CHEMISTRY LETTERS, pp. 1575-1578, 1981.

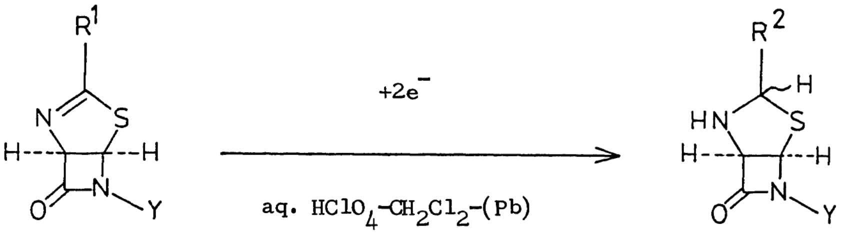
ELECTRO-HYDROGENATION OF THE C=N DOUBLE BOND OF THIAZOLINE-AZETIDINONES IN AN AQUEOUS PERCHLORIC ACID-DICHLOROMETHANE-(LEAD ELECTRODES)

Sigeru TORII,* Hideo TANAKA, Makoto SATSUKI, Takashi SIROI,
Norio SAITOH, Michio SASAOKA, and JUNZO NOKAMI†
Department of Industrial Chemistry, School of Engineering,
Okayama University, Okayama 700
†Okayama University of Science, Ridai, Okayama 700

Electro-hydrogenation of the C=N double bond of thiazoline-azetidinone derivatives derived from penicillins G and V in an aqueous $HClO_4$-CH_2Cl_2-(Pb electrodes) system by changing the current direction every 30 s gave thiazolidine-azetidinones in 77-100% yields.

Thiazolidine-azetidinones derivatives 2 are useful intermediates for the cephalosporin antibiotics synthesis.$^{1)}$ The hydrogenation of thiazoline-azetidinones 1 prepared from penicillins G and V$^{2)}$ must be a straightforward route, leading to 2. The hydrogenation of 1 (Y = H, $-C(COOCH_3)=C(CH_3)_2$, etc.) has been carried out on treatment of 1 with excess aluminum amalgam, giving 2 in 80-53% yields, depending on nature of substituents.$^{3)}$

We report here a novel procedure for the electro-hydrogenation of the C=N double bond of 1 in an aqueous $HClO_4$-CH_2Cl_2-(Pb electrodes) system. The present two-layer electrolysis procedure can be operated in an undivided cell



1 2

1a-c, 2a-c: $R^1 = R^2 = PhCH_2$;
1d, 1e; 2d, 2e: $R^1 = R^2 = PhOCH_2$;
1f: $R^1 = PhCCl_2$; 2d', 2e': $R^2 = CH_3$

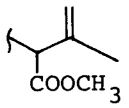
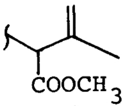
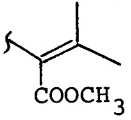
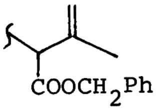
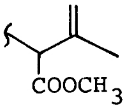
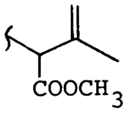
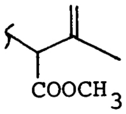
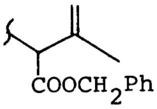
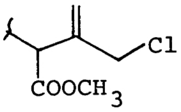
using Pb electrodes without doing strict controls[4)] and can provide the desired products 2 in 77-100% yields.

A typical electrolysis procedure (entry 1 in the Table) is as follows: A solution of 1a (R^1 = $PhCH_2$; Y =$CH_2{=}C(CH_3){-}CH(COOCH_3){-}$, 102 mg, 0.31 mmol) in CH_2Cl_2 (2 ml) and aqueous 10% $HClO_4$ (10 ml) was poured into a beaker (2.2 cm in diameter, 15 cm high) fitted with two Pb electrodes (1.5 x 2 cm^2) and a stirring bar. Under vigorous stirring, the mixture was electrolyzed at a constant current density of 20 mA/cm^2, changing the current direction every 30 s by a commutator, at 15-20 °C for 1 h (10 F/mol of electricity passed).[5)] Workup of the organic layer followed by column chromatography (SiO_2, benzene/AcOEt: 4/1) gave 2a (R^2 = $PhCH_2$, 97 mg, 94%): mp 128.0-128.5 °C (from hexane-benzene); IR (neat) 3320 (NH), 3010 (=CH), 1760 (β -lactam C=O), 1743 (C=O), 1660, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85 (3H, s), 2.09 (1H, bs), 3.28 (2H, m), 3.70 (3H, s), 4.68 (1H, s), 4.45-4.85 (1H, m), 4.89-5.19 (3H, m), 5.70 (1H, d, J = 8 Hz), 7.25 (5H, s). The reaction conditions and results are summarized in the Table.

The Pb cathode together with use of a commutator was indispensable to this procedure, because the use of the other cathode materials, e.g., Pt, C, stainless (SUS 27), and Ni, brought about no appreciable amounts of hydrogenation products. The use of Pb cathode with either C or Pt anode without changing the current direction provided 2 in 55-66% yields. The effect of acids in an aqueous layer is also remarkable. In place of the aqeous $HClO_4$, aqueous 10% CF_3COOH can be used successfully (entry 2), but the electrolysis with aqueous 10% H_2SO_4 or 10% HCl failed and only the starting material 1 was recovered (80-95%). These results can be reasonably explained by assuming that the protonation to the N=C double bond proceeds with very strong acids, such as $HClO_4$ and CF_3COOH, generating a $-\overset{H}{N}-\overset{+}{C}<$ intermediate, which, in turn, suffers from two-electron transfer on the cathode and subsequent protonation, producing a $-NH-CH<$ group.[6)]

Interestingly, the acid labile thiazoline and β-lactam ring systems were not affected by $HClO_4$ in the two-layer electrolysis procedure. In contrast, use of homogeneous systems, i.e., 10% H_2SO_4-EtOH, 10% HCl-MeCN, p-TsOH-Et_4NOTs-MeCN, p-TsOH-Et_4NOTs-MeOH, gave rise to complex products presumably due to the acid-catalyzed ring opening of the thiazoline and/or β-lactam ring. The neutral electrolysis systems such as Et_4NOTs-MeOH, LiCl-MeOH, Et_4NCl-MeOH did not give any hydrogenation products.

Table Electro-hydrogenation of Thiazoline-azetidinones a)

entry	thiazoline-azetidinone	R^1	Y	aqueous acid-CH_2Cl_2-(Pb) system	concentration of acid, %	product b)	yield, % c)
1	1a	$PhCH_2$		$HClO_4$	10	2a	94
2	1a	$PhCH_2$		CF_3COOH	10	2a	84
3	1b	$PhCH_2$		$HClO_4$	10	2b	100
4	1c	$PhCH_2$		$HClO_4$	10	2c	89
5	1d	$PhOCH_2$		$HClO_4$	10	2d/2d' d) (28/49)	77
6	1d	$PhOCH_2$		$HClO_4$	5	2d/2d' d) (17/66)	83
7	1d	$PhOCH_2$		$HClO_4$	1	2d/2d' d) (16/82)	98
8	1d	$PhOCH_2$		$HClO_4$	10	2e/2e' e) (12/73)	85
9	1f	$PhCCl_2$		$HClO_4$	10	2a	88

a) Carried out at 20 mA/cm^2, applied voltage: 1.5-2 V, 10-15 F/mol of electricity passed, at 15-20 °C. b) Unless otherwise noted, R^2 is equal to R^1. c) Isolated yields after column chromatography. d) 2d': $R^2 = CH_3$. e) 2e': $R^2 = CH_3$.

The electro-hydrogenation of the substituent isomers 1b-f in the 10% $HClO_4$-CH_2Cl_2-(Pb) system also gave the hydrogenated products 2a-e in good yields (entries 3-9). In the hydrogenation of 1d (R^1 = $PhOCH_2$-), a considerable amount of 2d' (R^2 = CH_3) was obtained along with 2d (R^2 = $PhOCH_2$-) and lower concentration of $HClO_4$ can provide 2d' preferentially (entry 7). The conversion of 2d to 2d' did not take place under the electrolysis conditions, suggesting that reductive cleavage of the carbon-oxygen bond of 1d proceeds competitively in the course of the electro-hydrogenation of the C=N double bond.[7] Upon the electrolysis of 1f (R^1 = $PhCCl_2$; Y = CH_2=C(CH_2Cl)-CH($COOCH_3$)-), the reductive dechlorination along with the hydrogenation of the thiazoline ring took place on both benzylic and allylic positions (entry 9).

REFERENCES

1) (a) R. B. Woodward, K. Heusler, J. Gosteli, P. H. Vorbruggen, J. Am. Chem. Soc., 88, 852 (1966); (b) R. Scartazzini and H. Bickel, Helv. Chim. Acta, 55, 423 (1972); (c) "Topics in Antibiotic Chemistry" Vol 4, P. G. Sammes ed., John Wiley & Sons, New York, p 13 (1980) and references cited therein.

2) R. D. G. Cooper and F. L. José, J. Am. Chem. Soc., 92, 2575 (1970).

3) (a) R. D. G. Cooper and F. L. José, J. Am. Chem. Soc., 94, 1021 (1972); (b) W. J. E. Underwood and A. G. Long, Japan Kokai, 47-4272 (1972).

4) The electro-hydrogenation of a variety of the C=N double bond has been carried out in a divided cell fitted with a Hg pool cathode under the careful control of the pH value and the electrode potential: (a) H. Lund, Acta Chem. Scand., 13, 249 (1959); (b) M. R. Lifi, "Technique of Electroorganic Synthesis" Part II, N. L. Weinberg ed., John Wiley & Sons, New York, p 227 (1975) and references cited therein.

5) The electrode surface was covered with black precipitates (PbO_2) in a few minutes.

6) The (-$\overset{+}{N}$H=C-) group is reducible at a less negative potential than the (-N=C-) group: see references (4).

7) The reductive removal of the phenoxy group of 1 (R^1 = $PhOCH_2$, Y = H or -C($COOCH_3$)=C$(CH_3)_2$) has also been observed in the aluminum amalgam reduction: see reference (3a).

(Received August 24, 1981)