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Highly selective and facile synthesis of dihydro- and tetrahydropyridine dicarboxylic acid derivatives using electroreduction as a key step☆

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Abstract—Electroreduction of pyridinedicarboxylic acid derivatives **1a–g** in methanol containing ammonium chloride using a divided cell brought about highly selective hydrogenation to give the corresponding dihydropyridines in good yields. From the electrolysis of dimethyl 2,3- and 2,5-pyridinedicarboxylates **1a**,**c**, only the corresponding 1,2-dihydropyridine derivatives **2a**,**c** were obtained in a regioselective manner while that of 2,4-, 2,6-, and 3,4- disubstituted pyridines **1b**,**d**,**e** afforded the corresponding 1,4-dihydropyridines **2b**,**d**,**e** selectively in good yields. Further hydrogenation of the resultant dihydropyridines by several methods led to the selective and facile formation of the corresponding tetrahydropyridines **6**. Furthermore, Mg-promoted hydrosilylation of the N-acetylated product **5a** gave C-silylated tetrahydropyridines in a stereoselective manner. © 2001 Elsevier Science Ltd. All rights reserved.

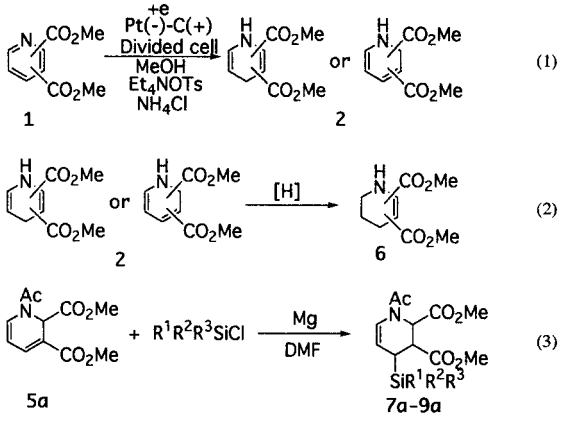
1. Introduction

Direct and selective hydrogenation of pyridine rings is important in the synthesis of dihydro- and tetrahydropyridine skeletons, being useful as synthetic intermediates of nitrogen-containing biologically active substances.[1] Among the dihydropyridine skeletons, 3,5-disubstituted-1,4-dihydropyridine derivatives can be prepared by base-catalyzed condensation between aromatic aldehydes, 1,3-dicarbonyl compounds and amines including ammonia,[2] reduction of pyridinium salts [3–5] or photochemical cycloaddition.[6]

Most of the known methods for this purpose, however, have suffered from some disadvantages, particularly unsatisfactory yield and/or formation of mixtures of the regioisomers or that of mixtures of dihydro-, tetrahydro- and hexahydro-isomers.[7–9] For example, the $NaBH_3CN$-reduction of dimethyl and diethyl 3,5-pyridinedicarboxylates was reported to afford the corresponding 1,4-dihydro-isomers selectively in 77% yields. A mixture of the 1,4- and 1,2-dihydro-isomers (the ratio of 1,4- and 1,2-dihydro-isomers: 78–79/22–21) was obtained in 54–35% yields by the catalytic hydrogenation or diborane-reduction of dimethyl and diethyl 3,5-pyridinedicarboxylates.[9] Electroreduction of pyridines in aqueous solution gave the corresponding piperidines,[10,11] or 1,4-dihydro-isomers[12] although the processes were generally inferior to catalytic hydrogenation or base-catalyzed condensation.[2]

We have already reported that regioselective and efficient hydrogenation of ring-substituted phthalic acid derivatives was successfully accomplished by electroreduction in aqueous acidic solvent to give the corresponding 1,2-dihydrophthalic acid derivatives in good to excellent yields.[13]

In this study, we present selective, facile and efficient synthesis of dihydropyridine derivatives **2** from pyridinedicarboxylic acid derivatives **1** by electroreduction in methanol containing ammonium chloride using a divided cell (Eq. 1



Scheme 1.

☆ See Ref. 1.

Keywords: electroreduction; dihydropyridinedicarboxylic acids; hydrogenation.

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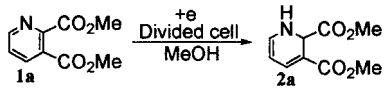
Table 1. Electroreductve hydrogenation of dimethyl 2,3-pyridinedicarboxylate **1a**



1a **2a**

Entry	Supporting electrolyte	Cathode material	Temperature	Additive	Yield of **2a**
1	H_2SO_4	Pt	rt[a]	–	0
2	KF	Pt	rt	–	0
3	AcOH–NEt_3	Pt	rt	–	19
4	Et_4NOTs	Pt	rt	–	36
5	Et_4NOTs	SUS	rt	–	32
6	Et_4NOTs	C	rt	–	0
7	Et_4NOTs	Pb	rt	–	0
8	Et_4NOTs	Pt	5–10°C	–	48
9	Et_4NOTs	Pt	5–10°C	NH_4Cl	83
10	Et_4NOTs	Pt	5–10°C	AcOH	89

[a] rt: Room temperature; current density: 15–20 mA/cm^2

in Scheme 1).[14] Subsequent reduction of some of the products **2** by various methods brought about selective transformation to the corresponding tetrahydropyridines **6** (Eq. 2) which were also useful nitrogen-containing heterocycles.[15] Furthermore, Mg-promoted reductive C-silylation of dimethyl *N*-acetyl-1,2-dihydropyridine dicarboxylate **5a** with various trialkylchlorosilanes in DMF led to regio- and stereoselective hydrosilylation to give the corresponding 4-trialkylsilylated tetrahydropyridines **7a**–**9a** in good yields (Eq. 3).

2. Results and discussion

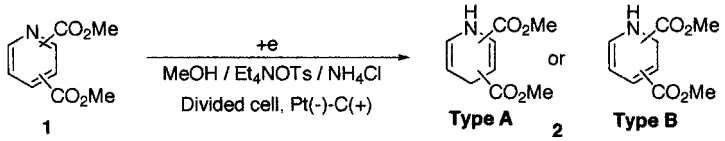
2.1. Electroreduction of dimethyl pyridinedicarboxylates (1a–e)

Electroreduction of five kinds of dimethyl pyridinedicarboxylates (2,3-$(CO_2Me)_2$(**1a**), 2,4-$(CO_2Me)_2$(**1b**), 2,5-$(CO_2Me)_2$(**1c**), 2,6-$(CO_2Me)_2$(**1d**), and 3,4-$(CO_2Me)_2$(**1e**)) in methanol was usually carried out using a divided cell under the constant current conditions (current density: 15–20 mA/cm^2). Some reaction conditions were studied using dimethyl 2,3-pyridinedicarboxylate (**1a**) as a model starting substrate (Table 1).

Use of tetraethylammonium *p*-toluenesulfonate (Et_4NOTs) as the supporting electrolyte and platinum (Pt) as the cathode material gave dimethyl 1,2-dihydro-2,3-pyridinedicarboxylate (**2a**) as the main product in a relatively better (36–89%) yield (Entries 1–10). Moreover, reaction temperature and pH of the reaction medium gave large influences on yield and selectivity of the product **2a** (Entries 4, 8–10). Thus, **2a** was obtained in a 36% yield from electroreduction of **1a** at room temperature without any additives while the same reaction at 5–10°C gave **2a** in a 48% yield (Entries 4, 8). It was noteworthy that the addition of a weak acid such as NH_4Cl or acetic acid into the reaction system brought about the increase in the yield of **2a** from 48 to 83–89% (Entries 8–10). This remarkable improvement may be elucidated by the fact that the weakly acidic conditions inhibited the decomposition of the product **2a**, which was unstable under the basic conditions, possibly caused by electrogenerated bases.

Under the optimum conditions, electroreduction of various ring-substituted dimethyl pyridinedicarboxylates (**1a**–**e**) led to highly selective and facile hydrogenation to give the corresponding dihydropyridinedicarboxylates (**2a**–**e**) in good to excellent yields (Table 2). A remarkable high regioselectivity was observed in the present electrochemical hydrogenation. Thus, dimethyl 1,2-dihydro 2,3- and

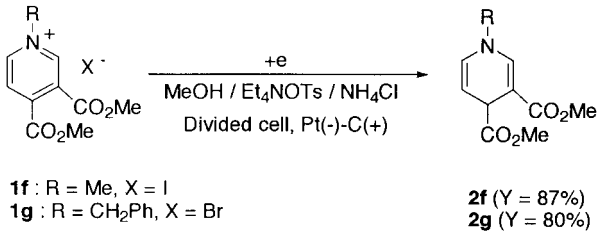
Table 2. Electrochemical reduction of various pyridinecarboxylic acid derivatives



1 **2**

Substrate		Reduction potential (V vs Ag/AgCl)	Product		
			Type		Yield (%)
Dimethyl 2,3-Pyridinedicarboxylate	**1a**	−1.98	**B**	**2a**	83
Dimethyl 2,4-Pyridinedicarboxylate	**1b**	−1.71	**A**	**2b**	67
Dimethyl 2,5-Pyridinedicarboxylate	**1c**	−1.60	**B**	**2c**	77
Dimethyl 2,6-Pyridinedicarboxylate	**1d**	−1.96	**A**	**2d**	92
Dimethyl 3,4-Pyridinedicarboxylate	**1e**	−1.87	**A**	**2e**	79

Preparative electrolysis was carried out in methanol containing Et_4NOTs and NH_4Cl, using a divided cell equipped with a Pt plate as the cathode, a carbon rod as the anode, and ceramic cylinder as a diaphragm at 5–10°C under the constant current conditions.



Scheme 2.

2,5-pyridinedicarboxylates (**2a** and **2c**) were obtained from the electroreduction of dimethyl 2,3- and 2,5-pyridinedicarboxylates (**1a** and **1c**) in 83 and 77% yields, respectively. In contrast to this result, dimethyl 1,4-dihydro 2,4-, 2,6- and 3,4-pyridinedicarboxylates (**2b**, **2d** and **2e**) were afforded from the same reaction of dimethyl 2,4-, 2,6- and 3,4-pyridinedicarboxylates (**1b**, **1d** and **1e**) in 67, 92 and 79% yields, respectively. It may be interesting that the nitrogen atoms of all the products (**2a**–**e**) were protonated. Pyridinium salts such as *N*-methyl (**1f**) and *N*-benzyl pyridinium salts (**1g**) efficiently underwent hydrogenation by electroreduction to give the corresponding 1,4-dihydro-products **2f** and **2g** in 87 and 80% yields, respectively (Scheme 2). Methyl nicotinate could not be hydrogenated because of its more negative reduction potential. Among these dihydro-products, **2b** and **2c** were very unstable at room temperature, and were easily subjected to air-oxidation to the original pyridine compounds.

Cyclic voltammogram of these pyridine compounds **1a**–**e** showed that they were readily accessible to usual electroreduction (Fig. 1). Thus, the reductive potentials of **1a**, **1d** and **1e** were −1.98, −1.96 and −1.87 V (vs Ag/AgCl), respectively, and their reversal oxidation peaks were negligible. On the other hand, the reduction potentials of **1b** and **1c** indicated more positive values, that is, −1.71 and −1.60 V (vs Ag/AgCl), respectively, their oxidation peaks being observed in part. These results show that the former compounds are relatively difficult to reduce. Therefore, we suggest that the electrogenerated radical anions abstract protons very quickly from the medium methanol. Conversely, the latter compounds may give relatively stable anionic species whose lifetime is sufficiently long since the corresponding oxidation peak can be observed on the reverse cyclic voltammetric sweep.

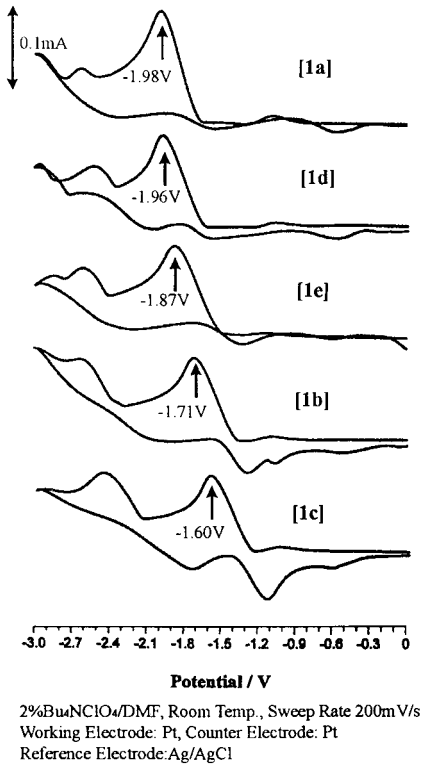
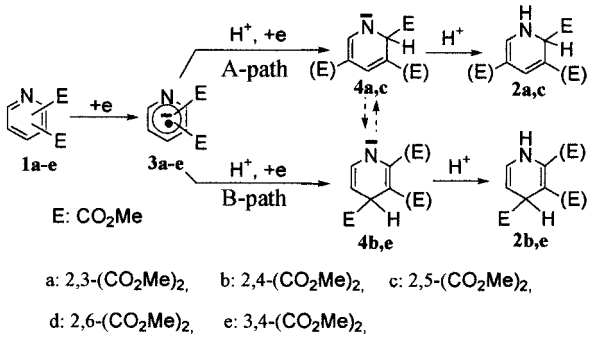


Figure 1. Cyclic voltammogram of various pyridinedicarboxylic acid derivatives.



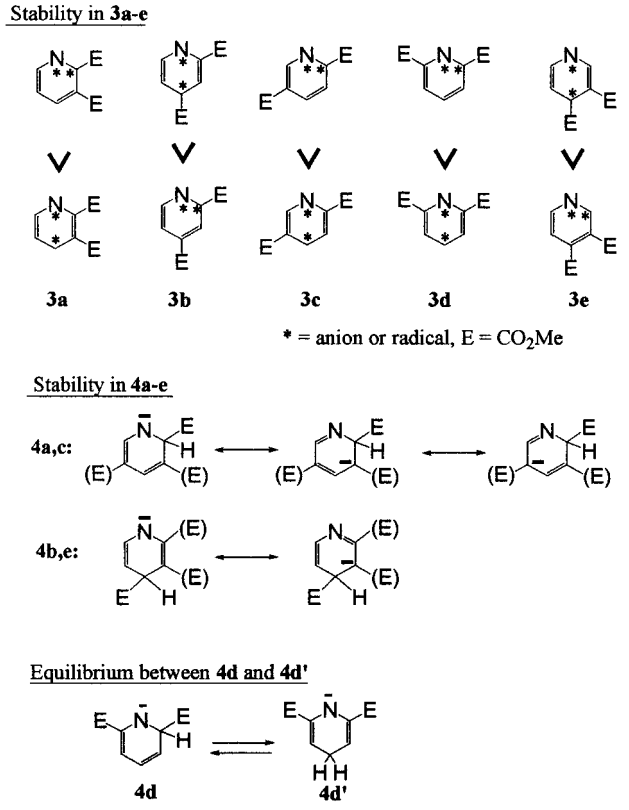
Scheme 3.

One of the plausible mechanism may be postulated for the present hydrogenation of pyridinedicarboxylates **1** by electroreduction, as shown in Scheme 3. Particularly, the difference in regioselectivity of the hydrogenated position of **2** depends on the position of the carboxylate groups in **1**.

The first electron transfer to the starting substrates **1** generates the corresponding radical anions **3**, which can be protonated at the 2-position (A-path) or the 4-position (B-path) of the pyridine ring, followed by the second electron transfer affording the corresponding the hydrogenated *N*-anion species **4a**,**c** or **4b**,**d**,**e**. Then, the final products, 1,2- and 1,4-dihydrogenated isomers, **2a**,**c** and **2b**,**d**,**e**, were formed through the subsequent protonation to **4a**,**c** and **4b**,**d**,**e**, respectively.

The most important effect for regioselectivity in the hydrogenation of **1** may be speculated to be the distribution of anion or radical on the nitrogen atom and each of the carbon atoms of the pyridine ring in radical anions (or dianions) **3** and *N*-anion species **4**. Thus, for each of **3a**–**e**, the structures shown at the upper row of Scheme 4 would be more important for protonation than those of the lower row, in which anion or radical on the carbon atom possessing a methoxycarbonyl group (*E*) and at the more remote position from the nitrogen atom would be more stable. On the basis of this hypothesis, 1,2-dihydro-isomers **2a**,**c** and 1,4-dihydro-isomers **2b**,**e** would be formed from those structures according to the Scheme 4.

Since **1d** showed rather negative reduction potential, both of the radical anion **3d** and the nitrogen anion species **4d** are so unstable, that the more stable product, 1,4-dihydro-isomer



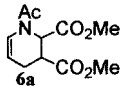
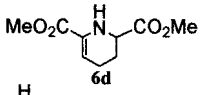
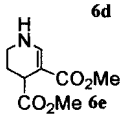
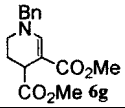
Scheme 4.

2d, would be formed exclusively through thermodynamic control between **4d** and **4d′** as shown in Scheme 4.

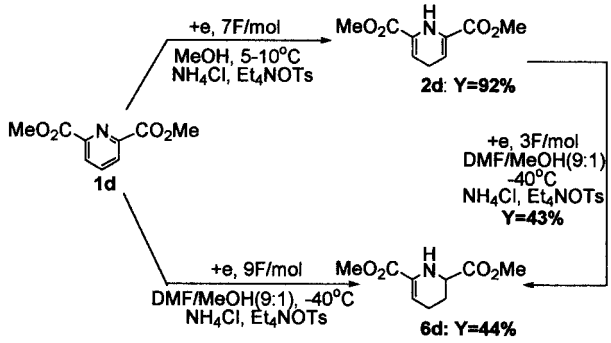
2.2. Selective transformation to tetrahydropyridinedicarboxylates 6[15]

As one of synthetic applications, some of dihydropyridines **5a**,**2d**,**e**,**g** obtained were transformed selectively to the corresponding tetrahydropyridines **6a**,**d**,**e**,**g** by three kinds of reduction methods, i.e. $NaBH_4$ reduction (Method A),

Table 3. The synthesis of tetrahydropyridine by selective hydrogenation of dihydropyridine

Substrate	Method[a]	Tetrahydropyridine/%	
5a	A	 **6a**	81 (*cis*/*trans*=3/2)
	B		Complex mixture
	C		31 (*cis*/*trans*=2/5)
2d	A	 **6d**	Mixture
	B		43
	C		12
2e	A	 **6e**	No reaction
	B		No reaction
	C		98
2g	A	 **6g**	No reaction
	B		No reaction
	C		100

[a] Method A: $NaBH_4$, THF, room temperature. Method B: electroreduction (Pt–C, divided cell, DMF/MeOH=9/1, Et_4NOTs, NH_4Cl, −40°C. Method C: H_2 (1 atm), Rh-C, EtOH (AcOEt was used in the case of **2d**).



Scheme 5.

electroreduction (Method B) and catalytic hydrogenation (Method C), as shown in Table 3.

In Method A, **5a**, prepared by usual N-acetylation of **2a** in a 60% yield, was hydrogenated selectively in THF to give dimethyl 1,2,3,4-tetrahydropyridine-2,3-dicarboxylates **6a** in a 81% yield. However, the reduction of **2d** by Method A yielded a mixture of tetra- and hexa-hydrogenated products while Method B (electroreduction in a mixed solvent of DMF/MeOH=9/1) for **2d** afforded dimethyl 1,2,3,4-tetrahydropyridine-2,6-dicarboxylate **6d** selectively in a 43% yield.

Moreover, Method C (catalytic hydrogenation by Rh-C catalyst) gave the corresponding tetrahydropyridines among these three methods of all the dihydropyridines **5a**,**2d**,**e**,**g** in a wide range of yields. Especially, the reduction of the dihydropyridines **2e** and **2g** afforded the corresponding tetrahydropyridine **6e** and **6g** quantitatively only by the method C among these three methods.

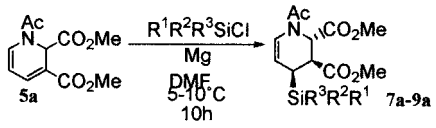
Interestingly, the electroreduction of dimethyl pyridine-2,6-dicarboxylate **1d** gave different products depending upon the reaction conditions. Thus, the reduction in methanol at 5–10°C gave dihydropyridine **2d** in a 92% yield. On the other hand, electroreduction in DMF/MeOH (9/1) at −40°C resulted in direct formation of tetrahydropyridine (44% yield), while that at 5–10°C led to exclusive formation of tarry products (Scheme 5).

2.3. Stereo- and regioselective hydrosilylation of dimethyl *N*-acetyl-1,2-dihydropyridine-2,3-dicarboxylate(5a)

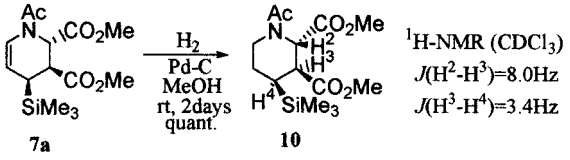
We have already reported that the Mg-promoted hydrosilylation of α,β-unsaturated esters such as ethyl cinnamate, with trialkylchlorosilanes in DMF effects reductive cross-coupling to give the corresponding β-silylated compounds in good to excellent yields.[16]

It was found that when the reaction system was applied to dihydropyridine **5a** that has a conjugated diene skeleton, tetrahydropyridines **7a**–**9a** were obtained as the sole products regio- and stereoselectively. As shown in Table 4, the yield of the silylated product **7a** is dependent upon reaction temperatures and the amounts of trialkylchlorosilanes. Thus, the reaction at 5–10°C gave better yield of the product **7a** than that at room temperature (Entries 1 and

Table 4. Mg-promoted hydrosilylation of dihydropyridine **5a**



Entry	$R^1R^2R^3SiCl$ (equiv.)	Mg/equiv.	Temperature	Product (yield %)
1	Me_3SiCl (10)	5	rt	**7a** (35)
2	Me_3SiCl (10)	5	5–10°C	**7a** (64)
3	Me_3SiCl (7)	3.5	5–10°C	**7a** (40)
4	Me_3SiCl (3)	1.5	5–10°C	**7a** (23)
5	$EtMe_2SiCl$ (10)	5	5–10°C	**8a** (51)
6	Et_3SiCl (10)	5	5–10°C	**9a** (32)

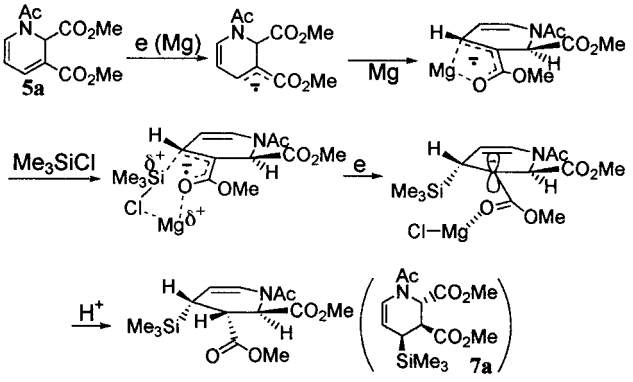


Scheme 6.

2), and the yield of **7a** increased with the increase in the amount of trimethylchlorosilane (Entries 2–4). Use of ethyldimethyl- and triethylchlorosilane instead of trimethylchlorosilane under the similar reaction conditions gave the analogous β-silylated tetrahydropyridines **8a**, **9a** as the sole products but in decreased yields (Entries 5,6).

The stereochemistry of the 4-silylated product **7** was determined by ^1H NMR spectrometry of the hydrogenated piperidine **10**, as shown in Scheme 6. The coupling constant between H^2 and H^3 was 8.0 Hz and that between H^3 and H^4 was 3.4 Hz. From these results, the stereochemistry of H^2–H^3 and H^3–H^4 was determined to be *trans* and *cis* conformation, respectively.[17]

From the experimental results, the following reaction mechanism may be proposed for the present Mg-promoted regio- and stereoselective β-silylation of dihydropyridine **5a**. The first electron transfer from Mg-metal to dihydropyridine **5a** generated the anion radical coordinated with an Mg^{2+} cation from the sterically less hindered opposite side of the carbomethoxy group at the 2-position. Subsequently, electrophile attack of trimethylchlorosilane to the β-carbon occurred from the opposite side of the carbomethoxy group



Scheme 7.

at the 2-position possessing coordination of Me_3SiCl with the Mg^{2+} cation to generate a more stable α-carbanion after very fast or almost simultanous second electron transfer. And it is considered that the product is finally formed by subsequent protonation from the sterically less hindered opposite side of the Mg^{2+} ion (Scheme 7).

In conclusion, a new method for synthesis of dimethyl 1,2- or 1,4-dihydropyridine-dicarboxylates has been successfully developed through electroreduction of dimethyl pyridinedicarboxylates in this study. Particularly, 1,2-dihydroisomers have been first synthesized by this electrochemical method, which is characterized with good yield, convenient procedure, mild conditions, high chemoselectivity and specific regioselectivity depending on the position of the carboxylate groups in the starting substrates. Furthermore, the corresponding C-silylated tetrahydropyridines were obtained by Mg-promoted regio- and stereoselective transformation of the resultant 1,2-dihydro-derivative **5a**.

3. Experimental

3.1. General

Methanol (MeOH) was distilled from Mg. *N*,*N*-Dimethylformamide (DMF) was distilled from CaH_2. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ prior to use. Unless otherwise mentioned, all the materials commercially obtained were used without further purification. Organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure on a rotary evaporator. Flash chromatography was carried out using Merck 60 (Mesh 230–400) silica gel. Reactant and chromatography fractions were analyzed using precoated silica gel 60 F_{254} plates (Merck). ^1H NMR spectra at 400 MHz were measured in the $CDCl_3$ solutions. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane (0 ppm). The apparatus of cyclic voltammetry was HABF501 (Hokuto Denko).

3.2. Cyclic voltammetry analysis

Cyclic voltammogram was measured in a beaker-type cell equipped with Pt electrodes as the both electrodes, a reference electrode (Ag/AgCl) at room temperature. The solvent was DMF containing 2 wt% Bu_4NClO_4 as a supporting electrolyte. Sweep rate was 200 mV/s.

3.3. General procedure for the synthesis of dimethyl dihydropyridinedicarboxylates 2a–2g

Electroreduction of pyridinedicarboxylic acid derivatives (**1a–g**) (5 mmol) was carried out in methanol (40 ml) containing Et_4NOTs (2.0 g) as the supporting electrolyte and NH_4Cl (0.25 g) as the pH buffer at 5–10°C under the constant current conditions (current density; 15–20 mA/cm^2) using a divided cell equipped with a Pt plate (12 cm^2) as the cathode and a carbon rod as the anode, and a ceramic cylinder as the diaphragm until 7 F/mol of electricity passed through the reaction system. After the electrolysis, the solution was poured into saturated aqueous $NaHCO_3$ and then the solution was extracted with AcOEt. The organic layer was washed with H_2O, saturated aqueous NaCl, dried, filtered and evaporated to give the crude products. Column chromatographic treatment of the reaction mixture gave the dihydropyridine derivatives **2** exclusively as the almost sole products.

3.3.1. Dimethyl 1,2-dihydro-2,3-pyridinedicarboxylate (2a). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.69 (s, 3H), 3.78 (s, 3H), 5.03 (ddd, 1H, J=1.5, 6.3, 6.4 Hz), 5.16 (d, 1H, J=3.4 Hz), 5.36 (m, 1H), 6.68 (dd, 1H, J=5.8, 6.4 Hz), 7.19 (d, 1H, J=6.3 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ 51.5, 51.6, 52.3, 95.8, 108.2, 135.3, 139.2, 166.6, 173.4 ppm. IR (neat) 3320, 1730, 1455, 1440, 1250 cm^{-1}. MS (EI) m/z 197 (M^+, 2), 166 (3), 138 (100), 78 (29). Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.76; H, 5.49; N, 7.25.

3.3.2. Dimethyl 1,4-dihydro-2,4-pyridinedicarboxylate (2b). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.73 (s, 3H), 3.80 (s, 3H), 4.12 (dd, 1H, J=3.6, 4.0 Hz), 4.51 (m, 1H), 5.63 (ddd, 1H, J=2.0, 2.8, 4.0 Hz), 5.88 (bs, 1H), 6.20 (dd, 1H, J=4.8, 8.0 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ 40.0, 52.2, 52.3, 93.8, 102.9, 127.1, 129.8, 163.4, 173.4 ppm. IR (neat) 3405, 2950, 1730, 1440, 1260, 1260 cm^{-1}. MS (EI) m/z 195 ($(M-H_2)^+$, 2), 137 (100), 59 (35). **2b** was not stable enough to perform elemental analysis.

3.3.3. Dimethyl 1,2-dihydro-2,5-pyridinedicarboxylate (2c). ^{1}H NMR($CDCl_3$, 400 MHz): δ 3.69 (s, 3H), 3.78 (s, 3H), 4.90 (ddd, 1H, J=1.6, 2.0, 4.0 Hz), 5.26 (ddd, 1H, J=2.0, 4.0, 10.0 Hz), 5.53 (bs, 1H), 6.47 (ddd, 1H, J=1.6, 2.0, 10.0 Hz), 7.48 (dd, 1H, J=1.6, 6.4 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ 50.4, 52.2, 54.1, 97.2, 108.0, 123.4, 143.0, 166.3, 171.5 ppm. IR (neat) 3375, 2950, 1730, 1680, 1640, 1440, 1290, 1110 cm^{-1}. MS (EI) m/z 195 ($(M-H_2)^+$, 1) 137 (100), 59 (29). **2c** was not stable enough to perform elemental analysis.

3.3.4. Dimethyl 1,4-dihydro-2,6-pyridinedicarboxylate (2d). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.20 (t, 2H, J=3.9 Hz), 3.80 (s, 3H), 5.48 (dt, 2H, J=1.5, 3.9 Hz), 6.11 (broad s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 24.2, 52.0, 104.9, 130.5, 162.9 ppm. IR (nujol) 3320, 1730, 1455, 1440, 1250 cm^{-1}. MS (EI) m/z 196 ($(M-H)^+$, 100), 136 (96), 105 (48), 78 (61). Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.99; H, 5,80; N, 7.33. Mp 74.0–75.8°C.

3.3.5. Dimethyl 1,4-dihydro-3,4-pyridinedicarboxylate (2e).[6] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.68 (s, 3H), 3.71 (s, 3H), 7.27 (d, 1H, J=4.8 Hz), 4.83 (dd, 1H, J=4.8, 7.8 Hz), 6.08 (dd, 1H, J=4.4, 7.8 Hz), 6.57 (bs, 1H), 7.35 (d, 1H, J=5.8 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ 39.5, 51.1, 52.1, 97.0, 100.7, 125.4, 137.7, 168.2, 174.2, 207.1 ppm. IR (nujol) 3330, 1730, 1660, 1510, 1440, 1235, 1100 cm^{-1}. MS (EI) m/z 197 (M^+, 3), 138 (100), 78 (83), 52 (62). Mp 82.0–84.0°C.

3.3.6. Dimethyl *N*-Methyl-1,4-dihydro-3,4-pyridinedicarboxylate (2f). ^{1}H NMR ($CDCl_3$,400 MHz): δ 2.98 (s, 3H), 3.61 (s, 3H), 3.63 (s, 3H), 4.16 (d, 1H, J=4.8 Hz), 4.81 (dd, 1H, J=4.8, 8.0 Hz), 5.81 (dd, 1H, J=1.6, 8.0 Hz), 7.14 (d, 1H, J=1.6 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ 38.9, 40.8, 50.9, 52.0, 96.6, 101.9, 130.0, 141.5, 167.7, 173.6 ppm. IR (neat) 2950, 1740, 1690, 1635, 1590, 1440, 1310, 1260, 1200, 700 cm^{-1}. MS (EI) m/z 211 (M^+, 2), 152 (100), 92 (49). Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 57.00; H, 6.01; N, 6.54.

3.3.7. Dimethyl *N*-benzyl-1,4-dihydro-3,4-pyridinedicarboxylate (2g). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.68 (s, 3H), 3.72 (s, 3H), 4.28 (d, 1H, J=4.9 Hz), 4.40 (s, 2H), 4.92 (ddd, 1H, J=1.5, 4.9, 7.8 Hz), 5.91 (dd, 1H, J=1.5, 7.8 Hz), 7.34 (s, 1H), 7.21–7.38 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$): δ 39.7, 51.5, 52.5, 57.9, 97.9, 102.9, 127.3, 128.3, 129.3, 129.7, 136.9, 141.7, 168.2, 173.9 ppm. IR (nujol) 2950, 1740, 1700, 1680, 1600, 1210, 1170 cm^{-1}. MS (EI) m/z 287 (M^+, 94), 91 (100), 65 (40). Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.92; H, 6.12; N, 4.68. Mp 68.0–68.9°C.

3.4. The preparation of dimethyl *N*-acetyl-1,2-dihydro-2,3-pyridinedicarboxylate (5a)

To a slurry of NaH (1.46 g, 60% oil suspension, 24.4 mmol, washed twice with hexane) in DMF (20 ml) was added the DMF (20 ml) solution of **2a** 4.0 g: 20.3 mmol) at −40°C. After 10 min, the solution of acetyl chloride (1.91 g: 24.4 mmol) was added and stirred for 1.5 h at −40°C. The reaction mixture was poured into cold water and extracted with Et_2O. Organic layer was washed with H_2O, saturated aqueous NaCl, dried, filtered and evaporated to give crude mixture. Recrystallization from a mixed solvent of hexane–AcOEt gave **5a** as a pale yellow crystal (yield 60%).

3.4.1. Dimethyl *N*-acetyl-1,2-dihydro-2,3-pyridinedicarboxylate (5a). ^{1}H NMR ($CDCl_3$,400 MHz): δ 2.33 (s, 3H), 3.68 (s, 3H), 3.83 (s, 3H), 5.54 (dd, 1H, J=5.9, 7.3 Hz), 6.41 (s, 1H), 6.96 (d, J=7.3 Hz, 1H), 7.13 (d, 1H, J=5.9 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ 21.3, 50.9, 52.4, 53.1, 105.9, 119.3, 131.4, 132.2, 165.5, 169.6, 169.8 ppm. IR (nujol) 1740, 1705, 1690, 1550, 1440, 1320, 1300, 1230 cm^{-1}. MS (EI) m/z 239 (M^+, 1), 180 (30), 138 (100), 78 (94), 43 (86). Anal. Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.86; O, 33.44. Found: C, 55.32; H, 5.60; N, 5.62. Mp 80.5–81.7°C.

3.5. Reduction of dihydropyridines using $NaBH_4$ (Method A)

To a solution of dihydropyridine (5 mmol) in THF (10 ml) was added $NaBH_4$ (0.152 g: 4 mmol), and stirred for 14 h at

room temperature. The reaction mixture was poured into aqueous NH_4Cl and extracted with AcOEt. The organic layer was washed with H_2O, saturated aqueous NaCl, dried, filtered, evaporated to give the crude mixture. The crude mixture was purified by column chromatography (hexane–AcOEt).

3.6. Electroreduction of dihydropyridines (Method B)

Electroreduction of dihydropyridine (5 mmol) was carried out in a mixed solvent of DMF and MeOH (9/1) (40 ml) containing Et_4NOTs (2.0 g) as the supporting electrolyte and NH_4Cl (0.25 g) as the pH buffer at 5–10°C under the constant current conditions (current density; 17 mA/cm^2) using a divided cell equipped with a Pt plate (12 cm^2) as the cathode and a carbon rod as the anode, and a ceramic cylinder as the diaphragm until 4 F/mol of electricity passed through the reaction system. The procedure for work-up was the same as that for the preparation of dihydropyridines. The crude mixture was purified by column chromatography (hexane–AcOEt).

3.7. Catalytic hydrogenation of dihydropyridines (Method C)

To a solution of dihydropyridine (1 mmol) in EtOH (40 ml) was added 5%-Rh/C (10 mg) and stirred until the dihydropyridine was consumed under the H_2 atmosphere (1 atm) at room temperature. The reaction solution was filtered through Celite and evaporated to give the crude mixture. The crude mixture was purified by column chromatography (hexane–AcOEt).

3.7.1. Dimethyl *N*-acetyl-1,2,3,4-tetrahydro-2,3-pyridinedicarboxylate (6a). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.23 (s, 3H), 2.31 (m, 2H), 2.82 (ddd, 1H, J=4.0, 8.8, 10.0 Hz), 3.65 (s, 3H), 3.75 (s, 3H), 4.99 (ddd, 1H, J=3.6, 4.0, 8.4 Hz), 5.87 (d, 1H, J=4.0 Hz), 6.60 (d, 1H, J=8.4 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ 21.3, 21.4, 39.9, 52.5, 52.6, 52.6, 106.4, 124.8, 168.1, 169.2, 171.3 ppm. IR (neat) 2950, 1745, 1680, 1650, 1420, 1380, 1220, 1015 cm^{-1}. MS (EI) m/z 241 (M$^+$, 17), 140 (100), 80 (74). Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.90; H, 6.40; N, 5.70.

3.7.2. Dimethyl 1,4,5,6-tetrahydro-2,6-pyridinedicarboxylate (6d). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.93–1.96 (m, 1H), 2.11–2.15 (m, 1H), 2.21–2.27 (m, 2H), 3.75 (s, 3H), 3.78 (s, 3H), 3.92–3.93 (m, 1H), 4.41 (bs, 1H), 5.71 (t, 1H, J=4.1 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ 21.4, 24.3, 52.3, 52.6, 53.7, 107.4, 133.0, 164.9, 173.5 ppm. IR (nujol) 3420, 2950, 1740, 1720, 1645, 1440, 1270, 1220 cm^{-1}. MS (EI) m/z 199 (M$^+$, 21), 140 (97), 108 (100), 80 (62), 53 (44). Anal. Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.38; H, 6.65; N, 7.12. Mp 37.0–38.1°C.

3.7.3. Dimethyl 1,4,5,6-tetrahydro-3,4-pyridinedicarboxylate (6e). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.84 (dddd, 1H, J=5.2, 5.6, 10.8, 13.6 Hz), 2.15 (ddd, 1H, J=3.0, 6.8, 13.6 Hz), 3.19–3.28 (m, 2H), 3.59 (dd, 1H, J=3.0, 5.6 Hz), 3.66 (s, 3H), 3.73 (s, 3H), 5.14 (bs, 1H), 7.60 (d, 1H, J=6.4 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ 23.6, 36.7, 37.6, 50.6, 51.9, 92.8, 143.93, 168.4, 175.7 ppm. IR (neat) 3375, 2950, 1730, 1670, 1615, 1440, 1350, 1180, 1100 cm^{-1}. MS (EI) m/z 199 (M$^+$, 13), 140 (100), 80 (45). Anal. Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.00; H, 6.83; N, 7.22.

3.7.4. Dimethyl *N*-benzyl-1,4,5,6-tetrahydro-3,4-pyridinedicarboxylate (6g). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.81 (ddt, 1H, J=4.4, 5.6, 13.6 Hz), 2.07 (ddt, 1H, J=3.2, 3.6, 13.6 Hz), 2.97 (ddd, 1H, J=3.2, 4.4, 12.4 Hz), 3.18 (ddd, 1H, J=3.2, 5.6, 12.4 Hz), 3.58 (dd, 1H, J=3.6, 4.4 Hz), 3.68 (s, 3H), 3.69 (s, 3H), 4.41 (s, 2H), 7.21–7.38 (m, 5H), 7.67 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 24.0, 36.0, 42.3, 50.7, 52.0, 59.7, 92.4, 127.2, 127.8, 128.8, 136.4, 146.9, 168.2, 175.4 ppm. IR (neat) 2950, 1740, 1680, 1620, 1430, 1360, 1275, 1190, 1160 cm^{-1}. MS (EI) m/z 289 (M$^+$, 11), 230 (92), 91 (100). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.49; H, 6.85; N, 4.99.

3.8. Direct preparation of 6d by electroreduction of 1d

The electrolysis conditions were almost the same as those for Method B except temperature (−40°C) and supplied electricity (9 F/mol).

3.9. General procedure of the Mg-promoted hydrosilylation of 5a

To a suspension of trialkylchlorosilane (25 mmol) and Mg turning (0.3 g: 12.5 mmol) in DMF (10 ml) was added dropwise a solution of **5a** (0.7 g: 2.5 mmol) in DMF (10 ml) at 5°C, and stirring was continued until **5a** was consumed completely at 5°C. The reaction mixture was poured into saturated $NaHCO_3$. Organic layer was extracted with AcOEt and washed with H_2O, saturated aqueous NaCl, dried, filtered and evaporated to give the crude products, which was purified by column chromatography (hexane–AcOEt).

3.9.1. *N*-Acetyl-4-trimethylsilyl-2,3-dicarbomethoxy-1,2,3,4-tetrahydropyridine (7a). ^{1}H NMR ($CDCl_3$, 400 MHz): δ −0.01 (s, 9H), 2.04 (bs, 1H), 2.18 (s, 3H), 3.18–3.21 (m, 1H), 3.64 (s, 3H), 3.66 (s, 3H), 4.95–4.99 (m, 1H), 5.36–5.37 (m, 1H), 6.54 (d, 1H, J=8.3 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ −1.2, 21.1, 25.0, 42.6, 51.4, 52.0, 53.2, 108.6, 122.5, 167.9, 169.0, 170.4 ppm. IR (neat) 2950, 1750, 1680, 1650, 1380, 1250, 1220, 1020 cm^{-1}. MS (EI) m/z 313 (M$^+$, 3), 80 (73), 43 (100). Anal. Calcd for $C_{14}H_{23}NO_5Si$: C, 53.65; H, 7.40; N, 4.47. Found: C, 53.48; H, 7.53; N, 4.52.

3.9.2. *N*-Acetyl-4-ethyldimethylsilyl-2,3-dicarbomethoxy-1,2,3,4-tetrahydropyridine (8a). ^{1}H NMR ($CDCl_3$, 400 MHz): δ −0.04 (s, 3H), 0.01 (s, 3H), 0.51–0.59 (m, 2H), 0.90–0.95 (m, 3H), 2.06–2.09 (m, 1H), 2.21 (s, 3H), 3.24 (dd, 1H, J=4.8, 6.0 Hz), 3.67 (s, 3H), 3.68 (s, 3H), 4.99 (dd, 1H, J=4.4, 8.4 Hz), 5.30 (d, 1H, J=4.4 Hz), 6.57 (dd, 1H, J=2.4, 8.4 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ −3.7, −3.6, 7.4, 7.5, 21.5, 24.1, 43.0, 51.7, 52.4, 54.1, 108.9, 123.1, 168.4, 169.4, 170.7 ppm. IR (neat) 2950, 1750, 1740, 1670, 1640, 1410, 1250, 1010 cm^{-1}. MS (EI) m/z 327 (M$^+$, 18), 268 (34), 80 (80), 59 (100). Anal. Calcd for $C_{15}H_{25}NO_5Si$: C, 55.02; H, 7.70; N, 4.28. Found: C, 54.94; H, 7.60; N, 4.37.

3.9.3. *N*-Acetyl-4-triethylsilyl-2,3-dicarbomethoxy-1,2,3,4-tetrahydropyridine (9a). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.60 (q, 6H, J=7.8 Hz), 0.96 (t, 9H, J=7.8 Hz), 2.03–2.06 (m, 1H), 2.21 (s, 3H), 3.26 (dd, 1H, J=4.9, 5.4 Hz), 3.65 (s, 3H), 3.70 (s, 3H), 4.81 (d, 1H, J=4.9 Hz), 5.03 (dd, 1H, J=3.4, 7.8 Hz), 6.61 (dd, 1H, J=2.4, 7.8 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ 2.9, 7.6, 21.7, 21.9, 42.5, 51.7, 52.4, 56.5, 108.1, 124.3, 168.8, 169.3, 170.9 ppm. IR (neat) 2950, 2875, 1740, 1680, 1640, 1440, 1380, 1260, 1210, 1010 cm^{-1}. MS (EI) *m/z* 355 (M^+, 25), 296 (49), 122 (53), 80 (96), 59 (100). Anal. Calcd for $C_{17}H_{29}NO_5Si$: C, 57.43; H, 8.22; N, 3.94. Found: C, 57.29; H, 8.12; N, 3.85.

3.9.4. *N*-Acetyl-2,3-dicarbomethoxy-4-trimethylsilyl-piperidine (10). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.01 (s, 9H), 0.90–1.01 (m, 1H), 1.65–1.81 (m, 2H), 2.11 (s, 3H), 3.28 (dd, 1H, J=3.4, 8.0 Hz), 3.67 (s, 3H), 3.68 (s, 3H), 3.70–3.80 (m, 2H), 4.88 (d, 1H, J=8.0 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ −2.90, 21.31, 21.42, 22.70, 40.99, 42.20, 51.65, 52.06, 56.85, 170.09, 170.58, 173.03 ppm. IR (nujol) 2950, 1750, 1725, 1650, 1440, 1200, 840 cm^{-1}. MS (EI) *m/z* 315 (M^+, 5), 272 (64), 256 (87), 73 (100). Anal. Calcd for $C_{14}H_{25}NO_5Si$: C, 53.31; H, 7.99; N, 4.44. Found: C, 53.40; H, 7.67; N, 4.24. Mp 64.5–65.1°C.

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