3690 © 1986 The Chemical Society of Japan NOTES Bull. Chem. Soc. Jpn., 59, 3690—3692 (1986) [Vol. 59, No. 11

Catalytic and Electrocatalytic Hydrogenation of Benzylideneazlactone and Benzylidenehydantoin

Tomokazu MATSUE, Tsukasa YAMADA, Hiroko TAKAHASHI, and Tetsuo OSA*
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980

(Received March 3, 1986)

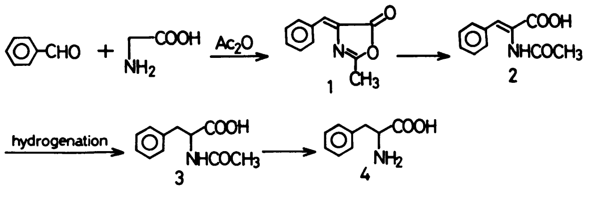
Synopsis. The electrocatalytic hydrogenatoin of benzylideneazlactone and 5-benzylidenehydantoin with Raney-nickel cathode proceeded smoothly to afford *N*-acetylphenylalanine and 5-benzylhydantoin, respectively. In addition, refluxing the electrolyte solution after the electrolysis finally yielded phenylalanine with satisfactory chemical yields and current efficiencies. This electrocatalytic process showed slightly higher reactivity than the ordinary catalytic hydrogenation.

The previous studies[1–5] have demonstrated that Raney-nickel (R-Ni) powder acts as an effective cathode for electrocatalytic hydrogenation of various reducible compounds. The electrocatalytic hydrogenation has several unique characteristics in comparison with direct, uncatalyzed electroreduction or ordinary catalytic hydrogenation, as described previously.[4,5] In this paper, we report the hydrogenation of benzylideneazlactone and 5-benzylidenehydantoin aimed at preparing finally phenylalanine by using the electrocatalytic and ordinary catalytic processes. The present results have shown that the electrocatalytic process has slightly higher reactivity than the ordinary catalytic one.

Results and Discussion

The Erlenmeyer method[6] via benzylideneazlactone (**1**) as an intermediate has been widely used for preparing α-amino acids, especially phenylalanine derivatives (Scheme 1). This method contains several reaction steps involving one for catalytic hydrogenation of 2-acetamide-3-phenyl-2-propenoic acid (**2**). The most widely adopting method for this step is the catalytic hydrogenation with platinum catalysts such as PtO_2 under a hydrogen pressure of about 3×10^5 Pa.[6] We have applied the electrocatalytic hydrogenation with R-Ni powder cathode to this step. The results are summarized in Table 1.

The electrocatalytic hydrogenation of **2** produced *N*-acetylphenylalanine (**3**) with satisfactory isolating yields and current efficiencies. The present hydrogenation proceeds smoothly under mild conditions (atmospheric pressure and room temperature). The isolating yield and the current efficiency were dependent on the electrolysis time. The long electrolysis time assures a high chemical yield but turns out a low current efficiency. The electrochemical process of the present electrolysis is the discharge of proton in the electrolyte solution to form active hydrogen at the R-Ni cathode surface. This active hydrogen is then transferred to a substrate to give a hydrogenation product. If the concentration of the substrate is not sufficiently high, two active hydrogens combine each other to form hydrogen gas. This is a main side reaction. The decrease in the current efficiency with the electrolysis time is caused by



Scheme 1.

Table 1. Hydrogenation of **2** to **3**

Run	Method	W_R[a)]	Condition	Reaction time/h	Yield %	Q[b)] 96500C/mol	CE[c)] %
1	EC[d)]	0.5	2.0 M NaOH aq	3.7	78	2.6	60
2		0.5	1.0 M NaOH/H_2O : MeOH(1 : 1)	2.6	50	1.8	56
3		0.5	1.0 M NaOH/H_2O : MeOH(1 : 1)	4.3	72	3.0	48
4		0.5	2.0 M NaOMe/MeOH	4.3	70	3.0	47
5		0.5	1.0 M $NaClO_4$/H_2O : MeOH(1 : 1)		63		
6		0.25	2.0 M NaOMe/MeOH	5.7	78	4.0	39
7		0.13	2.0 M NaOMe/MeOH	5.7	71	4.0	36
8		0.08	2.0 M NaOMe/MeOH	6.4	70	4.5	31
9	C[e)]	0.5	2.0 M NaOH aq, H_2 3.8×10^5 Pa	12	55		
10		0.5	MeOH, H_2 3.0×10^5 Pa	4.5	62		
11		0.25	MeOH, H_2 3.0×10^5 Pa	12	63		
12		0.08	MeOH, H_2 3.0×10^5 Pa	12	5		
13		0.08	2.0 M NaOMe/MeOH, H_2 3.0×10^5 Pa	12	69		

a) Weight ratio of R-Ni to **2**. b) Charge passed. c) Current efficiency. d) Electrocatalytic hydrogenation. e) Catalytic hydrogenation. M = mol dm^{-3}

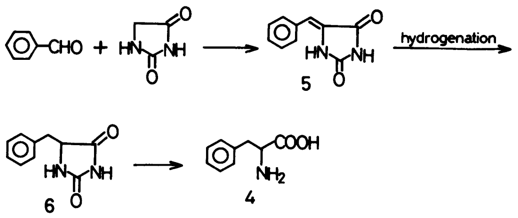
formation of hydrogen gas due to the lowering the concentration of substrate in the solution. Indeed, the bubble formation became noticeable as the electrolysis proceeded. The ordinary catalytic hydrogenation also produced **3**. However, the yields observed in the latter hydrogenation are slightly lower than those observed in the former.

The relative amount of the R-Ni to the substrate affected the hydrogenation. Table 1 also lists the W_R values (the weight ratio of the R-Ni to the substrate) used in this hydrogenation. In both types of the hydrogenation, the decrease in the W_R value reduces the reactivity as is shown by the prolonged reaction time to obtain satisfactory isolating yields. The influence of the W_R ratio is serious on the catalytic hydrogenation (Runs 10, 11, and 12). On the other hand, the electrocatalytic hydrogenation proceeded fairly smoothly even at W_R=0.08 and afforded a satisfactory chemical yield and a current efficiency (Run 8). It is ovbious from the table that the electrocatalytic process has higher reactivity than the ordinary catalytic process.

The use of a base as a supporting electrolyte showed good chemical yields and current efficiencies since basic solution enhanced the reactivity of R-Ni.[7] Perchlorate salts such as $NaClO_4$ also acted as a supporting electrolyte, but the chemical yield was relatively low. The effect of the basic atmosphere is eminent in the catalytic hydrogenation. The hydrogenation of **2** at W_R=0.08 in methanol (Run 12) proceeded very slowly and the chemical yield of **3** was only ca. 5% even after 12 h of the reaction time. However, the addition of NaOH to the methanol solution accelerated the hydrogenation more than 10 times (Run 13). In this case, the isolating yield of **3** was 69%, comparable to that observed in the electrocatalytic hydrogenation.

Since the present electrolysis was usually conducted in a basic solution, the use of **1** as a starting material burings about concurrent opening of the lactone ring during the electrolysis besides hydrogenation of the carbon-carbon double bond. Thus, the hydrogenation of **1** yielded **3** (Table 2). There is no significant difference in reactivity between **1** and **2**. The both substrates afforded **3** with almost same isolating yields and current efficiencies. The ordinary catalytic hydrogenation of **1** also gave **3**. However, the isolating yield was slightly low compared with that obtained in the electrocatalytic hydrogenation under the same conditions (Runs 14 and 21). In this case, use of water:ethanol (1:1 in volume) as a solvent showed good results. When the reaction solution was basic enough to hydrolyze the amide linkage of **3**, the reflux of the reaction solution after the hydrogenation gave phenylalanine (**4**), the final product, without isolating intermediates (Runs 20, 21, and 24).

The Wheeler method[8] via 5-benzylidenehydantoin (**5**) is also a typical method for preparing **4** (Scheme 2). This method contains a hydrogenation step. As shown in Table 3, the ordinary catalytic hydrogenation of **5** in ethanol at 5×10^6 Pa (Run 29) of hydrogen pressure gave 5-benzylhydantoin (**6**) with a high yield, whereas no hydrogenation proceeded at 2.6×10^5 Pa of hydrogen pressure (Run 28). On the other hand, the electrocatalytic hydrogenation under the equivalent conditions (Run 26) afforded **6** with a 57% chemical yield. In this case, the hydrogenation proceeded solwly and the current efficiency was quite unsatisfactory. The addition of NaOH to the solution facilitated the reaction to proceed due to the enhancement of the catalytic activity by the basic atmosphere.[7] This effect is pronounced on the ordinary catalytic hydrogenation (Runs 28 and 30). This is also true in the electrocatalytic hydrogenation.



Scheme 2.

Table 2. Hydrogenation of **1**[a)]

Run	Method	Condition	Reaction time/h	Product	Yield %	Q 96500C/mol	CE %
14	CE	2.0 M NaOH aq	4.0	**3**	77	2.8	55
15		1.0 M $NaOH/H_2O$: EtOH (2 : 1)		**3**	70		
16		1.0 M $NaOH/H_2O$: MeOH (1 : 1)	4.3	**3**	70	3.0	47
17		1.0 M $NaClO_4/H_2O$: MeOH (1 : 1)		**3**	51		
18		2.0 M NaOMe/MeOH	4.3	**3**	75	3.0	50
19		2.0 M $NaOH/H_2O$: THF (5 : 1)	3.9	**3**	75	2.7	56
20		2.0 M NaOMe/MeOH, reflux[b)]	4.3	**4**	70	3.0	47
21		2.0 M $NaOH/H_2O$: THF (5 : 1), reflux[b)]	7.2	**4**	68	5.0	27
22	C	2.0 M NaOH aq, H_2 3.8×10^5 Pa	24	**3**	60		
23		1.0 M $NaOH/H_2O$: EtOH (1 : 1), H_2 3.0×10^5 Pa	2	**3**	66		
24		1.0 M $NaOH/H_2O$: EtOH (1 : 1), H_2 2.8×10^5 Pa, reflux[b)]	3	**4**	64		

a) W_R=0.5. b) Reaction solution was refluxed for 10 h after the hydrogenation.

Table 3. Hydrogenation of **5**[a)]

Run	Method	Condition	Reaction time/h	Product	Yield %	Q 96500 C/mol	CE %
25	EC	2.0 M NaOH aq	3.6	**6**	90	2.5	72
26		1.0 M $NaClO_4$/EtOH	11.5	**6**	57	8.0	14
27		2.0 M NaOH aq , reflux	3.3	**4**	74	2.3	64
28	C	EtOH, H_2 2.6×10^5 Pa	12	No reaction			
29		EtOH, H_2 5×10^6 Pa	5	**6**	94		
30		2.0 M NaOH aq, H_2 2.6×10^5 Pa	12	**6**	80		

a) $W_R=0.5$.

The use of NaOH as a supporting electrolyte resulted in a reduction of the reaction time as well as an improvement of the chemical yield and the current efficiency (Runs 25 and 26). If the electrolyte solution was basic enough, reflux of the solution after the electrolysis gave **4** (Run 27).

In the hydrogenation of **5**, the electrocatalytic hydrogenation showed slightly higher yields than the ordinary process. Similar trend was also observed in the hydrogenation of **1** or **2** as described above. These phenomena may be accounted for by the following argument. As pointed out previously,[5)] the concentration of the active hydrogen on the R-Ni surface could be higher in the electrocatalytic hydrogenation than that in the ordinary catalytic one. The present electrocatalytic process will produce 8×10^{-8} mol of hydrogen in an apparent unit area (1 cm^2) in every second under the present conditions if a substrate is absent. If we dare to caluculate roughly by using the diffusion coefficient of hydrogen of 3.6×10^{-5} cm^2 s^{-1},[9)] the concentration of hydrogen in an aqueous system is estimated to be ca. 1×10^{-2} M (mol dm^{-3}) in the vicinal region from the cathode under the nonequilibrium state. On the other hand, the concentration is calculated to be ca. 8×10^{-4} M in the ordinary catalytic hydrogenation under the hydrogen pressure of around 3×10^5 Pa since the absorption coefficient is 0.018.[10)] Thus, the calculated concentration of hydrogen is ca. 13 times higher in the electrocatalytic process than that in the ordinary catalytic one. Although the effective concentration of dissolved hydrogen may be low due to the bubble formation in the electrocatalytic process, it is probably still higher than that in the ordinary catalytic hydrogenation. This in turn indicates high surface concentration of the active hydrogen at the cathode. Another considerable important factor is the basicity of the electrolyte solution near the R-Ni cathode. The discharge of proton makes the solution basic and thus the R-Ni is activated by the basic atmosphere, resulting in high chemical yields and short reaction time.

In conclusion, the hydrogenation of **1**, **2**, and **5** was accomplished by the electrocatalytic and ordinary catalytic hydrogenation with R-Ni powder. The addition of a base into the solution facilitated the hydrogenation to proceed and the reflux of the reaction mixture after the hydrogenation afforded **4** without isolating intermediates. In this hydrogenation, the electrocatalytic process showed slightly higher reactivity than the ordinary catalytic one.

Experimental

Electrolysis was carried out with a conventional H-type cell equipped with a R-Ni cathode and a Pt gauze anode under a constant current density (16 mA cm^{-2}). The preparation of R-Ni cathode was described previously.[4,5)] The electrolyte consisted of 2.0 g of a substrate dissolved in a solution (60 cm^3) described in Tables 1—3. After the electrolysis, the R-Ni cathode was filtered off from the solution. The solution was acidified, extracted with ethyl acetate three times, and dried over magnesium sulfate for a day. The products were obtained as crystalline forms by concentration of the solution. The products were identified by ir and mass spectroscopies. In order to evaluate the electrocatalytic hydrogenation, the ordinary catalytic hydrogenation was also carried out with a Burgess-Parr instrument under the hydrogen pressure of around 3×10^5 Pa with the basically same solution and R-Ni as used in the electrocatalytic hydrogenation.

This work was supported in part by Grant-in-Aids for Scientific Research (Nos. 59470070 and 60219003) from the Ministry of Education.

References

1) B. Sakurai and T. Arai, *Bull. Chem. Soc. Jpn.*, **28**, 93 (1962).

2) T. Chiba, M. Okimoto, H. Nagai, and Y. Takata, *Bull. Chem. Soc. Jpn.*, **56**, 719 (1983).

3) M. Fujihira, A. Yokozawa, H. Kinoshita, and T. Osa, *Chem. Lett.*, **1982**, 1089.

4) T. Osa, T. Matsue, A. Yokozawa, and T. Yamada, *Denki Kagaku*, **52**, 629 (1984).

5) T. Osa, T. Matsue, A. Yokozawa, T. Yamada, T. Osa, and M. Fujihira, *Denki Kagaku*, **53**, 104 (1985).

6) R. M. Herbst and D. Shemin, *Org. Synth.*, II, 1 (1943); H. B. Gillespie and H. R. Snyder, *ibid.*, II, 491 (1943).

7) H. E. Ungnade and D. V. Niphtingale, *J. Am. Chem. Soc.*, **66**, 1218 (1944); M. Paty, *Compt. Rend.*, **220**, 827 (1945).

8) E. T. Borrows, J. C. Clayton, and B. A. Hems, *J. Chem. Soc., Suppl. Issue* No. 1, 185 (1949); W. J. Boyd and W. Robson, *Biochem. J.*, **29**, 2256 (1935).

9) W. Jost, "Diffusion in Solids, Liquids, Gases," Academic Press, New York (1960), p. 475.

10) J. A. Dean, "Lange's Handbook of Chemistry," Mcgraw Hill, New York (1973), Section 10.