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OXIDATIVE COUPLING OF URACIL DERIVATIVES WITH MALEIMIDES BY PALLADIUM ACETATE

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Treatment of uracil derivatives and maleimides in the presence of palladium acetate gave the coupling products.

Some 5-vinyluracils are of importance as anti-cancer and antiviral agents.[1] Increasing interest is being shown in the reaction with palladium compounds as an effective method for the synthesis of 5-vinyluracils from uracils. The previous investigation has, however, dealt almost exclusively with the reaction of uracils which bear mercury or halogens at the 5-position.[2] On the other hand, oxidative coupling of aromatic compounds with olefins by palladium(II) salts has been extensively studied since the pioneering work of Moritani and Fujiwara.[3] This paper describes oxidative coupling of uracil derivatives with maleimides by palladium(II) acetate.

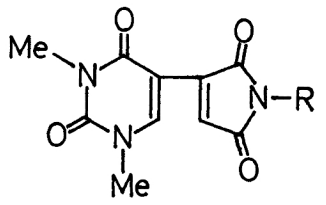
Treatment of 1,3-dimethyluracil (1) with N-methylmaleimide in the presence of palladium acetate in acetic acid gave the coupling product (2b)[4] in good yield based on 1 consumed. Similar treatment of 1 with N-ethyl-, N-phenyl-, and N-benzyl-maleimides gave the corresponding coupling compounds 2c, 2d, and 2e. Also, 1 reacted with maleimide in the presence of palladium acetate in acetonitrile to give 2a but the use of acetic acid instead of acetonitrile decreased the yield of 2a. These results are summarized in Table 1.

Similar reaction occurred in the case of uridine (3), 2',3',5'-tri-O-acetyl-uridine (5), and 2'-deoxyuridine (7). Treatment of 3 with maleimide and with N-methylmaleimide in the presence of palladium acetate in acetonitrile gave the expected coupling products 4a and 4b, respectively. The compound 5 also reacted with N-methylmaleimide to give 6b. Under similar conditions the reaction of 7 with maleimide and with N-methylmaleimide gave 8a and 8b, respectively. The compounds 4a, 4b, 8a, and 8b were expected to exhibit some biological and physiological activities because of structural resemblance to some antibiotics such as showdomycin[5] and sparsomycin.[6] In fact it was found that these compounds inhibited E. Coli.

The previous investigation concerning oxidative coupling of aromatic compounds with olefins by palladium(II) salts[3] suggests that the oxidative coupling of uracils with maleimides proceeds via palladation of uracils with palladium acetate. The direct palladation of uridines 3 and 7 with palladium acetate is of interest in connection with a possibility of metallation of double bonds in pyrimidine bases in nucleic acids, since nickel compounds are known to be carcinogens and platinum

compounds are important cancerocidal substances.[7)]

The present palladium acetate -catalyzed oxidative coupling of 1 with N-alkylmaleimides was accomplished by using AgOAc, $Na_2S_2O_8$, and $Cu(OAc)_2$ as re-oxidants. These results are summarized in Table 2.



	R
2a	H
2b	Me
2c	Et
2d	Ph
2e	CH_2Ph

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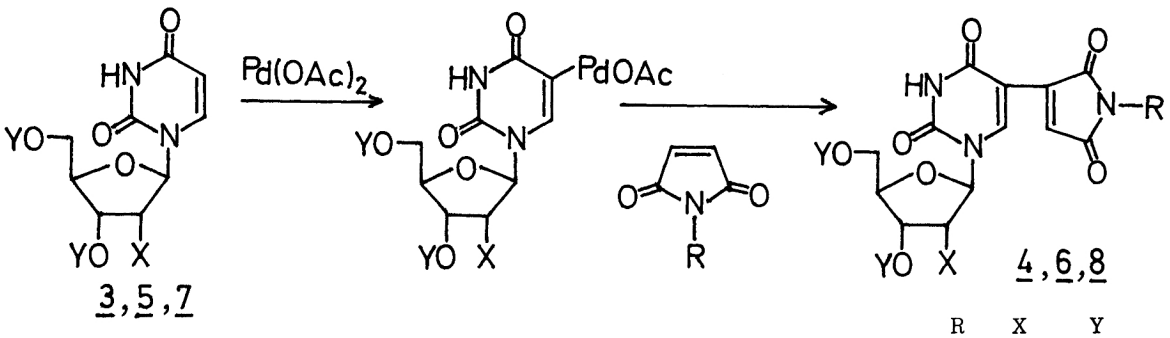


3,5,7

	X	Y
3	OH	H
5	OAc	Ac
7	H	H

4,6,8

	R	X	Y
4a	H	OH	H
4b	Me	OH	H
6b	Me	OAc	Ac
8a	H	H	H
8b	Me	H	H

Table 1. Oxidative Coupling of Uracil Derivatives with Maleimides by Palladium Acetate[a)]

Uracils (mmol)	N-R-Maleimides R	(mmol)	$Pd(OAc)_2$ mmol	Solvents (ml)	Reaction time/h	Products : Yield/%[b)]	Yield/%[c)]
1 (1)	H	(1)	1	MeCN (100)	17	2a: 31	67
1 (1)	H	(1)	1	AcOH (50)	7	2a: 4	10
1 (1)	Me	(1)	1	AcOH (50)	7	2b: 56	82
1 (1)	Et	(1)	1	AcOH (50)	7	2c: 52	81
1 (1)	Ph	(1)	1	AcOH (50)	7	2d: 23	88
1 (1)	CH_2Ph	(1)	1	AcOH (50)	7	2e: 41	73
3 (4)	H	(4)	4	MeCN (400)	17	4a: 4	d)
3 (4)	Me	(4)	4	MeCN (400)	17	4b: 5	d)
5 (1)	Me	(1)	1	MeCN (100)	7	6b: 22	d)
7 (2)	H	(2)	2	MeCN (200)	17	8a: 10	d)
7 (2)	Me	(2)	2	MeCN (200)	17	8b: 11	d)

a) All reactions performed at reflux temperature under nitrogen atmosphere.

b) Yield based on uracils 1, 3, 5, and 7 used.

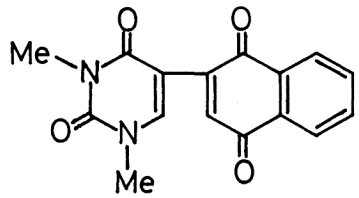
c) Yield based on uracils 1, 3, 5, and 7 consumed.

d) Amount of the uracils recovered was not determined.

Table 2. Palladium Acetate-Catalyzed Oxidative Coupling of 1,3-Dimethyluracil 1 with N-Alkylmaleimides in the Presence of Re-Oxidants[a)]

N-R-Maleimides R	Re-Oxidants (mmol)	Reaction time/h	Products : Yield/%[b)]	Yield/%[c)]	(Conversion/%[d)])
Me	AgOAc (2)	17	2b: 149	72	(42)
Me	$Na_2S_2O_8$ (1)	7	2b: 125	57	(44)
Me	$Cu(OAc)_2$ (1)	17	2b: 62	59	(21)
Ph	AgOAc (2)	17	2d: 113	70	(32)
Ph	$Na_2S_2O_8$ (1)	7	2d: 122	58	(42)
Ph	$Cu(OAc)_2$ (1)	17	2d: 64	61	(21)
CH_2Ph	AgOAc (2)	17	2e: 121	48	(50)

a) A mixture of 1 (1 mmol), N-alkylmaleimides (1 mmol), $Pd(OAc)_2$ (0.2 mmol), and re-oxidants (1 or 2 mmol) in AcOH (70 ml) was refluxed in air.
b) Yield based on $Pd(OAc)_2$ used.
c) Yield based on 1 consumed.
d) Conversion of 1.



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Treatment of 1 (1 mmol) with 1,4-naphthoquinone (1 mmol) in the presence of $Pd(OAc)_2$ (1 mmol) in AcOH (50 ml) gave the expected coupling product (9) (0.47 mmol) together with recovered 1 (0.44 mmol) and 1,4-naphthoquinone (0.41 mmol). However, similar treatment of 1 with methyl acrylate gave a somewhat complex reaction mixture. The further investigation concerning oxidative coupling of uracil derivatives with olefins of several types is now in progress.

References

1) For reviews see E. De Clercq and R. T. Walker, Pharmac. Ther., 26, 1 (1985); R. T. Walker, A. S. Jones, E. De Clercq, J. Descamps, H. S. Allaudeen, and J. W. Kozarich, Nucleic Acids Res. Symposium Series, No. 8, 95 (1980).
2) For a review see D. E. Bergstrom, Nucleosides & Nucleotides, 1, 1 (1982).
3) For a review see I. Moritani and Y. Fujiwara, Synthesis, 1973, 524.
4) All new compounds were fully characterized by ^{1}H-NMR, IR, and mass spectroscopy and by elemental analyses. The spectral data are given below.
2a: Mp 232-235 °C: NMR($CDCl_3$) δ3.37(s, 3H), 3.51(s, 3H), 7.44(s, 1H), 8.84 (s, 1H): IR(Nujol) 3220, 1730, 1715, 1670, 1620 cm^{-1}: mass spectrum, m/e (relative intensity) 236(13), 235(M^+, 100), 164(38), 150(23), 107(34).
2b: Mp 202.5-205 °C: NMR($CDCl_3$) δ3.00(s, 3H), 3.37(s, 3H), 3.52(s, 3H), 7.31(s, 1H), 8.85(s, 1H): IR(Nujol) 1710(broad), 1660, 1625 cm^{-1}: mass spectrum, m/e(relative intensity) 250(12), 249(M^+, 100), 164(52), 136(10), 107(29).
2c: Mp 184-186 °C: NMR($CDCl_3$) δ1.20(t, 3H, J=7 Hz), 3.40(s, 3H), 3.53(s, 3H), 3.60(q, 2H, J=7 Hz), 7.38(s, 1H), 8.88(s, 1H): IR(Nujol) 1700(broad), 1660, 1620 cm^{-1}: mass spectrum, m/e(relative intensity) 264(15), 263(M^+, 100), 248(28), 165(16), 164(39), 107(21).

2d: Mp 187-189 °C: NMR($CDCl_3$) δ3.42(s, 3H), 3.50(s, 3H), 7.33-7.48(m, 5H), 7.56(s, 1H), 8.90(s, 1H): IR(Nujol) 1710(broad), 1660, 1630, 1600 cm^{-1}: mass spectrum, m/e(relative intensity) 312(17), 311(M^+, 88), 266(14), 164(100), 119(12), 107(39).

2e: Mp 150-151 °C: NMR($CDCl_3$) δ3.39(s, 3H), 3.51(s, 3H), 4.68(s, 2H), 7.28-7.38(m, 5H), 7.44(s, 1H), 8.88(s, 1H): IR(Nujol) 1710, 1695, 1660, 1620 cm^{-1}: mass spectrum, m/e(relative intensity) 326(21), 325(M^+, 100), 297(14), 220(31), 193(75), 192(22), 165(22), 164(75), 107(21).

4a: Mp 257-260 °C: NMR(D_2O) δ3.8-4.5(m, 5H), 6.02(d, 1H, J=4 Hz), 7.20(s, 1H), 9.00(s, 1H): IR(Nujol) 3550-2700, 1750-1700, 1680, 1620 cm^{-1}: mass spectrum, m/e(relative intensity) 207(M^+-132, 100), 136(48), 112(25), 93(50), 73(41).

4b: Mp 243-246 °C: NMR(D_2O) δ3.03(s, 3H), 3.7-4.5(m, 5H), 6.05(d, 1H, J=4 Hz), 7.28(s, 1H), 8.97(s, 1H): IR(Nujol) 3580-3000, 1730, 1710-1650 cm^{-1}: mass spectrum, m/e(relative intensity) 353(M^+, 2), 264(4), 222(19), 221(100), 150(12), 136(39), 93(31), 73(21).

6b: Mp 114-116 °C: NMR($CDCl_3$) δ2.11(s, 3H), 2.16(s, 6H), 3.02(s, 3H), 4.26-4.50(m, 5H), 6.10(d, 1H, J=4 Hz), 7.40(s, 1H), 9.10(s, 1H): IR(Nujol) 1750, 1730, 1710(broad), 1620 cm^{-1}: mass spectrum, m/e(relative intensity) 479(M^+, 2), 260(12), 259(95), 157(16), 139(100): high resolution mass spectrum, m/e 479.1177(M^+).

8a: Mp >280 °C: NMR(D_2O) δ2.43(t, 2H, J=7 Hz), 3.7-4.4(m, 4H), 6.34(t, 1H, J=7 Hz), 7.20(s, 1H), 8.94(s, 1H): IR(Nujol) 3600-2600, 1730, 1710-1670, 1610 cm^{-1}: mass spectrum, m/e(relative intensity) 207(M^+-116, 35), 179(9), 136(16), 117(76), 98(75), 97(98), 81(92), 73(88), 71(71), 70(44), 69(100).

8b: Mp >280 °C: NMR(D_2O) δ2.43(t, 2H, J=7 Hz), 3.00(s, 3H), 3.7-4.5(m, 4H), 6.33(t, 1H, J=7 Hz), 7.21(s, 1H), 9.03(s, 1H): IR(Nujol) 3600-3100, 1730, 1700, 1670, 1620 cm^{-1}: mass spectrum, m/e(relative intensity) 337(M^+, 2), 319(2), 221(100), 136(49), 117(64), 93(48), 81(30), 74(54), 73(41).

9: Mp 207-209.5 °C: NMR($CDCl_3$) δ3.39(s, 3H), 3.53(s, 3H), 7.59(s, 1H), 7.6-8.2(m, 4H), 7.95(s, 1H): IR(Nujol) 1720, 1670-1650, 1595 cm^{-1}: mass spectrum, m/e(relative intensity) 297(20), 296(M^+, 100), 268(18), 211(25), 183(45), 170(46), 155(15).

5) H. Nishimura, M. Mayama, Y. Komatsu, H. Kato, N. Shimaoka, and Y. Tanaka, J. Antibiot., 17A, 148 (1964); S. Matsuura, O. Shiratori, and K. Katagiri, ibid., 17A, 234 (1964).

6) A. D. Argoudelis and R. R. Herr, Antimicrob. Ag. Chemoth., 1962, 780; P. F. Wiley and F. A. Mackellar, J. Am. Chem. Soc., 92, 417 (1970).

7) B. Rosenberg, L. VanCamp, J. E. Trosko, and V. H. Mansour, Nature, 222, 385 (1969).

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