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Synthesis of pyrido[2,3-*d*]pyrimidines via palladium-catalyzed reaction of iodouracil with acetylenes

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Abstract

The reactions of iodouracils having a formamidine or acetamidine moiety **1** with various acetylenes **2** in DMF at 120°C using potassium carbonate and a catalytic amount of palladium acetate gave a mixture of pyrido[2,3-*d*]pyrimidine derivatives in good to high yields. Addition of lithium chloride to the reaction solution resulted in a change of reaction selectivity.

Keywords: iodouracil; acetylene; palladium acetate; LiCl; pyridopyrimidine.

Palladium-catalyzed reactions have attracted the attention of synthetic organic chemists, since they are known to be an alternative to classical organic reactions. In particular, palladium-catalyzed annulation methodology has been effectively employed for the preparation of new aromatic systems.[1]

The pyridopyrimidines have received attention due to their potential biological activities.[2] Recently, we reported an efficient method for the syntheses of pyrido[2,3-*d*]pyrimidines by the reactions of iodouracil, having a formamidine or acetamidine moiety, with various olefins in DMF using a catalytic amount of palladium acetate.[3,4]

As a continuation of this work, the reactions of iodouracils having a formamidine or acetamidine moiety **1** with various acetylenes **2** were studied in the presence or absence of lithium chloride, which might play a crucial role in the reaction selectivity (Scheme 1).

The reaction of iodouracil **1a** with diphenylacetylene **2a** in DMF in the presence of palladium acetate as catalyst and potassium carbonate as base at 120°C gave two pyridopyrimidines **3a** (dehydrogenated one) and **4a** (deaminated one) in 67 and 27% yields, respectively (Table 1, entry 1). The selectivity was increased when the same reaction was tried in the presence of 1 equiv. of lithium chloride.[5] Pyridopyrimidine **3a** was obtained in 93% yield and only a trace amount of

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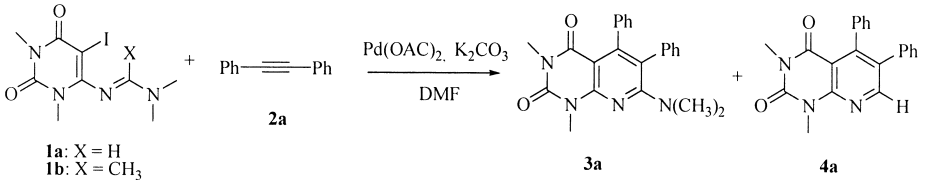


1a: X = H
1b: X = CH_3

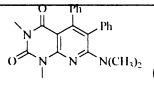
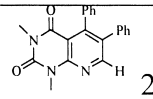
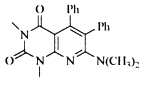
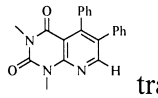
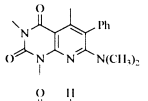
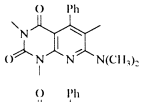
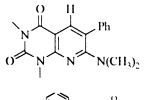
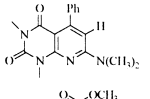
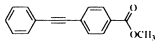
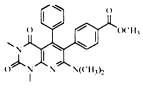
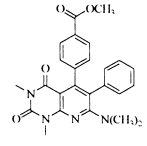
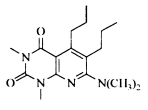
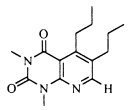
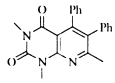
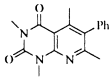
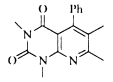
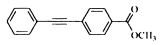
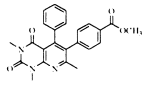
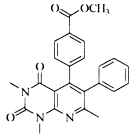
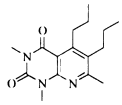
2a

3a

4a

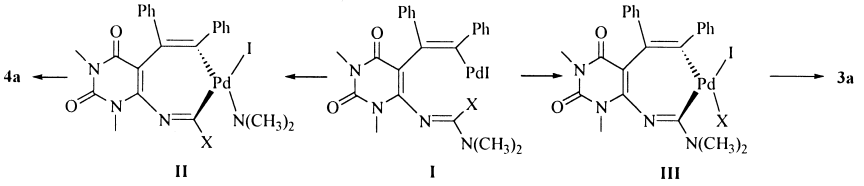
Scheme 1.

Table 1
Synthesis of pyrido[2,3-*d*]pyrimidines via palladium-catalyzed reaction

Entry	Amidine	Acetylene (2)	Salt	Time (h)	Products [a]
1	1a	Ph—≡—Ph	none	1.5	 67%  27%
2			LiCl		 93%  trace
3		Ph—≡—	LiCl	1.5	 60%  36%
4		Ph—≡—H	LiCl	1.5	 54%  32%
5			LiCl	1.5	 83%  0%
6		C_3H_7—≡—C_3H_7	LiCl	1.5	 96%  0%
7	1b	Ph—≡—Ph	none	1.5	 70%
8		Ph—≡—	none	1.5	 48%  18%
9			none	1.5	 80%  0%
10		C_3H_7—≡—C_3H_7	none	1.5	 54%

a) Isolated yields. All products gave spectra consistent with the assigned structures.

pyridopyrimidine **4a** was observed by TLC.[8] A similar selectivity was observed using 1 equiv. of lithium bromide instead of 1 equiv. of lithium chloride. However, selectivity was not observed at all when tetra-*n*-butylammonium bromide or tetra-*n*-butylammonium chloride was used instead of lithium bromide or lithium chloride. On the basis of these experimental results, the selectivity seems to be due to the lithium cation. Lithium cations in this reaction might prevent the insertion of palladium of intermediate **I** (X = H) into the C–N(Me)$_2$ bond to form intermediate **II** (X = H), which is necessary for the formation of pyridopyridmidine **4a** (Scheme 2). However, the exact mechanism to prevent the formation of the intermediate **II** (X = H) by a lithium cation is not clear.



Scheme 2.

The reactions of iodouracil **1a** with asymmetric acetylenes were tried in the presence of 1 equiv. of lithium chloride.[6] The reactions gave pyridopyrimidines with some regioselectivity (Table 1, entries 3–5). In these cases, the other product (the deaminated one) was not observed. The tendency of regioselectivity for these reactions is similar to that reported previously on the basis of electronic and steric effects.[1b]

The reaction of iodouracil having an acetamidine moiety **1b** with diphenylacetylene was tried under the same conditions in DMF (Table 1, entry 7). The reaction in the presence of lithium chloride did not give any coupling product and gave only deiodinated starting material. This might be explained by considering the role of the lithium cation. The palladium ion of intermediate **I** (X = Me) in the presence of lithium cation cannot insert into the C–N(Me)$_2$ bond to form intermediate **II** (X = Me), and also the insertion of palladium ion of intermediate **I** into the C–CH$_3$ bond to form intermediate **III** (X = Me) is difficult (Scheme 2).

However, the reactions of iodouracil **1b** with acetylenes in the absence of lithium chloride gave the pyridopyrimidines in high yields with regioselectivity (Table 1, entries 7–10).[7] However, the reaction of **1b** with phenylacetylene gave decomposition products with none of the desired cyclic compounds.

In conclusion, the reaction of iodouracils having a formamidine moiety **1a** with acetylenes using palladium acetate in DMF in the presence of lithium chloride at 120°C gave pyridopyrimidines with regioselectivity. The reaction of iodouracil having an acetamidine moiety **1b** with acetylenes without lithium chloride also gave pyridopyrimidines. Further work to determine the role of lithium cations in the palladium-catalyzed reaction of iodouracils with alkynes is in progress.

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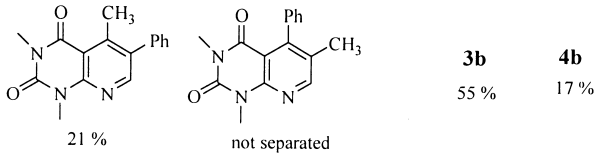
3. Rho, K. Y.; Kim, J. H.; Kim, S. H.; Yoon, C. M. *Heterocycles* **1998**, *12*, 2521.
4. Rho, Y. H.; Bae, J. W.; Nam, G. S.; Kim, J. H.; Kim, S. H.; Yoon, C. M. *Synth. Commun.* **2000**, *30*, 81.
5. One equivalent of lithium chloride in the reaction was identified to be the optimal amount for the selectivity. When 2 equiv. of lithium chloride was used, several other side products were observed by TLC. When 0.5 equiv. of lithium chloride was used, the selectivity was decreased. In this case, 14% of deaminated product **3a** was obtained.
6. The reaction of iodouracil **1a** with 1-phenyl-1-propyne **2b** in the absence of lithium chloride resulted in less selectivity, as shown below.



7. Insertion of palladium ion of the intermediate **I** into the C–N(Me)$_2$ bond in the absence of lithium chloride is possible to form intermediate **II** (Scheme 2).
8. Representative experimental procedure. To a solution of 5-iodo-6-(dimethylaminomethylene)amino-1,3-dimethyluracil **1a** (100 mg, 0.297 mmol) in DMF (10 ml) was added $Pd(OAc)_2$ (3.3 mg, 0.014 mmol), anhydrous K_2CO_3 (82 mg, 0.595 mmol), lithium chloride (12.6 mg, 0.297 mmol) and diphenylacetylene (80 mg, 0.446 mmol). The resulting solution was stirred at 120°C for 1.5 h under nitrogen, concentrated under reduced pressure and chromatographed on silica gel using a solution of ethyl acetate:hexane (1:10). Eluent concentration gave two pyrido[2,3-*d*]pyrimidines as a white solid.