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A NOVEL ELECTROCHEMICAL TRANSFORMATION OF ASPARTIC ACIDS INTO URACIL[1]

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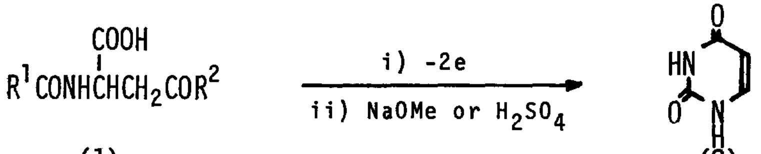
Uracil and its derivatives are of current interest in viewpoint of their biological activity[2]. During the past decade, uracil has been prepared mainly based on the concept of prebiotic molecular evolution[3]: fusion of maleic acid, fumaric acid or propiolic acid with urea leads to the formation of uracils[4]. There are a number of specialized and limited methods as well[5]. These methods, however, suffer seriously from lack of general acceptance, since the yields are rather low (20-50%) and drastic conditions are frequently required in these reactions. In a biological system, on the other hand, uracil moiety of uridylic acid is transformed effectively from carbamoylaspartic acid via enzyme-catalyzed oxidation and decarboxylation[6]. We now wish to report a novel transformation of carbamoylaspartic acids or ethoxycarbonylaspargine into uracil by electrochemically oxidative decarboxylation, as depicted in the following scheme.



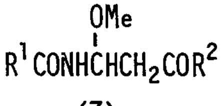
$$R^1CONH\overset{\overset{\displaystyle COOH}{|}}{C}HCH_2COR^2 \xrightarrow[\text{ii) NaOMe or } H_2SO_4]{\text{i) -2e}}$$

(1) (2)

a: $R^1=NH_2$; $R^2=OCH_3$, b: $R^1=OC_2H_5$; $R^2=NH_2$, c: $R^1=NH_2$; $R^2=OH$

Carbamoylaspartic acid β-methyl ester (1a) (5 g, 0.053 mol) was dissolved in 150 ml of methanol containing 3 ml of N-sodium methoxide. This solution was electrolyzed at a constant current of 1 A using graphite anode-graphite cathode (3 × 4 cm) in a nondivided cell. The electrolysis was discontinued when three times a theoretical amount of current was passed. N-Sodium methoxide (10 ml) was added to the electrolyzed solution, and the mixture was refluxed for 5 hr to afford uracil (2) in 94% yield[7]. N-Ethoxycarbonylaspargine (1b) was similarly treated as described above to give uracil in 93% yield. The physical constants of uracil obtained here were consistent with those of an authentic sample.

The intermediates (3a,b)[8] were also isolated in excellent yields from the electrolyzed solutions: 3a shows mp 130-131°C; 3b does mp 148-149°C.



$$R^1CONH\overset{\displaystyle OMe}{\overset{|}{C}}HCH_2COR^2$$

(3)

To develop a more versatile method, a one-step conversion of carbamoylaspartic acid (1c) into uracil was carried out. One of two carboxylic acid groups of 1c, the carboxylic acid group α to the ureido group, was selectively oxidized[9] at 0-5°C in methanol containing $^1/_{20}$ molar equivalent of N-sodium methoxide by using platinum anode in a nondivided cell[10]. The electrolyzed solution was treated with a catalytic amount of H_2SO_4[5] to afford uracil in 30% yield.

A significant feature of the electrochemical transformation under mild conditions will give promise of wide applications to a synthesis of a variety of pyrimidine bases.

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References and Footnotes

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3. S. W. Fox and K. Harada, Science, 113, 1923 (1961).
4. K. Harada and S. Suzuki, Tetrahedron Lett., 2321 (1976), and references cited therein.
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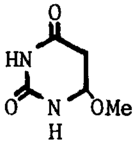
6. P. Beak and B. Siegel, J. Amer. Chem. Soc., 98, 3602 (1976) and references cited therein.
7. We confirmed that the cyclization reaction of 3 to uracil proceeds through the cyclized compound (4).



(4)

8. Treatment of 3a and 3b with sodium methoxide afforded uracil in 91 and 94% yields, respectively.
9. The selectivity of the reaction may be rationalized on the basis of the difference in ionization between the α-carboxylic acid group (pKa 3.2) and the β-carboxylic acid group (pKa 4.7); much greater ionization of the former group presumably results in the virtual exclusion of the oxidation of the latter group. The relative ease of anodic discharge of acids has been discussed. See, R. C. Peterson, M. Finkelstein, and S. D. Ross, J. Org. Chem., 32, 564 (1967).
10. The intermediate (3c) [mp 175°C (dec)] was isolated.

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