PREPARATION OF 4-PHENYLBUTYRIC [2,3-$^2H_2$]-, [4,4-$^2H_2$]-, [2,3,4,4-$^2H_4$]-, and [2,2,3,3,4,4-$^2H_6$]-ACIDS BY USE OF CROSSED KOLBE ELECTROLYSIS AS A KEY REACTION

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SUMMARY

The four deuteriated 4-phenylbutyric [2,3-$^2H_2$]-, [4,4-$^2H_2$]-, [2,3,4,4-$^2H_4$]-, and [2,2,3,3,4,4-$^2H_6$]-acids have been synthesized in high isotopic purity by utilizing crossed Kolbe electrolysis of methyl hydrogen [$^2H_0$]-, [2,3-$^2H_2$], and [2,2,3,3-$^2H_4$]-succinates and phenyl acetic [$^2H_0$]- and [$^2H_2$]-acids as a key reaction.

Key Words: Deuterium Labelling, Synthesis, Crossed Kolbe Electrolysis
Deuteriated 4-Phenylbutyric Acids

INTRODUCTION

Recently, we have reported that adipic [$^2H_2$]-, [$^2H_4$]-, [$^2H_6$]-, and[$^2H_8$]-acids were prepared in high isotopic purity by using Kolbe electrolysis as a key reaction.[1] Selectively deuteriated phenyl substituted aliphatic acids are attractive in metabolic study since there are many biologically important phenyl substituted aliphatic acids.

We report here that the crossed Kolbe electrolysis using methyl hydrogen succinates and phenylacetic acids was applied for the synthesis of 4-phenylbutyric acid which was used in the study of the reabsorption in the proximal tubule of the rat kidney[2] and 4-phenylbutyric [2,3-$^2H_2$]-, [4,4-$^2H_2$]-, [2,3,4,4-$^2H_4$]-, and [2,2,3,3,4,4-$^2H_6$]-acids were prepared in high isotopic purity.

RESULTS AND DISCUSSION

The preparation of phenylacetic [2,2-$^2H_2$]acid (2a) in high deuterium content was achieved directly from phenyl acetonitrile (1) via

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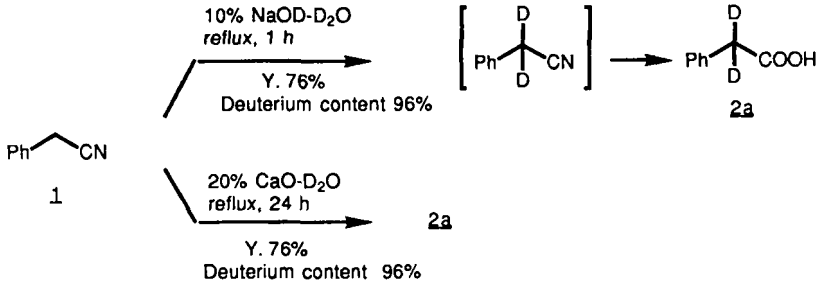
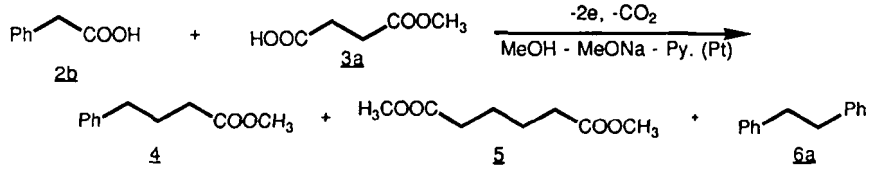
the base-catalyzed hydrogen-deuterium exchange with 10% NaOD-D_2O or 10 % CaO-D_2O, followed by hydrolysis, as shown in Scheme 1. The deuterium content, determined by ^1H n.m.r based on phenyl group as an internal reference, of (2a) shows that incorporation of deuterium is almost complete. It is noted that CaO-D_2O can be used as an alkaline media instead of expensive NaOD-D_2O, even though CaO-D_2O hydrolysis requires longer reaction times than those of NaOD-D_2O hydrolysis.



Scheme 1

The crossed Kolbe electrolysis is a coupling procedure using two different carboxylic acids or their esters at the same time. Interestingly, when one of the acids is used in an excess, the formation of symmetrical dimers can be reduced.[3] Therefore, as a preliminary investigation, the crossed electrolysis of non-deuteriated phenylacetic acid (2b) and methyl hydrogen succinate (3a) was carried out to examine the relationship between the molar ratios of (2b) and (3a) and the yield (Scheme 2 and Table 1).



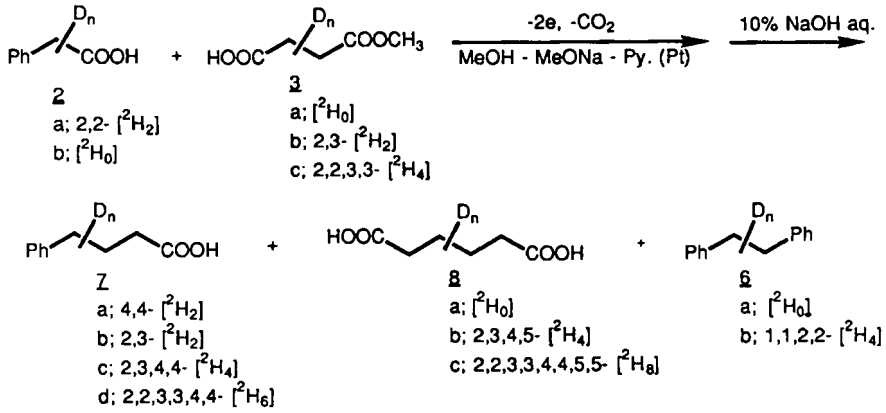
Scheme 2

Table 1 Crossed Kolbe Electrolysis of Phenylacetic acid (2b) and Methyl hydrogen succinate (3a).

Entry	Molar ratio [(2b)/(3a)]	Yield (%)[a] (4)	(5)	(6)
1	1/5	56	54	14
2	1/3	54	29	34
3	1/1	25	5	30
4	3/1	15	18	47

a) Relative yields were determined by v.p.c.

When the electrolysis of (2b) and (3a) was performed in a molar ratio of 3:1, the expected methyl 4-phenylbutyrate (4) was obtained in 54% yield, together with dimethyladipate (5) and diphenylethane (6a). In the presence of pyridine the electrolysis of phenylacetic acids (2a-b) and methyl hydrogen succinates (3a-c), leading to the deuteriated methyl 4-phenylbutyrates, was carried out with a mixture of MeONa and MeOH at a constant electric current (current density: 200 mA/cm^2) (Scheme 3 and Table 2). Hydrolysis of the methyl butyrates obtained readily proceeded with 10% aqueous NaOH, to give the deuteriated 4-phenylbutyric acids (7a-d).



Scheme 3

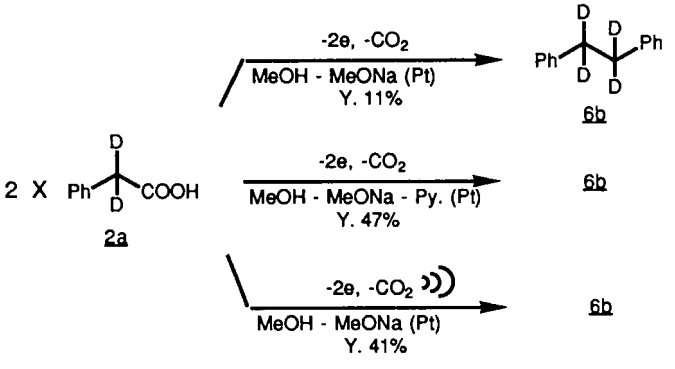
Table 2 Crossed Kolbe Electrolysis of Phenylacetic acids (2a-b) and Methyl hydrogen succinates (3a-c).

Entry	Substrate	Molar ratio of [(2)/(3)]	Product (%)[a]			Purity of 7 (%)[b]
1	(2a),(3a)	1/3	6b (15)	7a (13)	8a (22)	94
2	(2b),(3b)	1/1	6a (19)	7b (12)	8b (11)	99
3	(2a),(3b)	1/1	6b (31)	7c (4)	8c (9)	87
4	(2a),(3c)	1/1	6b (15)	7d (6)	8c (0)	79

a) Isolated yields are shown.

b) Isotopic purity was determined by mass spectroscopy.

As listed in Table 2, 4-phenylbutyric [4,4-$^2H_2$]- (7a), [2,3-$^2H_2$]- (7b), [2,3,4,4-$^2H_4$]- (7c), and [2,2,3,3,4,4-$^2H_6$]-acids (7d) were obtained in 4-13% yields but in 79-99% isotopic purity, accompanied by dimethyl adipates (8a-c) and diphenyl ethanes (6a-b). The electrolysis leading to [4,4-$^2H_2$]acid (7a) was accomplished by using a 3-fold equivalent of (3a) to (2a) since more available 3a than 3a could be effectively used. The deuterium content, which was determined based on phenyl group as an internal reference, of the products indicates that the contamination by hydrogen did not occur during the coupling procedure and the work-up process in all cases.



Scheme 4

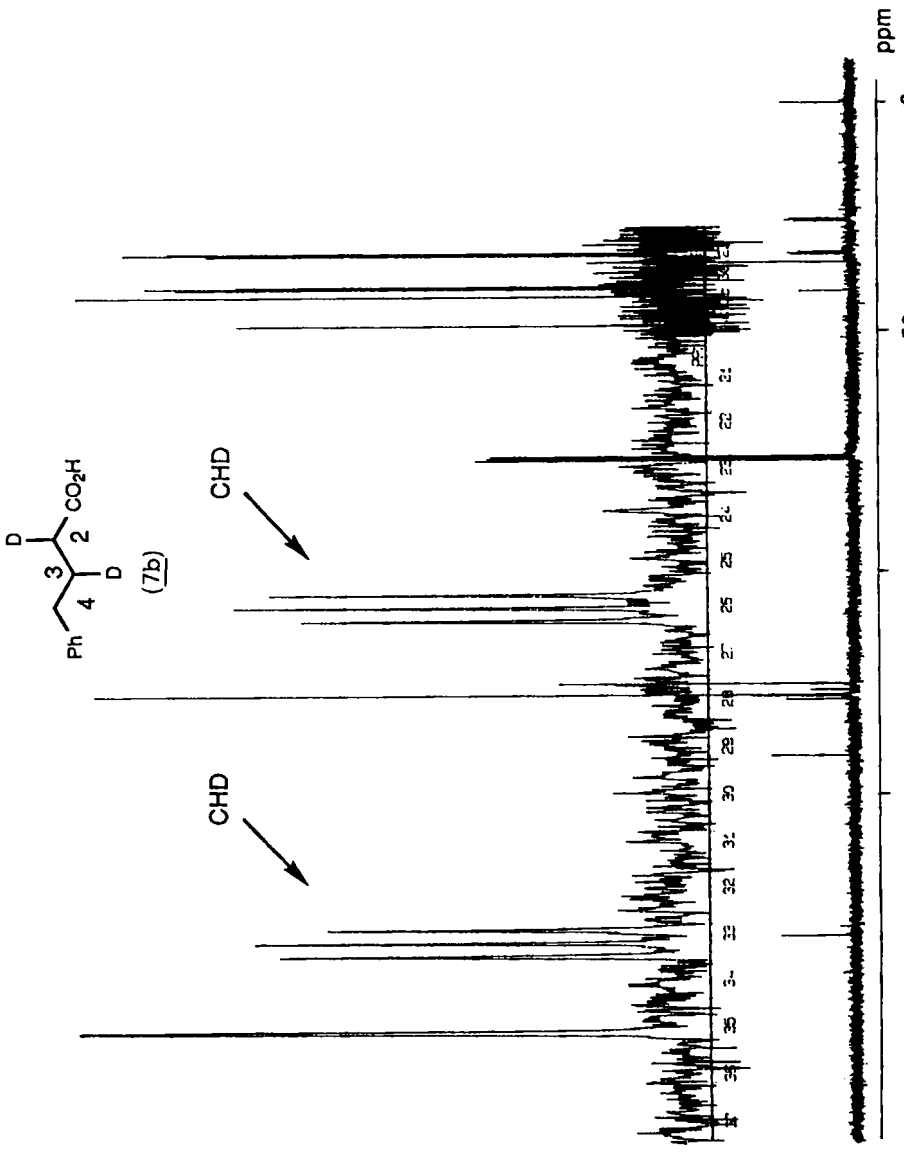


Figure 1. ^{13}C-n.m.r. Spectrum of 4-Phenylbutyric [2,3-^{2}H$_2$]acid (7b) at 67.94 MHz in $CDCl_3$.

Table 3 ^{13}C n.m.r. Chemical Shifts Values of 4-Phenylbutyric Acid and Deuteriated 4-Phenylbutyric Acids (7a-d) at 67.94 MHz in $CDCl_3$.

Substrate	C=O	Aliphatic position			Aromatic position			
		C2	C3	C4	m	o	p	i
[$^2H_0$]	180.2	33.4 (s)	26.2 (s)	35.0 (s)	128.5	128.4	126.0	141.1
4,4-[$^2H_2$] (7a)	180.4	33.5 (s)	25.3 (s)	34.5 (quint) (J=19.6 Hz)	128.7	128.7	126.3	141.4
2,3-[$^2H_2$] (7b)	180.2	33.2 (t) (J=20.1 Hz)	26.1 (t) (J=20.1 Hz)	35.2 (s)	128.8	128.7	126.3	141.5
2,3,4,4-[$^2H_4$] (7c)	180.4	32.9 (quint) (J=19.6 Hz)	25.6 (quint) (J=19.9 Hz)	35.0 (s)	128.8	128.7	126.3	141.5
2,2,3,3,4,4-[$^2H_6$] (7d)	180.1	32.6 (quint) (J=19.2 Hz)	25.5 (quint) (J=19.1 Hz)	34.0 (quint) (J=19.7 Hz)	128.5	128.4	126.1	141.2

Scheme 4 illustrates the electrolysis of phenyl acetic [2,2-$^2H_2$]-acid (2a) leading to 1,2-diphenyl [1,1,2,2-$^2H_4$]ethane (6b).

In the presence of pyridine, the yield of the electrolysis of (2a) giving the homo-coupled dimer, the diphenyl [1,1,2,2-$^2H_4$]ethane (6b), was fairly improved from 11% to 47%. We found that employment of sonic waves provides a beneficial effect to obtain (6a); under ultrasonic irradiation, interestingly, the reaction times were reduced more than 3 times and the yield increased to 41%. This means that the washing effect of ultrasonic waves allow the surface of the electrodes to keep clean.

The positions, at which deuterium atoms were introduced, of the deuteriated 4-phenylbutyric acids (7a-d) were confirmed from the ^{13}C spectra. As a representative example, the ^{13}C spectrum of the [2,3-$^2H_2$] acid (7b) is depicted in Figure 1. Table 3 lists the ^{13}C chemical shifts and coupling constants of (7a-d).

The peaks of deuterium-bounded carbon atoms were observed as a triplet or quintet with 19.1-20.1 Hz of coupling constants at 0.1-1.0 ppm higher field than those of non-deuteriated carbon atoms due to isotope effect.

In summary, the four deuteriated 4-phenylbutyric [$^2H_2$]-, [$^2H_4$]-, and [$^2H_6$]-acids could be prepared by use of the crossed Kolbe electrolysis of methyl hydrogen [$^2H_0$]-, [$^2H_2$]-, and [$^2H_4$]-succinates and phenylacetic [$^2H_0$]- and [$^2H_2$]-acids in high isotopic purity.

EXPERIMENTAL

D_2O (99.9 atom %D) was obtained from Division of Merck Frosst Canada inc. and 40% NaOD-D_2O (99.5 atom %D) from Merck & Co., Inc. M.p.s. were determined on a Yanagimoto micro-melting point apparatus and a Mitamula-riken MELT-THERMO instrument and are uncorrected. M.p.s. of the deuteriated compounds were almost the same with those of the corresponding parent compounds. ^1H n.m.r. spectra were recorded on a Nippon Denshi JEOL FX-100 and GSX-270 and ^{13}C n.m.r. spectra on a Nippon Denshi JEOL GSX-270 (67.94 MHz) in $CDCl_3$ or CD_3OD with Me_4Si as an internal reference. Vapor phase chromatography was carried out on a Yanagimoto Gas Chromatograph G-2800 (colum, OV-1; 4 m). Electrolysis

was carried out in a 50 mL beaker at a constant electric current (supplied by Hokuto Electric Potentiostat/ Galvanostat HA 301) using smooth Pt electrodes (1.5 cm × 1.5 cm), which were 2-3 mm apart and totally immersed in a solution. Ultrasonic cleaner of Bransonic B 2200 was used for sonication during electrolysis.

Methyl hydrogen [2,3-$^2H_2$]- (3b) and [2,2,3,3-$^2H_4$]-succinates (3c) were prepared following the reported method.[1]

(3b); colourless plates, m.p. 49-52 °C (lit.,[1] 58 °C), Y. 79%.

(3c); colourless plates, m.p. 51-53 °C (lit.,[1] 58 °C), Y. 75%.

Phenylacetic [2,2-$^2H_2$]acid (2a). Typical procedure.-To a 100 mL flask fitted with a Dimroth condenser, a $CaCl_2$ tube, and a stirring bar was added NaOD-D_2O (10%; 10 mL) prepared from NaOD-D_2O (40%; 2.5 mL) and D_2O (7.5 mL), and phenylacetonitrile (1) (1.0 g, 15 mmol). This operation was performed in a globe box under a nitrogen atmosphere. Then the flask was taken out from the box, and the mixture was heated under reflux for 2 h, cooled to room temperature, and the whole mixture was acidified with conc. aqueous HCl to pH.=1 under cooling and extracted with diethyl ether. The extracts were dried ($MgSO_4$) and concentrated in vacuo to leave a residue, which was recrystallized from hexane to give phenylacetic [2,2-$^2H_2$]acid (2a) (850 mg, 73%), as colourless plates, m.p. 71-72 °C (lit.,[4] 76.5 °C).

Kolbe electrolysis. Deuteriated 4-phenylbutyric acid (7). Typical procedure.-Phenylacetic acid (2b) (500 mg, 3.7 mmol) was dissolved into a solution of Na_2CO_3 (161 mg) in H_2O (20 mL), and the resulting solution was concentrated to dryness. To the solid material obtained was added phenylacetic acid (2b) (520 mg, 3.8 mmol) and methyl hydrogen [2,3-$^2H_2$]succinate (3b) (1.0 g, 7.5 mmol) in methanol (30 mL) and pyridine (5 mL), and the mixture was electrolyzed at a constant electric current of 450 mA for 90 min at room temperature. The reaction mixture was evaporated and extracted with diethyl ether. The extracts were washed with saturated aqueous $NaHCO_3$, dilute aqueous HCl and water, and dried ($MgSO_4$), and evaporated in vacuo to leave a residue. To it was added NaOH (10%; 6 mL), and the alkaline solution was stirred over night and then extracted with diethyl ether. The extracts were dried ($MgSO_4$) and concentrated to dryness to give 1,2-diphenyl-

ethane (6a) (129 mg, 19%). The aqueous layer was acidified with conc. aqueous HCl and extracted with diethyl ether. The extracts were evapotated in vacuo to leave a residue, which was filtered off, and a solid material obtained was washed with benzene, giving adipic [2,3,4,5-$^2H_4$] acid (8b) (64 mg, 11%) as colourless needles, m.p. 150-152 °C (lit.,[5] 152-154 °C as for [$^2H_0$] form). The filtrate and the benzene solution were combined, concentrated, and distilled under a reduced pressure with a Kuhgel rohr apparatus (b.p. 210 °C/10 mmHg) to afford 4-phenylbutyric [2,3-$^2H_2$]acid (7b) (146 mg, 12%) as colourless plates, m.p. 43 -45 °C (lit.,[6] 52 °C as for [$^2H_0$] form).

Diphenyl [1,1,2,2-$^2H_4$]ethane (6b).-A mixture of phenylacetic [2,2-$^2H_2$] acid sodium salt (1.60 g, 10 mmol) prepared following the above method and phenylacetic [2,2-$^2H_2$]acid (2a) (1.38 g,10 mmol) in CH_3OH (30 mL) and pyridine (5 mL) was electrolyzed at a constant electric current of 500 mA for 130 min at room temperature. The reaction mixture was filtered off and the filtrate was concentrated in vacuo. To a residue was added dilute aqueous HCl, and the mixture was extracted with diethyl ether. The extracts were washed with saturated aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated to dryness. A residue was chromatographed on silica gel (Wakogel C-300) with a mixed solvent of benzene and hexane (2:1/v:v), followed by recrystallization from ethanol to give diphenyl [1,1,2,2-$^2H_4$]ethane (6b) (598 mg, 32%) as colourless prisms, m.p. 42-46 °C (lit.,[7] m.p. 52 °C).

Kolbe electrolysis of phenylacetic acid (2b) under ultrasonic irradiation.-After to a solution of Na_2CO_3 (530 mg) in H_2O (20 mL) was dissolved phenylacetic acid (2b) (1.36 g, 10 mmol), the resulting solution was concentrated in vacuo, and a sodium salt obtained and phenylacetic acid (2b) (1.36 g, 10 mmol), pyridine (5 mL), and CH_3OH (30 mL) were added into a 50 mL beaker. The beaker was immersed in an ultrasonic cleaner and under sonication the above mixture was electrolized at a constant current of 450 mA for 160 min. Then the reaction mixture was treated and worked up as described above to afford diphenylethane (6a) (747 mg, 41%) as colourless prisms.

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