Pergamon

Tetrahedron Letters 40 (1999) 8587–8590

TETRAHEDRON LETTERS

Selective and facile electroreductive synthesis of dihydro- and tetrahydropyridine dicarboxylic acid derivatives

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Received 30 July 1999; accepted 10 September 1999

Abstract

Electroreduction of pyridinedicarboxylic acid derivatives in methanol using a divided cell brought about highly selective hydrogenation to give efficiently the corresponding dihydropyridines in good yields. From the electrolysis of dimethyl 2,3- and 2,5-pyridinedicarboxylates, 1,2-dihydropyridine derivatives were obtained while that of 2,6-, 3,4- and 2,4-disubstituted pyridines afforded the corresponding 1,4-dihydropyridines selectively in good yields.

Keywords: electrochemical reactions; hydrogenation; pyridines; reduction.

Dihydro- and tetrahydropyridine skeletons may possess high potentiality and much usefulness for synthesis of nitrogen-containing biologically active substances.[1] Many of hitherto known methods for synthesis of these important skeletons have, however, focused to 3,5-disubstituted-1,4-dihydropyridine derivatives by base-catalyzed condensation of 1,3-dicarbonyl compounds with amines including ammonia,[2] reduction of pyridinium salt[3–5] or photochemical cycloaddition.[6] Although direct hydrogenation of various ring-substituted pyridine derivatives has also been extensively studied,[7] most of these methods had suffered from some disadvantages, particularly lack of generality, unsatisfactory yield and/or formation of mixtures of regioisomers.[†8] On the other hand, we have shown that electroreduction of ring-substituted phthalic acid derivatives in aqueous acidic solvent brought about regioselective and efficient hydrogenation to the corresponding 1,2-dihydrophthalic acid derivatives.[10]

In this study, we wish to present selective and facile direct hydrogenation of a variety of pyridinecarboxylic acid derivatives **1** by electroreduction in methanol using a divided cell to give the corresponding dihydropyridine derivatives **2** in good to excellent yields (Scheme 1).

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† Eisner et al. reported[9] that reduction of dimethyl and diethyl 3,5-pyridinedicarboxylates with sodium cyanoborohydride afforded the corresponding 1,4-dihydro-isomers selectively in 77% yields, while the catalytic hydrogenation or diborane-reduction of these compounds gave the 1,4-dihydro-isomers (containing 78–79%) mainly in 54–35% yields.

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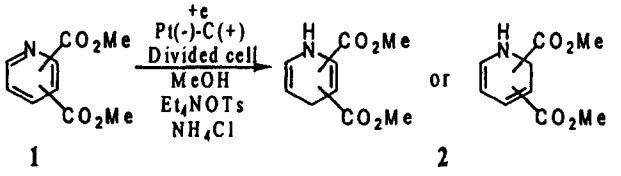
PII: S0040-4039(99)01789-X



Scheme 1.

The electroreductive hydrogenation of **1** (5 mmol) was always 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, usual work-up followed by column chromatographic treatment of the reaction mixture gave the dihydropyridine derivatives **2**‡ exclusively as the almost sole products.

It was found that reaction temperature and pH of the reaction medium had large influences on yield and selectivity of the product **2**. Thus, from the electroreduction of dimethyl 2,3-pyridinedicarboxylate (**1a**) without any additives, at room temperature (20–25°C) and 5–10°C, dimethyl 1,2-dihydro-2,3-pyridinedicarboxylate (**2a**) was obtained as the main product in 36 and 48% yields, respectively. It was noteworthy that the addition of a weak acid such as NH_4Cl or acetic acid into the reaction system brought about a remarkable increase in the yield of **2a**, which was improved to 83–89%. This remarkable improvement may be elucidated by the fact that the weakly acidic conditions inhibited easy decomposition of the product **2a**, which was unstable under the basic conditions, possibly caused by electrogenerated bases.

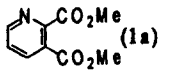
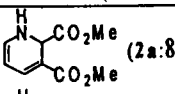
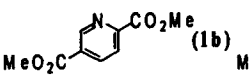
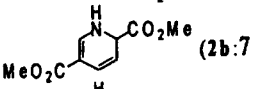
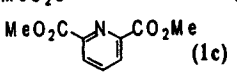
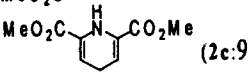
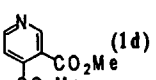
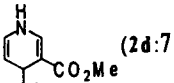
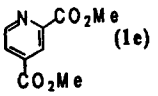
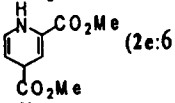
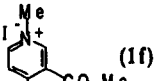
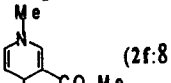
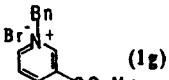
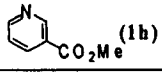
Table 1 shows the results of the present electroreductive hydrogenation of various ring-substituted dimethyl pyridinedicarboxylates (**1a–1e**) under the same conditions. From the electrolysis of dimethyl 2,3- and 2,5-pyridinedicarboxylates (**1a,1b**), 1,2-dihydro dicarboxylates (**2a,2b**) were obtained in 83 and 77% yields, respectively, while that of dimethyl 2,6-, 3,4- and 2,4-pyridinedicarboxylates (**1c–1e**) afforded the corresponding dimethyl 1,4-dihydropyridine dicarboxylates (**2c–2e**). It may be interesting to note that the nitrogen atoms of all the products (**2a–2e**) were protonated. Pyridinium salts such as *N*-methyl (**1f**) and *N*-benzyl pyridinium salt (**1g**) were also efficiently subjected to electroreductive hydrogenation to give the corresponding 1,4-dihydro products.§

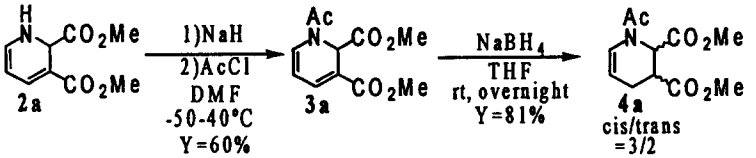
Furthermore, some of the obtained dimethyl dihydropyridinedicarboxylates and the acetylated derivatives were selectively transformed to the corresponding tetrahydro derivatives **4**. Thus, reduction of **3a**, prepared from the usual *N*-acetylation of **2a** in 60% yield, using $NaBH_4$ in THF afforded the stereoisomeric mixture (*cis*:*trans*=3:2) of dimethyl 1,2,3,4-tetrahydropyrdinedicarboxylate (**4a**) in 81% yield (Eq. 1). Further electroreduction of dimethyl 1,4-dihydropyridine-2,6-dicarboxylate (**2c**) in a mixed solvent of DMF and MeOH (volume ratio; 9:1) using a divided cell gave dimethyl 1,4,5,6-tetrahydropyridine-2,6-dicarboxylate (**4c**) in 43% yield (Eq. 2).

‡ Satisfactory spectroscopic spectra and chromatographic behavior were obtained for all the products **2a–2g**.

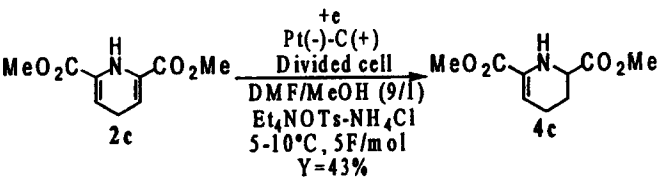
§ Any clear-cut explanation for selective formation of 1,2- and 1,4-dihydro-isomers depending upon the position of carboxylate groups is not available at the present stage, although the position of the most electron-deficient carbons on the pyridine ring and/or thermodynamic stability of the formed dihydro-products may take important roles for the selectivity.

Table 1
Electrochemical reduction of various pyridinecarboxylic acid derivatives

Substrate	Product (Yield/%)
 (1a)	 (2a:83)
 (1b)	 (2b:77)
 (1c)	 (2c:92)
 (1d)	 (2d:79)
 (1e)	 (2e:67)
 (1f)	 (2f:87)
 (1g)	 (2g:80)
 (1h)	No Reaction



(1)



(2)

Further study on the reaction mechanism of the electroreduction and synthetic application of the products **2a–2g** is in progress.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research on Priority Area No. 10208205 from the Ministry of Education, Science and Culture, Japan.

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