SYNTHESIS OF PYRIDO[2,3-d]PYRIMIDINES VIA PALLADIUM-CATALYZED COUPLING REACTION FOLLOWED BY ELECTROCYCLIC REACTION

Kee Yoon Rho, Joong Hyup Kim, Sung Hoon Kim, and Cheol Min Yoon

*Department of Chemistry, College of Science and Technology, Korea University, Jochiwon, Choong-nam, 339-700, Korea, \(^{b}\)Biochemicals Research Center, Korea Institute of Science and Technology P.O. Box 131, Cheongryang, Seoul, Korea

Abstract—Pyrido[2,3-d]pyrimidines (5a–h) were regioselectively synthesized by the reaction of 5-iodo-6-(dimethylaminomethylene)amino-1,3-dimethyluracil (3), which was prepared from the reaction of 6-amino-1,3-dimethyluracil with dimethylformamide dimethyl acetal followed by iodination, with various olefins (4a–h) in the presence of a catalytic amount of Pd(OAc)\(_2\), Cul, and K\(_2\)CO\(_3\) in DMF at 100°C.

INTRODUCTION

Fused pyridopyrimidines have long 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 fused heterocycles, which usually involve cyclocondensation reactions of appropriate pyridine or pyrimidine intermediates with other reagents.\(^3\)–\(^5\)

In addition to these two classical condensation methods, two other type methods have been reported: Warnhoff's and Hirota's method. Warnhoff's group reported the synthesis of substituted pyrido[2,3-d]pyrimidines from 6-(dimethylaminomethylene)amino-1,3-dimethyluracil.
(2) via [4+2] cycloaddition reaction with electron-deficient olefins.\textsuperscript{6} Uracil (2) was used as electron-sufficient diene in this reaction. One of disadvantages in this method is the limitation to electron-deficient olefins and the other is low yield due to side reaction. Hirota's group synthesized substituted pyrido[2,3-\textit{d}]pyrimidines by the palladium-mediated C-C coupling reaction of electron-deficient olefins with the same uracil (2) in refluxing acetic acid in good yields.\textsuperscript{7} However, they used stoichiometric amount of Pd(OAc)\textsubscript{2} as a coupling reagent and only electron-deficient olefins.

In this paper, we want to report an efficient synthetic method of pyrido[2,3-\textit{d}]pyrimidines, which is a modified one of Wamhoff's method.

RESULTS AND DISCUSSION

The compound (2) was conveniently prepared by the reaction of 6-amino-1,3-dimethyluracil (1) with dimethylformamide dimethyl acetal (DMF-DMA) at room temperature. This condition is milder and the yield is better than Wamhoff's (66%). 6-(Dimethylaminomethylene)amino-1,3-dimethyluracil (2) was iodinated by the reaction with \textit{N}-iodosuccimide (NIS) in methylene chloride under reflux to give 5-iodo-6-(dimethylamino)methylenelamino-1,3-dimethyl-uracil (3) in 93% yield (Scheme 1).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme1}
\caption{Scheme 1.}
\end{figure}

Pyrido[2,3-\textit{d}]pyrimidines (5a-h) were synthesized by the reaction of 5-iodo-6-(dimethylamino)methylene)amino-1,3-dimethyluracil (3) with electron-rich or electron-deficient olefins in the presence of a catalytic amount of Pd(OAc)\textsubscript{2} and Cul in DMF at 100 °C in good to excellent yields. Anhydrous K\textsubscript{2}CO\textsubscript{3} was used as a base. When we used triethylamine instead of
anhydrous K$_2$CO$_3$ as a base or acetonitrile instead of DMF as a solvent, the reaction did not give any expected product at all and starting material was remained. In a harsh condition (higher temperature), uracil (3) was deiodinated. The reaction time and yield under these catalytic conditions are shown in Table 1.

Table 1. The results of the reactions of 3 with various olefins (4a–h)

<table>
<thead>
<tr>
<th>olefins</th>
<th>product</th>
<th>X</th>
<th>Y</th>
<th>reaction time</th>
<th>yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>5a</td>
<td>H</td>
<td>CO$_2$Et</td>
<td>5 h</td>
<td>76</td>
</tr>
<tr>
<td>4b</td>
<td>5b</td>
<td>H</td>
<td>CO$_2$Bu-t</td>
<td>4 h</td>
<td>80</td>
</tr>
<tr>
<td>4c</td>
<td>5c</td>
<td>H</td>
<td>CN</td>
<td>4 h</td>
<td>91</td>
</tr>
<tr>
<td>4d</td>
<td>5d</td>
<td>H</td>
<td>COMe</td>
<td>3 h</td>
<td>84</td>
</tr>
<tr>
<td>4e</td>
<td>5e</td>
<td>H</td>
<td>C$_6$H$_5$</td>
<td>4 h</td>
<td>94</td>
</tr>
<tr>
<td>4f</td>
<td>5f</td>
<td>OBu-t</td>
<td>H</td>
<td>4 h</td>
<td>99(4:1)$^a$</td>
</tr>
<tr>
<td>4f$'$</td>
<td>H</td>
<td>OBu-t</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4g(trans)</td>
<td>5g</td>
<td>CO$_2$Me</td>
<td>CO$_2$Me</td>
<td>6 h</td>
<td>61</td>
</tr>
<tr>
<td>4g$'$</td>
<td>H</td>
<td>CO$_2$Me</td>
<td>CO$_2$Me</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>4h(cis)</td>
<td>5h</td>
<td>CO$_2$Et</td>
<td>CO$_2$Et</td>
<td>6 h</td>
<td>70</td>
</tr>
<tr>
<td>5a</td>
<td>H</td>
<td>CO$_2$Et</td>
<td></td>
<td></td>
<td>25</td>
</tr>
</tbody>
</table>

All yields quoted are of column chromatographed material. $^a$Ratio of two isomers was based on $^1$H NMR.

The reaction seemed to proceed through palladium-catalyzed coupled intermediate (6) followed by electrocyclic reaction and elimination of dimethylamine as shown in Scheme 2.

Scheme 2.

Reagents and reaction condition: Pd(OAc)$_2$, Cul, K$_2$CO$_3$ in DMF.

The reaction did not give any expected product except for the formation of unidentifiable
decomposed compound for 10 h heating at 100 °C without Pd(OAc)$_2$ as a catalyst (even higher temperature). Another evidence for the palladium-catalyzed coupling reaction followed by electrocyclic reaction is the regioselectivity of the reaction with styrene (4e) and especially tert-butyl vinyl ether (4f), which is consistent with that of the palladium-catalyzed reaction of the aryl halide with styrene and tert-butyl vinyl ether.$^9$ In the case of electron-deficient olefins (4a–e), the regioselectivity is in good accord with that reported by Hirota.$^7$

The reaction of 3 with olefins (4a–e) gave one product respectively according to TLC. However, the reaction of 3 with olefins (4f–h) gave two products respectively. In the reaction with tert-butyl vinyl ether (4f), two regioisomers (5f) and (5f') (4:1 according to $^1$H NMR) are formed. Several attempts (recrystallization and chromatography) for the separation of these two isomers were failed. The reaction of 3 with fumarate (4g) and maleate (4h) gave two products respectively: one is decarboxylated pyridopyrimidines (5g’, 5a) and the other pyridopyrimidinedicarboxylic acid esters (5g, 5h). The formation mechanism of these pyridopyrimidines (5g’, 5a) is not clear. These decarboxylated products did not seem to be formed by the decarboxylation of pyridopyrimidines (5g, 5h) respectively because the amount of decarboxylated products did not increase during the extended reaction time. However, the decarboxylation seemed to proceed before the formation of coupling products (6).

In conclusion, we developed an efficient synthetic route to pyrido[2,3-d]pyrimidines using a catalytic amount of palladium reagent. The reactions go through palladium-catalyzed coupling followed by electrocyclization and elimination. This method allows an access to a range of structural variations of the C-5 or/and C-6 positions of pyridopyrimidine by the reaction of uracil (3) with olefins having the various functional groups (electron donating and withdrawing).

**EXPERIMENTAL**

All reactions were run under a nitrogen atmosphere. Flash chromatography was performed with Kiesel 60 (230–400 mesh) silica gel. NMR spectra were recorded on a Varian Gemini 200 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. HRMSs were recorded on a VG70–VSEQ Mass Spectrometer.
6-(Dimethylaminomethylene)amino-1,3-dimethyluracil (2). To a solution of 6-amino-1,3-dimethyluracil (1.55 g, 0.01 mol) in anhydrous methanol (30 mL) was added DMF-DMA (1.59 mL, 0.012 mol) at rt. The resulting solution was stirred at rt for 24 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 81.56% yield (1.81 g); mp 102-103°C; IR (KBr) 1700 and 1650 (CO), 1630 (C=N) cm⁻¹; ¹H NMR (CDCl₃): δ 3.07 and 3.13 (each s, each 3H, N(CH₃)₂), 3.34 and 3.41 (each s, each 3H, 2 x NCH₃), 5.07 (s, 1H, 5-H), 7.67 (s, 1H, 8-H). Anal. Calcd for C₉H₁₄N₄O₂: C, 51.42; H, 6.71; N, 26.65. Found: C, 51.08; H, 6.90; N, 26.50.

5-Iodo-6-(dimethylaminomethylene)amino-1,3-dimethyluracil (3). The solution of compound (2) (444 mg, 2 mmol) and NIS (540 mg, 2.4 mmol) in anhydrous methylene chloride (20 mL) was refluxed for 30 min. The solution was washed with water (20 mL x 3), dried with anhydrous MgSO₄ and concentrated to give a product (brown crystals) (3) in 93 % yield (650 mg); mp 108-110°C; IR (KBr) 1700 and 1651 (CO), 1620 (C=N) cm⁻¹; ¹H NMR (CDCl₃) δ 3.09 and 3.14 (each s, each 3H, N(CH₃)₂), 3.34 and 3.41 (each s, each 3H, 2 x NCH₃), 7.72 (s, 1H, 8-H). Anal. Calcd for C₉H₁₃N₄O₂I: C, 32.16; H, 3.90; N, 16.67; I, 37.75. Found: C, 32.38; H, 3.71; N, 16.55.

General procedure for the synthesis of pyridopyrimidines (5a-h). To the solution of compound (3) (100 mg, 0.287 mmol) in anhydrous DMF (8 mL) were added Pd(OAc)₂ (3.2 mg, 0.014 mmol), Cul (1.37 mg, 0.007 mmol), anhydrous K₂CO₃ (60 mg, 0.43 mmol), and an olefin (1.2 eq.). The resulting solution was stirred at 100°C for several hours (3-6 h) under dry argon atmosphere, concentrated under reduced pressure, and chromatographed on silica gel using a solution of ethyl acetate and hexane (1:4) as eluent. The concentration gave the pyridopyrimidines (5a-h) in moderate to high yield respectively.

6-Ethoxycarbonyl-1,3-dimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (5a). Yield: 76%, mp 133-134°C; IR (KBr) 1720 and 1668 (CO), 1610 (C=N) cm⁻¹; ¹H NMR (CDCl₃) δ 1.43 (t, 3H, J = 7.1 Hz, ethoxy CH₃), 3.51 and 3.76 (each s, each 3H, 2 x NCH₃), 4.42 (q, 2H, J =
7.1 Hz, ethoxy CH$_2$, 9.02 and 9.24 (each d, each J = 2.2 Hz, each 1H). HRMS Calcd for C$_{12}$H$_{13}$N$_3$O$_4$ 263.0900, Found 263.0894. Anal. Calcd for C$_{12}$H$_{13}$N$_3$O$_4$: C, 54.75; H, 4.97; N, 15.96. Found: C, 54.81; H, 4.99; N, 15.77.

6-tert-Butoxycarbonyl-1,3-dimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (5b). Yield 80%; mp 203-204 °C; IR (KBr) 1720 and 1682 (CO), 1610 (C=N) cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 1.62 (s, 9H, C(CH$_3$)$_3$), 3.50 and 3.76 (each s, each 3H, 2 x NCH$_3$), 8.94 and 9.20 (each d, each J = 2.2 Hz, each 1H). HRMS Calcd for C$_{14}$H$_{17}$N$_3$O$_4$ 291.1219, Found 291.1220. Anal. Calcd for C$_{14}$H$_{17}$N$_3$O$_4$: C, 57.72; H, 5.88; N, 14.42. Found: C, 57.73; H, 5.92; N, 14.70.

6-Cyano-1,3-dimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (5c). Yield 91%; mp 172-173 °C (lit.,$^7$ mp 181-182 °C).


1,3-Dimethyl-6-phenylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (5e). Yield 94%; mp 120 °C (lit.,$^7$ mp 138-139 °C).

5-tert-Butoxy-1,3-dimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (5f) and 6-tert-Butoxy-1,3-dimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (5f'). Yield 99%; mp 129-130 °C; IR (KBr) 1701 and 1661 (CO), 1590 (C=N) cm$^{-1}$; $^1$H NMR of 5f (CDCl$_3$) $\delta$ 1.63 (s, 9H, C(CH$_3$)$_3$), 3.43 and 3.69 (each s, each 3H, 2 x NCH$_3$), 6.80 and 8.35 (each d, each J = 5.9 Hz, each 1H); $^1$H NMR of 5f' (CDCl$_3$) $\delta$ 1.62 (s, 9H, C(CH$_3$)$_3$), 3.49 and 3.73 (each s, each 3H, 2 x NCH$_3$), 8.48 and 8.67 (each d, each J = 2.0 Hz, each 1H). HRMS Calcd for C$_{13}$H$_{17}$N$_3$O$_3$ 263.1271, Found 263.1273. Anal. Calcd for C$_{13}$H$_{17}$N$_3$O$_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.55; H, 6.44; N, 16.09.

5,6-Dimethoxycarbonyl-1,3-dimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (5g) and 6-Methoxycarbonyl-1,3-dimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (5g'). 5g: Yield
61%; mp 152 °C; IR (KBr) 1760, 1728 and 1672 (CO) cm⁻¹; ¹H NMR (CDCl₃) δ 3.46 and 3.78 (each s, each 3H, 2 x NCH₃), 3.95 and 4.09 (each s, each 3H, 2 x CO₂CH₃), 9.28 (s, 1H). HRMS Calcd for C₁₃H₁₃N₃O₆ 307.0804, Found 307.0805. Anal. Calcd for C₁₃H₁₃N₃O₆: C, 50.82; H, 4.26; N, 13.68. Found: C, 50.99; H, 4.51; N, 13.37. 5g*: Yield 27%; mp 121-122 °C; IR (KBr) 1738, 1716.5 and 1670 (CO), 1608.5 (C=N) cm⁻¹; ¹H NMR (CDCl₃) δ 3.50 and 3.76 (each s, each 3H, 2 x NCH₃), 3.98 (s, 3H, CO₂CH₃), 9.29 (s, 1H). HRMS Calcd for C₁₁H₁₁N₃O₄ 249.0748. Found 249.0749. 5h: Yield 70%; mp 115-116 °C; IR (KBr) 1737, 1715 and 1672 (CO) cm⁻¹; ¹H NMR (CDCl₃) δ 1.36 (t, 6H, J = 7.0 Hz, 2 x ethoxy CH₃), 3.46 and 3.76 (each s, each 3H, 2 x NCH₃), 4.41 and 4.56 (each q, each 2H, J = 7.0 Hz, 2 x ethoxy CH₂), 9.29 (s, 1H). HRMS Calcd for C₁₅H₁₇N₃O₆ 335.1117, Found 335.1116. Anal. Calcd for C₁₅H₁₇N₃O₆: C, 53.73; H, 5.11; N, 12.53. Found: C, 53.61; H, 5.03; N, 12.55. 5a: Yield 25%.

ACKNOWLEDGMENTS

This work was financially supported partly by the Korea Science and Engineering Foundation (Equipment Support Program) and partly by Korea University and KIST (2E15200).

REFERENCES


Received, 17th July, 1998