Electrochemical Oxidation of Benzyl Chlorides: A New Synthesis of 5-Methyl-2-pyrazinecarboxylic Acid

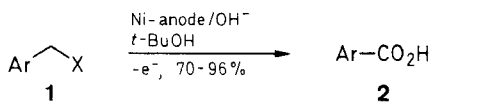
G.P. Borsotti,[a] M. Foa',[b] N. Gatti*[a]

[a] Instituto G. Donegani S.p.A., Via Fauser 4, I-28100 Novara, Italy
[b] Himont Italia, Novara Research Center, Via Caduti del Lavoro, I-28100 Novara, Italy

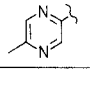
A new high yield and selective electrochemical oxidation of benzyl chlorides to the corresponding aromatic acids at the nickel hydroxide electrode is reported. The utility of this method is exemplified by the new synthesis of 5-methyl-2-pyrazinecarboxylic acid, an important pharmaceutical intermediate.

The use of nickel hydroxide electrodes has recently been reviewed by Schäfer.[1] This electrode is mainly used in organic synthesis for the oxidation of alcohols and related functional groups. In this paper we report on the direct conversion of benzyl chlorides to carboxylic acids in high yield on a nickel hydroxide electrode.

The direct oxidation of benzyl halides into carboxylic acids is an useful reaction and the use of sodium hypochlorite has been recently reported.[2] This reaction gives high yields only with benzyl bromides bearing electron-withdrawing substituents and is not selective with benzyl chlorides. Our results presented here show that the oxidation at the nickel hydroxide electrode is of general application for benzyl chlorides bearing both electron-withdrawing and electron-releasing substituents as well as for heterocycles compatible with the electrolytic conditions. It is noteworthy that good results were obtained also with 1,4-bis(chloromethyl)benzene, terephtalic acid being the reaction product.



1 2

1 Ar	X	1 Ar	X	2 Ar
a Ph	Cl	e 	Cl	a Ph
b 4-ClC$_6$H$_4$	Cl			b 4-ClC$_6$H$_4$
c 4-CH$_3$C$_6$H$_4$	Cl	f 	OH	c 4-CH$_3$C$_6$H$_4$
d 4-ClCH$_2$C$_6$H$_4$	Cl	g 	OAc	d 4-HO$_2$CC$_6$H$_4$
				e 

In some cases this reaction can be sensitive to the experimental conditions as reported in the Table. For example in the case of 2-chloromethyl-5-methylpyrazine hydrochloride (**1e**) very good results were obtained carrying out the oxidation in a *tert*-butyl alcohol/water mixture in the presence of potassium carbonate, on the contrary the yield was very low when 1 mole aqueous sodium hydroxide was used (entry 6). Entry 1 shows the great importance of the strength of the base.

5-Methyl-2-pyrazinecarboxylic acid (**2e**) was chosen as an example of the utility of this new oxidation because it is an intermediate[3] in the synthesis of the recently commercialized drug 2-carboxy-5-methylpyrazine-4-oxide (Acipimox), which shows high hypolipaemic and hypoglycaemic activities.[4,5] Acid **2e** is manufactured by condensation of diaminomaleonitrile with pyruvic aldehyde and reaction of the resultant dicyanopyrazine derivative with an acid.[6] This hydrolysis leads to a mixture of isomers, 5- and 6-methyl-2-pyrazinecarboxylic acids, which cannot be easily separated. A new synthesis of acid **2e** by cyclization of aliphatic precursors[7] has been recently reported.

Our electrochemical method is a useful alternative[8] to the methods reported above since we have developed a selective radical chlorination of the commercially available 2,5-dimethylpyrazine[9] leading to 2-chloromethyl-5-methylpyrazine.

Table. Electrochemical Oxidation at the Nickel Hydroxide Electrode

Entry	Product	Electrolyte[a]	Current Density I (mA/cm^2)	Temp. (°C)	Yield[b] (%)	mp (°C) found	mp (°C) reported
1	**2a**	A	16	60	70	121–122	122.4[10]
		B	16	70	92		
2	**2a**[1]	C	16	25	86	–	–
3	**2b**	B	16	70	96	240–241	241.5[10]
4	**2c**	B	16	70	96	181–182	182[10]
5	**2d**	B	16	70	78	–[c]	–[c,10]
6	**2e**	A	12	60	82	164–167	163–167[6]
		C	12	60	< 5		
7	**2e**	C	12	40	93	as above	–
8	**2e**	C	12	40	87	as above	–

[a] Electrolyte A: *tert*-butyl alcohol/water (1 : 5) mixture containing K_2CO_3 (1 mol/L).
Electrolyte B: *tert*-butyl alcohol/water (1 : 10) mixture containing NaOH (1 mol/L).
Electrolyte C: 1 N aq. NaOH.
[b] Yield of isolated products. Purity was checked using GLC after esterification with CH_2N_2 (conditions: OV 1 capillary column, 25 m, Carlo Erba Mega HRGC 5300).
[c] Sublimes.

The electrolytic oxidations of 2-hydroxymethyl-5-methylpyrazine (**1f**) and 2-acetoxymethyl-5-methylpyrazine (**1g**), prepared from **1e**, are also reported in the Table for comparison (entries 7 and 8). However, the better yields of **2e** from **1f** and **1g** in the electrolytic reaction, do not justify the additional reaction step.

The comparison between our results on benzyl chloride and those obtained by Schäfer on benzyl alcohol[1] (entries 1 and 2), using the same current density, indicates that our method is fully comparable with the reported technique and gives further examples of the versatility of the nickel hydroxide electrode.

^{1}H-NMR spectra were recorded with a Bruker AC 200 spectrometer and mass spectra with a Varian-MAT 112 S spectrometer.

The electrolysis is carried out in a 150 mL double-walled cylindrical undivided glass cell equipped with magnetical stirring, thermostatic temperature control, thermometer and reflux condenser. The anode is a 24 cm^2 nickel net, converted to the nickel hydroxide anode before each electrolysis as described by Schäfer et al.[1] The cathode is a wire of a nickel alloy (incoloy 825). The electrolysis is performed at constant current. Values of reaction currents and temperatures are listed in the Table.

2-Chloromethyl-5-methylpyrazine Hydrochloride (1e):

A 500 mL round-bottomed flask equipped with magnetical stirring, dropping funnel and reflux condenser is charged under argon atmosphere with 2,5-dimethylpyrazine (25.0 g, 231 mmol), lauroyl peroxide (1.7 g, 4.2 mmol) and CCl_4 (250 mL). The mixture is heated to reflux temperature and a solution of SO_2Cl_2 (9.45 mL, 116 mmol) in CCl_4 (30 mL) is added dropwise in 0.5 h. The stirring is maintained for an additional 0.5 h, then gaseous HCl (3.0 g) is bubbled into the mixture. The mixture is then cooled down to r.t. and the crystalline precipitate filtered, washed with CCl_4 and dried to give the recovered 2,5-dimethylpyrazine hydrochloride (20.7 g). A second treatment of the filtrate with gaseous HCl (3.0 g) at r.t. causes the complete precipitation of crude **1e** (85% pure, GC analysis, remainder 2,5-dimethylpyrazine); yield: 13.6 g (74%); 38% conversion. 2-Chloromethyl-5-methylpyrazine hydrochloride (**1e**) is purified by dissolving in saturated solution of Na_2CO_3 and extracting with CH_2Cl_2.

MS (70 eV): *m/z* (%) = 142 (M^+, 46), 144 (15), 107 ($M^+ - Cl$, 100), 80 ($M^+ - Cl-HCN$, 36), 76 ($C_2H_3NCl^+$, 5), 39 ($C_3H_3^+$, 59).

2-Hydroxymethyl-5-methylpyrazine (1f):

Crude 2-chloromethyl-5-methylpyrazine hydrochloride (**1e**; 9.9 g, 85% pure, 47 mmol) is dissolved in anhydrous EtOH (250 mL) containing KOAc (40 g) and $KHCO_3$ (7.0 g) and refluxed for 6 h. EtOH is then distilled off under reduced pressure and the mixture is extracted with Et_2O (5 × 30 mL). The crude product obtained after removal of solvent is purified by recrystallization from isopropyl ether; yield: 4.3 g (74%); mp 33–35°C.

$C_6H_8N_2O$	calc.	C 58.04	H 6.51	N 22.57
(124.2)	found	58.18	6.46	22.52

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.56 (s, 3H), 3.38 (s, 1H), 4.79 (s, 2H), 8.40 (s, 1H), 8.50 (s, 1H).

MS (70 eV): *m/z* (%) = 124 (M^+, 100), 123 ($M^+ - H$, 47), 95 ($M^+ - CHO$, 85), 93 ($M^+ - CH_2OH$, 20), 55 ($C_3H_5N^+$, 19), 42 ($C_2H_4N^+$, 46), 39 ($C_3H_3^+$, 43).

2-Acetoxymethyl-5-methylpyrazine (1g):

Crude 2-chloromethyl-5-methylpyrazine hydrochloride (**1e**; 85% pure, 10.7 g, 51 mmol) is dissolved in anhydrous EtOH (250 mL) containing KOAc (40 g) and refluxed for 6 h. EtOH is distilled off under reduced pressure and the mixture is extracted with Et_2O (3 × 30 mL). After removal of the solvent, the crude product is distilled under reduced pressure to afford **1g**; yield: 5.5 g (65%); bp 76–77°C/0.7 mbar.

$C_8H_{10}N_2O_2$	calc.	C 59.25	H 6.23	N 17.28
(162.2)	found	59.18	6.30	17.32

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.13 (s, 3H), 2.56 (s, 3H), 5.20 (s, 2H), 8.43 (s, 1H), 8.51 (s, 1H).

MS (70 eV): *m/z* (%) = 166 (M^+, 5), 124 ($M^+ - COCH_2$, 100), 123 ($M^+ - CH_3CO$, 48), 43 (CH_3CO^+, 72), 39 ($C_3H_3^+$, 35).

Electrochemical oxidation of Benzyl Chlorides 1, 4-Chlorobenzoic Acid (2b); Typical Procedure:

A mixture of 4-chlorobenzyl chloride (**1b**; 2.45 g, 15 mmol) in 1 N NaOH (100 mL) and *tert*-butyl alcohol (10 mL) is heated at 70°C and electrolyzed at a constant current of 400 mA until 5 F/mol are supplied. The mixture is extracted with Et_2O (2 × 50 mL) and aqueous phase acidified with 12 N HCl to pH 1. The resulting white precipitate is extracted with Et_2O (2 × 100 mL), the organic phase dried (Na_2SO_4) and the solvent removed under reduced pressure to give **2b**; yield: 2.25 g (96%); mp 240–241°C (Lit.[10] mp 241.5°C) (Table).

5-Methyl-2-pyrazinecarboxylic Acid (2e):

2-Chloromethyl-5-methylpyrazine hydrochloride (**1e**; 2.1 g, 85% pure, 10 mmol) is dissolved in water (75 mL) containing *tert*-butyl alcohol (15 mL) and K_2CO_3 (12 g) heated at 60°C and electrolyzed at a constant current of 300 mA until 6 F/mol are supplied. The mixture is distilled to remove the water/*tert*-butyl alcohol azeotrope, acidified with 12 N HCl to pH 1.5 (isoelectric pH of the acid), and the water is distilled off under reduced pressure. The resulting solid is extracted with methyl ethyl ketone (3 × 50 mL) and the organic solution is distilled to dryness to afford 5-methyl-2-pyrazinecarboxylic acid (**2e**); yield 1.13 g (82%); mp 164–167°C) (Lit.[6] mp 163–167°C).

^{1}H-NMR (200 MHz, CD_3OD): δ = 2.84 (s, 3H), 8.83 (s, 1H), 9.32 (s, 1H), 10.80 (s, 1H).

MS (70 eV) (after esterification with diazomethane): *m/z* (%) = 152 (M^+, 8), 122 ($M^+ - CH_2O$, 53), 94 ($M^+ - CO_2CH_2$, 100), 93 ($M^+ - CO_2CH_3$, 62), 66 ($C_3H_2N_2^+$, 29), 59 (CH_3OCO^+, 7), 39 ($C_3H_3^+$, 49).

This work was sponsored by the Ministro della Ricerca Scientifica e Tecnologica in the frame of the "Programma Nazionale di Ricerca per la Chimica".

Received: 5 May 1989; revised: 28 August 1989

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