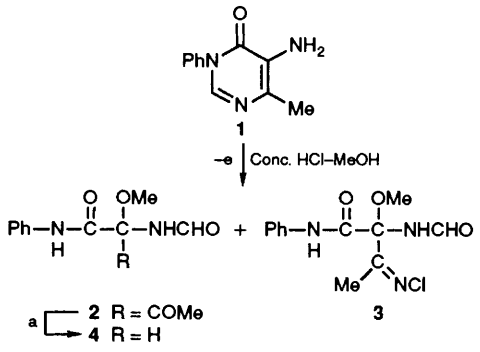
Electrochemical Transformation of 5-Aminopyrimidin-4(3*H*)-one: Indirect Anodic Oxidation Mediated by Electrochemically Generated Chlorine

Izumi Matsuura, Taisei Ueda, Nobutoshi Murakami, Shin-ichi Nagai, Jinsaku Sakakibara,* Yukihisa Kurono and Keiichiro Hatano

Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya 467, Japan

Anodic oxidation of 5-amino-6-methyl-3-phenylpyrimidin-4(3*H*)-one **1** in conc. HCl–MeOH gave 2-(formamido)-2-methoxy-3-oxobutananilide **2** (the crystal structure of which has been determined) and 3-(*N*-chloroimino)-2-(formamido)-2-methoxybutananilide **3** *via* cleavage of the C(2)–N(3) bond and the migration of C(2) to the 5-amino group by the mediation of electrochemically generated chlorine.

Electrochemical transformations of several pyrimidines such as 5,6- diaminouracil,[1] uric acid,[2] xanthine[2] and pteridine[3] have been studied in connection with the elucidation of their metabolic pathways. However, there have been no electrochemical studies of 5-aminopyrimidin-4(3*H*)-ones. In the course of medicinal and chemical studies of pyrimidinones in our laboratory,[4] we recently found a novel oxidative ring transformation of 5-amino-6-methyl-3-phenylpyrimidin-4(3*H*)-one **1**[5] into 2-alkoxy-1*H*-imidazoles using oxidative metal salts in alcohols,[6] and we became interested in the



Scheme 1 *Reagent*: a, 5% NaOMe–MeOH

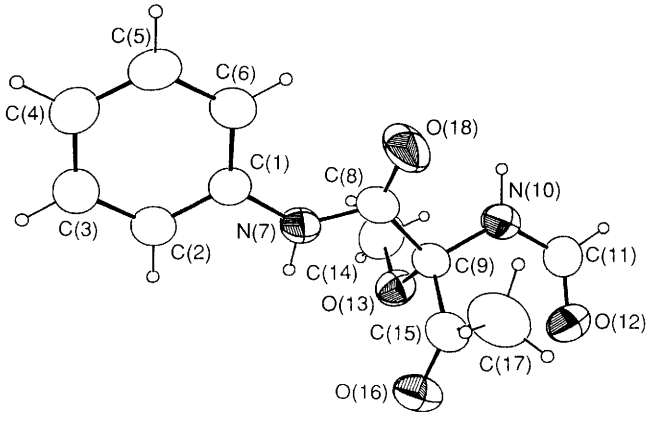
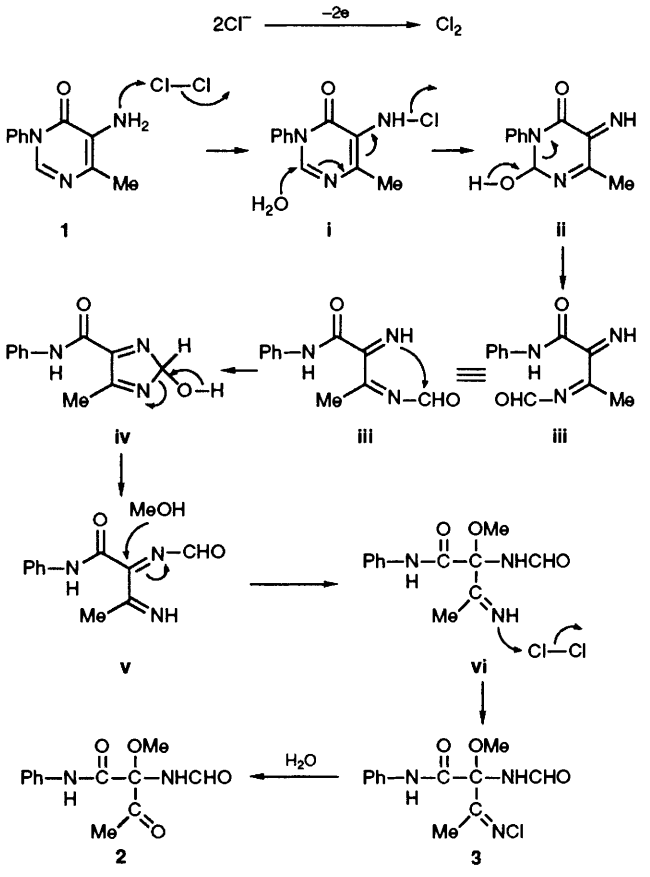


Fig. 1 Perspective view of **2** with thermal ellipsoids at 50% probability for non-hydrogen atom. Hydrogens in calculated positions are shown as arbitrary circles. Octant shaded ellipsoids are heteroatoms.



Scheme 2

anodic oxidation of **1**. Here we describe the electrochemical transformation of **1** leading to the butananilides **2** and **3** *via* the unprecedented cleavage of the C(2)–N(3) bond and the migration of C(2) to the 5-amino group.

The anodic oxidation of **1** was carried out as follows: into a beaker equipped with a platinum anode (20 × 80 mm) and a glassy carbon cathode (4 mm diam.) was added a solution of **1** (1 mmol) in methanol (50 ml) containing conc. HCl (0.05 ml). A constant current (current density: 2.5 mA cm^{-2}; electricity passed: 3.0 F mol^{-1}) was passed for 30 min through the solution externally cooled with ice and water (0 °C). The usual work-up of the reaction mixture gave **2** and **3** in 41 and 22% yield, respectively (Scheme 1).

The electron-impact mass spectrum (EI-MS) of **2** showed the molecular ion peak at *m/z* 250, and the high-resolution spectrum showed that its molecular formula was $C_{12}H_{14}N_2O_4$. Its ^1H NMR spectrum showed signals due to a phenyl, two secondary amide, a formyl, a methoxy, and an acetyl group. The ^{13}C NMR spectrum (DEPT) indicated the presence of a ketone (δ_C 199.0), and two amide functions (δ_C 163.6, 160.7) as well as one quaternary carbon (δ_C 87.7). Furthermore, the IR spectrum showed absorption bands ascribable to amide (3300, 1700 and 1660 cm^{-1}) and the ketone groups (1740 cm^{-1}). However, these physical data did not provide unambiguous proof of the structure for compound **2**,† and so its crystal structure was determined (Fig. 1).‡ This showed that **2** was 2-(formamido)-2-methoxy-3-oxobutananilide, as depicted in Scheme 1.

Deacylation of **2** with 5% NaOMe–MeOH gave **4** quantitatively.§ Detailed comparison of the ^1H and ^{13}C NMR spectra of **4** with those of **2** revealed the absence of the acetyl group and the presence of a methine proton (δ_H 6.72, 1H, d, *J* 9 Hz) and a tertiary carbon (δ_C 77.9) in **4**. The IR spectrum of **4** showed the disappearance of the ketone, and the molecular ion peak was observed at *m/z* 208 in the EI-MS. Thus, the structure of compound **2** was also chemically substantiated.

The EI-MS of **3** showed molecular ion peaks at *m/z* 283 (16%) and 285 (5%) indicating the presence of chlorine. The high resolution spectrum showed that **3** had the formula $C_{12}H_{14}N_3O_3Cl$. The other physicochemical properties (^1H,

† *Spectral data for* **2**: m.p. 154–155 °C (Pr^i_2O–EtOAc); M^+, *m/z* 250.0945, $C_{12}H_{14}N_2O_4$ requires M, 250.0953; ν_{max}(KBr)/cm^{-1} 3300, 1740, 1700 and 1660; δ_H (270 MHz, $CDCl_3$) 8.80 (1H, br s), 8.36 (1H, s), 7.60–7.14 (5H, m), 7.40 (1H, br s), 3.31 (3H, s) and 2.31 (3H, s); δ_C (67.5 MHz, $CDCl_3$) 199.0, 163.6, 160.7, 136.6, 129.1, 125.1, 120.1, 87.7, 51.7 and 23.4.

‡ *Crystal data for* **2**: $C_{12}H_{14}N_2O_4$, *M* = 250.3, monoclinic, *a* = 8.244(1), *b* = 9.178(1), *c* = 17.691(2) Å, β = 100.93(1)°, *U* = 1314.2(5) $Å^3$, *Z* = 4, space group $P2_1/n$, D_c = 1.265 g cm^{-3}, μ(Mo-Kα) = 0.9 cm^{-1}. Data were collected on an Enraf-Nonius CAD4 diffractometer with monochromated Mo-Kα radiation. The data were corrected for Lorentz–polarization. No absorption correction was made. Full-matrix least-squares refinement of 163 parameters gave *R* = 0.053 for 1722 observed reflections. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

§ *Spectral data for* **4**: m.p. 116–117 °C (n-hexane–EtOAc); M^+, *m/z* 208.0850, $C_{10}H_{12}N_2O_3$ requires M, 208.0849; ν_{max}(KBr)/cm^{-1} 3300, 1685, 1680 and 1560; δ_H (270 MHz, $CDCl_3$) 8.84 (1H, s), 8.42 (1H, br s), 7.56–7.13 (5H, m), 6.72 (1H, br d), 5.69 (1H, d, *J* 9 Hz) and 3.54 (3H, s); δ_C (67.5 MHz, $CDCl_3$–CD_3OD) 165.6, 162.9, 136.9, 129.2, 125.1, 120.1, 83.3 and 56.1.

^{13}C NMR)¶ were fairly analogous to those of compound **2**. However, a ketone signal was absent and an imine carbon signal (δ_C 174.1) appeared instead in the ^{13}C NMR spectrum. The IR spectrum also showed the presence of the amido and imine functions (3250, 1700, 1685 and 1665 cm^{-1}). Thus, **3** was 3-(*N*-chloroimino)-2-(formamido)-2-methoxybutananilide.

The conversion of **1** into **2** and **3** may be rationalized by the involvement of electrochemically generated chlorine from chloride ion[7] (Scheme 2). Initially, the 5-amino group of **1** would be oxidized by chlorine accompanied by nucleophilic attack of H_2O on C(2) to give intermediate **ii** *via* **i**. Subsequent cleavage of the C(2)–N(3) bond would form **iii**. Intramolecular cyclization between the imino and the formyl groups would afford **iv**, and ring opening would afford the intermediate **v**, addition of methanol to which would form **vi**. *N*-Chlorination of the imino function would give compound **3**, hydrolysis of which would yield **2**. Thus, chlorine functions as a catalytic oxidizing agent as well as an electron carrier.

¶ *Spectral data for* **3**: m.p. 121–122 °C (light petroleum–EtOAc); M^+, *m/z* 283.0732, $C_{12}H_{14}N_3O_3Cl$ requires M, 283.0724; ν_{max}(KBr)/cm^{-1} 3250, 1700, 1685 and 1665; δ_H (270 MHz, $CDCl_3$) 8.88 (1H, br s), 8.30 (1H, s), 7.74 (1H, br s), 7.60–7.12 (5H, m), 3.30 (3H, s) and 2.21 (3H, s); δ_C (67.5 MHz, $CDCl_3$) 174.1, 163.8, 160.1, 136.7, 129.1, 125.1, 120.1, 88.2, 51.3 and 17.3.

The present type electrochemically mediated conversion involving cleavage of the C(2)–N(3) bond and the migration of C(2) to the 5-amino group has not been found in chemical transformation of pyrimidine derivatives.

Received, 3rd February 1992; Com. 2/00596D

References

1 B. M. Visinski and G. Dryhurst, *J. Electroanal. Chem.*, 1976, **70**, 199.
2 G. Dryhurst, *J. Electrochem. Soc.*, 1972, **119**, 1659.
3 D. L. McAllister and G. Dryhurst, *J. Electroanal. Chem., Interfacial Electrochem.*, 1974, **55**, 69.
4 T. Ueda, I. Matsuura, N. Murakami, S. Nagai, J. Sakakibara and M. Goto, *Tetrahedron Lett.*, 1988, **29**, 4607; T. Ueda and J. Sakakibara, *Chem. Pharm. Bull.*, 1984, **32**, 2863.
5 T. Ueda, N. Oda and I. Ito, *Chem. Pharm. Bull.*, 1980, **28**, 2144.
6 I. Matsuura, T. Ueda, N. Murakami, S. Nagai and J. Sakakibara, *J. Chem. Soc., Chem. Commun.*, 1991, 1688.
7 S. Torii, H. Tanaka and M. Ukida, *J. Org. Chem.*, 1979, **44**, 1554; S. Torii, H. Tanaka and N. Sayo, *J. Org. Chem.*, 1979, **44**, 2938; T. Shono, Y. Matsumura, J. Hayashi and M. Mizoguchi, *Tetrahedron Lett.*, 1979, 165; S. Torii, N. Sayo and H. Tanaka, *Tetrahedron Lett.*, 1979, 4471.