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PALLADIUM-CATALYZED COUPLING REACTION OF IODOURACIL HAVING ACETAMIDINE MOIETY WITH OLEFINS

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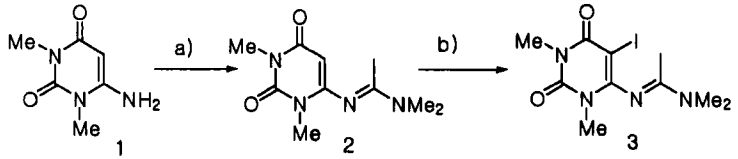
Abstract-The reaction of 6-[1-Aza-2-(dimethylamino)prop-1-enyl]-5-iodo-1,3-dimethyluracil (**3**) with various olefins in the presence of a catalytic amount of $Pd(OAc)_2$ and 1.5 equiv. of K_2CO_3 in DMF at 120 °C gave the pyrido[2,3-*d*]pyrimidine derivatives (**5a-b** and **7a-d**) in moderate to high yield.

Pyridopyrimidines have received an attention due to their potential biological activities[1] and especially 5,10-didezatetrahydrofolic acid (DDATHF) analogs[2] as antifolates over the past years. As such, a large number of works have been published on the synthesis of these heterocycles, which involve cyclocondensation reactions of appropriate pyridine or pyrimidine intermediates with other reagents,[3-5] [4+2] cycloaddition reaction of uracil with olefins,[6] and the coulping reaction of iodouracil with various olefins using stoicheometric amount of palladium acetate in acetic acid.[7] Recently, we also reported one efficient method for the synthesis of pyrido[2,3-*d*]pyrimidine by the reaction of iodouracil having formamidine moiety with vaious olefins in DMF using catalytic amount of palladium acetate instead of stoicheometric amount of palladium acetate.[8]

As a continuous work, we tried the reaction of iodouracil (3) having acetamidine moiety with olefins (4) in the presence of potassum carbonate in DMF at 120 °C. The reaction of iodouracil having acetamidine moiety (3) with olefins having acetyl, methoxycarbonyl or nitrile group give a unexepcted demethylated pyrido[2.3-*d*]pyrimidine (**5a** and **5b**), which has not been reported as far as we know. However, the reaction of compound (3) with styrene derivative or vinyl ether gave the expected deaminated product, which is consistent with the result of the reported one.[8]

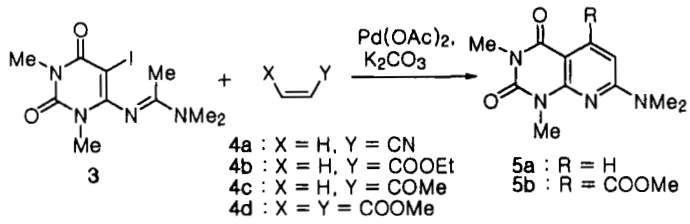
The iodouracil (3) was prepared as follows. The compound (2) was prepared by the reaction of 6-amino-1,3-dimethyluracil (1) with dimethylacetamide dimethylacetal (DMA-DMA) in methanol at reflux. 6-[1-Aza-2-(dimethylamino)prop-1-enyl]-1,3-dimethyluracil (2) was iodinated by the reaction with *N*-iodosuccimide (NIS) in methylene chloride under reflux to give 6-[1-Aza-2-(dimethylamino)prop-1-enyl]-5-iodo-1,3-dimethyluracil (3) (Scheme 1).



a) DMA-DMA in MeOH at reflux b) NIS in MC at reflux

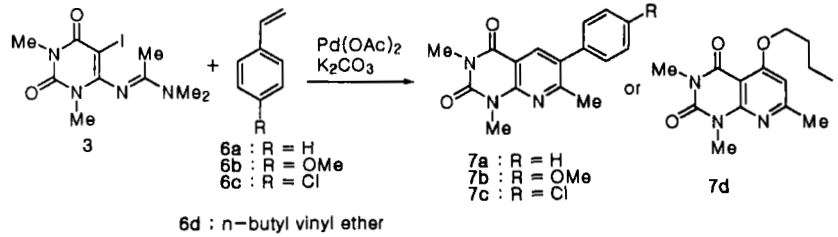
Scheme 1

The reaction of iodouracil (3) with olefins (4) (ethyl acrylate, acrylonitrile, methyl vinyl ketone) in the presence of catalytic amount of palladium acetate using potassium carbonate (1.5 equiv.) as base in DMF gave a single product (**5a**) in high yield (77%-88%) (Scheme 2). The reaction was carried out at about 120 °C using oil bath. The reaction was very clean and no other side product was not found in TLC. The reaction of iodouracil (3) with dimethyl maleate (**4d**) in the same condition gave a pyrido[2,3-*d*]pyrimidine (**5b**) with methoxycarbonyl group at C-5 position in 55% yield. The result was different from that of the palladium-catalyzed reaction of iodouracil having formamidine moiety with dimethyl maleate,[8] in which the product was pyrido[2,3-*d*]pyrimidine having methoxycarbonyl group at C-7 position. We speculate that this reaction involves elemination of CH_3CN, CH_3COOEt, CH_3COCH_3 or CH_3COOMe,



Scheme 2

even if the methyl group of acetamidine moiety is not good leaving group. The products obtained showed ^{1}H NMR, IR and GC-MS data compatable with the structures. Table 1 summarizes the results of the palladium-catalyzed reaction of iodouracil (**3**) with various alkenes.



Scheme 3

However, the palladium-catalyzed reaction of iodouracil (**3**) with styrene derivatives (**6a-c**) gave the pyridopyrimidines (**7a-c**) with methyl group at C-7 position (Scheme 3) in high yield as shown in Table 1. The reaction of iodouracil (**3**) with n-butyl vinyl ether gave the product (**7d**), which have ether linkage at C-5. This result is similar to the result of the reported one.[8]

In conclusion, We run the palladium catalyzed reaction of iodouracil (**3**) with various alkenes to give pyrido[2,3-*d*]pyrimidine in medium to high yield. If olefins have functional groups such as acetyl, ester or nitrile, the reaction product is the demethylated pyrido[2,3-*d*]pyrimidines (**5a**, **5b**). Otherwise, the products is the deaminated pyrido[2,3-*d*]pyrimidines (**7a-d**). The reason is not clear. The mechanism are under further investigation.

EXPERIMENTAL

All reactions were run under a nitrogen atmosphere. Flash chromatography was performed with Kiesel 60 (230-400 mesh) silica gel. NMR

Table 1. The results of the reactions of 3 with olefins

Entry	Substrates	Reation time	Product	yield(%)
1	Acrylonitrile	3 h	**5a**	88 %
2	Ethyl acrylate	3 h	**5a**	77 %
3	Methyl vinyl ketone	3 h	**5a**	88 %
4	Dimethyl maleate	3 h	**5b**	65 %
5	Styrene	3 h	**7a**	94 %
6	4-Methoxystyrene	3 h	**7b**	90 %
7	4-Chlorostyrene	3 h	**7c**	81 %
8	n-Butyl vinyl ether	3 h	**7d**	80 %

All yields quoted are of column chromatographed material.

spectra were recorded on a Varian Gemni 300 MHz. Mps were determined on Electrothermal IA9000 Series Digital Melting Point Apparatus and are uncorrected. The IR spectra were obtained on a Shimadzu FT-IR spectrophotometer. GC-MS were recorded on a VG70-VSEQ Mass Spectrometer.

6-[1-Aza-2-(dimethylamino)prop-1-enyl]-1,3-dimethyluracil (2). To a solution of 6-amino-1,3-dimethyluracil (100 mg, 0.644 mmol) in anhydrous methanol (15 mL) was added DMA-DMA (172 mg, 288 mol). The resulting solution was heated to reflux for 12 h under argon. The reaction was concentrated under reduced pressure and the formed yellow solid was recrystallized using ethyl acetate to give yellow crystals in 90 % yield (130 mg); mp 144-145 °C; IR (KBr) 1688 (C=O), 1654 (C=O), 1604 (C=C), 1440 (C=C, C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.83 (s, 1H), 3.34 (s, 3H), 3.29 (s, 3H), 3.10 (s, 6H), 2.12 (s, 2H); Mass m/z (relative intensity) (EI, 70 eV) 224 (M^+, 100), 180 (32), 140(72), 112(15), 82(54), 55(78).

6-[1-Aza-2-(dimethylamino)prop-1-enyl]-5-iodo-1,3-dimethyluracil (3). The solution of compound (2) (130 mg, 0.579 mmol) and NIS (196 mg, 0.869 mmol) in anhydrous methylene chloride (20 mL) was refluxed for 2 h. The solution was washed with water (20 ml x 3), dried with anhydrous $MgSO_4$, concentrated and chromatographed on silica gel using a solution of EA and Hexane as eluent (1:2) to give a product (yellow crystals) (3) in 87 % yield (175 mg); mp 117-120 °C; IR (KBr) 1688, 1641, 1560, 1400, 1192, 1008, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.41 (s, 3H), 3.33 (s, 3H), 3.12 (s, 6H), 1.99 (s, 3H); Mass m/z (relative intensity) (EI, 70 eV) 224 (M^+-I, 58), 209 (16), 180(26), 140(69), 123(16), 112(21), 82(77), 55(100).

General procedure for the reaction of iodouracil (3) with alkenes. To the solution of compound (3) (100 mg, 0.285 mmol) in anhydrous DMF (8 mL) were added $Pd(OAc)_2$ (3.2 mg, 0.014 mmol), anhydrous K_2CO_3 (59 mg, 0.43 mmol), and an olefin (1.2 equiv.). The resulting solution was stirred at 120 ℃ for 3 h under dry argon atmosphere, concentrated under reduced pressure, and chromatograped on silica gel using a solution of ethyl acetate and hexane (1:2) as eluent. The concentration gave the pale yellow pyrido[2,3-*d*]pyrimidines (**5a, 5b, 7a-d**).

8-*N*,*N*-Dimethylamino-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(*1H,3H*)-dione (5a). Yield: see Table 1, mp 177 ℃; IR (KBr) 1690, 1661, 1576, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.11 (d, J = 7.96 Hz, 1H), 6.33 (d, J = 7.96, 1H), 3.69 (s, 3H), 3.41 (s, 3H), 3.20 (s, 6H); Mass m/z (relative intensity) (EI, 70 eV) 234 (M^+, 100), 219 (35), 205 (64), 162 (12), 148 (10), 133 (8), 93 (6), 64 (8). HRMS Calcd for $C_{11}H_{14}N_4O_2$ 234.11, Found 234.1125.

5-Methoxycarbonyl-1,3-dimethyl-8-*N*,*N*-dimethylaminopyrido[2,3-*d*]pyrimidine-2,4(*1H,3H*)-dione (5b). Yield 65 %; mp 195 ℃; IR (KBr) 1746, 1690, 1644, 1612, 1562, 1494, 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.26 (s, 1H), 3.99 (s, 1H), 3.69 (s, 3H), 3.41(s, 3H), 3.21 (s, 6H); Mass m/z (relative intensity) (EI, 70 eV) 292 (M^+, 100), 277 (16), 263 (43), 232 (10), 205 (26), 149 (7), 105 (12), 78 (9). HRMS Calcd for $C_{13}H_{16}N_4O_4$ 292.12, Found 292.1172.

1,3,8-Trimethyl-6-phenylpyrido[2,3-*d*]pyrimidine-2,4(*1H,3H*)-dione (7a). Yield 94 %; mp 130-132 ℃; IR (KBr) 1708, 1664, 1608, 1462, 1406, 1352 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.26 (s, 1H), 7.42 (m, 3H), 7.34 (m, 2H), 3.76 (s, 3H), 3.49 (s, 3H), 2.57 (s, 3H); Mass m/z (relative intensity) (EI, 70 eV) 281 (M^+, 100), 252 (38), 169 (21), 140 (5), 73 (2). HRMS Calcd for $C_{16}H_{15}N_3O_2$ 281.12, Found 281.1168.

6-(4-Methoxyphenyl)-1,3,8-trimethylpyrido[2,3-*d*]pyrimidine-2,4(*1H,3H*)-dione (7b). Yield 90 %; mp 149-150 ℃; IR (KBr) 1708, 1656, 1604, 1460, 1246 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.25 (s, 1H), 7.26 (d, J = 6.0 Hz, 2h), 6.99 (d, J = 6.0 Hz, 2H), 3.87 (s, 3H), 3.75 (s, 3H), 3.49 (s, 3H), 2.57 (s, 3H); Mass m/z (relative intensity) (EI, 70 eV) 311 (M^+, 100), 296 (15), 282 (19), 199 (17), 170 (4), 127 (7), 100 (4), 77 (3). HRMS Calcd for $C_{17}H_{17}N_3O_3$ 311.13, Found 311.1270.

6-(4-Chlorophenyl)-1,3,8-trimethylpyrido[2,3-*d*]pyrimidine-2,4-(*1H,3H*)-dione (7c). Yield 81%; mp 169-170 ℃; IR (KBr) 1718, 1666, 1608, 1464 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.24 (s, 1H), 7.46 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8..6 Hz, 2H), 3.76 (s, 3H), 3.50 (s, 3H), 2.61 (s, 3H); Mass m/z (relative intensity) (EI, 70 eV) 315 (M^+, 100), 286 (34), 203 (31), 167 (9), 139 (6), 127 (4), 115 (4). HRMS Calcd for $C_{16}H_{14}ClN_3O_2$ 315.08, Found 315.0790.

6-(4-methoxycarbonyl)phenyl-1,3,8-trimethylpyrido[2,3-*d*]pyrimidine-2,4(*1H,3H*)-dione (7d) Yield 80%; mp 108 ℃; IR (KBr) 2956, 2874, 1706, 1660, 1596, 1568, 1354, 1288, 1232 cm^{-1}; ^1H NMR δ 6.51 (s, 1H), 4.13 (t, J = 6.4 Hz, 2H), 3.69 (s, 3H), 3.42 (s, 3H), 2.51 (s, 3H), 1.91 (m, 2H), 1.57 (m, 2H), 1.01 (t, J = 7.1 Hz, 3H); Mass m/z (relative intensity) (EI, 70 eV) 277 (M^+, 10), 248 (47), 234 (100), 221 (14), 192 (30), 177 (16), 135 (9), 109 (22).

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