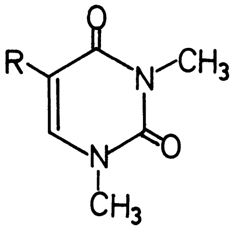
CHEMISTRY LETTERS, pp. 127-128, 1983.

# CARBOXYLATION OF 1,3-DIMETHYLURACIL AND THIOPHENES WITH CARBON MONOXIDE AND PALLADIUM(II) ACETATE IN THE PRESENCE OF SODIUM PEROXODISULFATE

Toshio ITAHARA
Institute of Chemistry, College of Liberal Arts,
Kagoshima University, Korimoto, Kagoshima 890

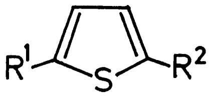
Treatments of 1,3-dimethyluracil and of thiophenes with palladium(II) acetate and sodium peroxodisulfate under a carbon monoxide atmosphere gave 1,3-dimethyluracil-5-carboxylic acid and the corresponding thiophene-2-carboxylic acids, respectively.

Previously we reported the carboxylation of 1-acylindoles with carbon monoxide and palladium(II) acetate in the presence of sodium peroxodisulfate.$^{1)}$ In a course of further investigation, it was found that the treatment of 1,3-dimethyluracil (1) and of thiophenes (3a-d) gave 1,3-dimethyluracil-5-carboxylic acid (2) and the corresponding thiophene-2-carboxylic acids (4a-d), respectively.



1: R=H

2: R=COOH



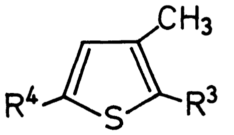
| | | | | | |
|---|---|---|---|---|---|
| 3a: | $R^1$=H, | $R^2$=H | 4a: | $R^1$=H, | $R^2$=COOH |
| 3b: | $R^1$=$CH_3$, | $R^2$=H | 4b: | $R^1$=$CH_3$, | $R^2$=COOH |
| 3c: | $R^1$=Cl, | $R^2$=H | 4c: | $R^1$=Cl, | $R^2$=COOH |
| 3d: | $R^1$=Br, | $R^2$=H | 4d: | $R^1$=Br, | $R^2$=COOH |

In recent years increasing interest is being shown in chemical reactions of nucleic acid-bases. Furthermore, uracil-5-carboxylic acids are of interest in connection with the existence of nucleoside antibiotics such as polyoxins$^{2)}$ and octosyl acids$^{3)}$. Previously two types of reactions of 5-uracilylmercury(II) salts with palladium(II) salts have been reported, that is, dimerization$^{4)}$ and coupling with olefins$^{5)}$. We found the carboxylation of 1 with palladium(II) acetate and carbon monoxide. This will be the first report concerning carboxylation of uracils.

Carbon monoxide was bubbled for 7h at reflux temperature through a solution of of 1 (2 mmol), palladium(II) acetate (1 mmol), and sodium peroxodisulfate (3 mmol) in acetic acid (40 ml). The reaction mixture was evaporated to give a yellow semicrystalline residue which was triturated with ethyl acetate to give 2: mp. 193-194 °C (lit.$^{6)}$ 193.5-194 °C; cf. 1,3-dimethyluracil-6-carboxylic acid: mp.$^{7)}$ 150-151 °C), in 61% yield based on 1 consumed (Conv. 26%).

In an effort to determine the effects of substituents on the carboxylation of aromatic heterocycles, the reaction of thiophenes was further studied. The treatment of thiophene (3a) and 2-substituted thiophenes (3b-d) with palladium(II) acetate and sodium peroxodisulfate under a carbon monoxide atmosphere resulted in clean carboxylation to yield 4a and the corresponding 5-substituted thiophene-2-carboxylic acids (4b-d), respectively. Under similar conditions, the treatment of 3-methylthiophene (5) gave a mixture of 6e and 6f. On the other hand, the reaction of 2,5-dichlorothiophene (7) gave a small amount of 8 together with a complex reaction mixture. These results suggest that the treatment of thiophenes with palladium(II) acetate and sodium peroxodisulfate under carbon monoxide preferentially results in carboxylation at the 2- or 5-position. Carboxylation of thiophenes with palladium black instead of palladium(II) acetate was also investigated. These results are summarized in Table.

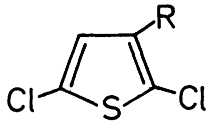
It is well known that the treatment of bromobenzene with carbon monoxide and palladium complexes in alcohols yields alkyl benzoate.$^{8)}$ In the contrast to the fact, it is interesting that the treatment of 2-bromothiophene (3d) with carbon monoxide, palladium(II) acetate, and sodium peroxodisulfate gave 5-bromothiophene-2-carboxylic acid (4d) in good yield but not 4a, although the treatment of 3d with palladium black gave a mixture of 4a and 4d.



5 : $R^3$=H, $R^4$=H

6e: $R^3$=COOH, $R^4$=H

6f: $R^3$=H, $R^4$=COOH



7 : R=H

8 : R=COOH

Table. Carboxylation of thiophenes$^{a)}$

| Thiophenes | Pd | Products (% yield$^{b)}$; % yield$^{c)}$) | |
|---|---|---|---|
| 3a | $Pd(OAc)_2$ | 4a (21.2; 106) | |
| 3b | $Pd(OAc)_2$ | 4b (22.0; 110) | |
| 3c | $Pd(OAc)_2$ | 4c (19.6; 98) | |
| 3d | $Pd(OAc)_2$ | 4d (23.6; 118) | |
| 3d | Pd black$^{d)}$ | 4a ( 4.4; 22), | 4d ( 8.8; 44) |
| 5 | $Pd(OAc)_2$ | 6e (13.0; 65), | 6f ( 9.6; 48) |
| 5 | Pd black$^{d)}$ | 6e ( 9.6; 48), | 6f ( 4.8; 24) |
| 7 | $Pd(OAc)_2$ | 8 ( 1.6; 8) | |

a) Conditions used: thiophenes (5 mmol), $Pd(OAc)_2$ or Pd black (1 mmol), $Na_2S_2O_8$ (3 mmol), AcOH (40 ml), at reflux temperature except for the reaction of 3a (70-80 °C), 7h reaction. b) Yield based on thiophenes used. c) Yield based on $Pd(OAc)_2$ or Pd black used. d) Adding of NaOAc (3 mmol).

References
1) T. Itahara, Chem. Lett., 1982, 1151.
2) K. Isono, K. Arai, and S. Suzuki, J. Am. Chem. Soc., 91, 7490 (1969).
3) K. Isono, P. F. Crain, and J. A. McClosky, J. Am. Chem. Soc., 97, 943 (1975).
4) I. Arai, R. Hanna, and G. D. Deves, Jr., J. Am. Chem. Soc., 103, 7684 (1981).
5) D. E. Bergstrom and J. L. Ruth, J. Am. Chem. Soc., 98, 1587 (1976); I. Arai and G. D. Deves, Jr., J. Org. Chem., 21, 4110 (1978); C. F. Bigge, P. Kalaritis, J. R. Deck, and M. P. Mertes, J. Am. Chem. Soc., 101, 2033 (1979).
6) R. Alcantara and S. Y. Wang, Photochem. Photobiol., 4, 465 (1965).
7) W. Corran and R. Angier, J. Org. Chem., 31, 201 (1966).
8) A. Schoenberg, I. Bartolletti, and R. F. Heck, J. Org. Chem., 39, 3318 (1974); H. Hidai, T. Hikita, Y. Wada, Y. Fujikura, and Y. Uchida, Bull. Chem. Soc. Jpn., 48, 2075 (1975).

(Received November 20, 1982)