**, 97.

10. E. Steckhan, Angew. Chem. Int. Ed. Engl., 1986, **25**, 683; Topics Curr. Chem., 1987, **142**, 1.

11. M. Ahmed, T. A. Chaudhari, and M. Ahmed, Pakistan J. Sci. Ind. Res., 1986, **29**, 336; M. Ahmed, T. A. Chaudhari, and M. Azam, ibid., 1987, **30**, 182.

12. V. Boekelheide and W. J. Linn, J. Am. Chem. Soc., 1954, **76**, 1286.

13. F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry", Fifth Edition, John Wiley & Sons, New York, 1988, p. 732.

14. T. Morimoto, T. Machida, M. Hirano, and X. Zhung, J. Chem. Soc., Perkin Trans. II, **1988**, 909.

15. E. I. Heiba, R. M. Dessau, and W. J. Koehl, Jr., J. Am. Chem. Soc., 1969, **91**, 6830.

16. A. Onopchenko and J. G. D. Schulz, J. Org. Chem., 1973, **38**, 909, 3729.

17. Y. Kamiya and M. Kashima, Bull. Chem. Soc. Japan, 1973, **46**, 905.

18. J. Hanotier and M. Hanotier-Bridoux, J. Chem. Soc., Perkin Trans. II, **1973**, 1035.

19. E. Bacciocchi, L. Eberson, and C. Rol, J. Org. Chem., 1982, **47**, 5106.

20. L. Eberson, Adv. Phys. Org. Chem., 1981, **18**, 79.

21. E. I. Heiba, R. M. Dessau, and W. J. Koehl, Jr., J. Am. Chem. Soc., 1969, **91**, 138.

22. W. E. Fristad and J. R. Peterson, J. Org. Chem., 1985, **50**, 10.

23. K.-H. Grosse Brinkhaus, E. Steckhan, and D. Degner, Tetrahedron, 1986, **42**, 553.

24. V. J. Traynelis and A. J. Gallagher, J. Org. Chem., 1970, **35**, 2792; T. Cohen and G. L. Deets, J. Am. Chem. Soc., 1972, **94**, 932.