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Alkynylation of halo pyrimidines under Pd/C–copper catalysis: regioselective synthesis of 4- and 5-alkynylpyrimidines☆

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Abstract—5-Bromo-4-chloro-6-methylpyrimidines underwent facile Pd/C–Cu catalyzed coupling reactions with a variety of terminal alkynes, which resulted in the corresponding 4-alkynyl-5-bromopyrimidines, regioselectively, with good yields. 4-Chloro-5-iodo-6-methylpyrimidine, however, yielded the corresponding 5-alkynyl-4-chloropyrimidines under the same reaction conditions.

Alkynyl substituted pyrimidines are the focus of research because of their notable biological activities,[1,2] in particular, adenosine kinase inhibitory activity for the treatment of pain and inflammatory diseases[3] and thymidylate synthase inhibitory properties for the treatment of cancer.[4] They are also useful intermediates for the synthesis of various heterocyclic structures.[5,6] In connection with our studies on the development of various heterocycles[7–9] of potential biological significance, we became interested in the synthesis of 4-alkynyl-substituted pyrimidines as precursors of novel pyrimidine enediynes[10a] as anticancer agents (Fig. 1). We reasoned that synthetic enediynes may show reduced toxicity and therefore may have a distinct advantage over the naturally occurring products as therapeutic agents.[10b] Recently, 10-membered cyclic pyrimidine enediynes, synthesized from alkynyl pyrimidines, were found to be effective for DNA cleavage at reasonable concentrations under physiological conditions.[2a]

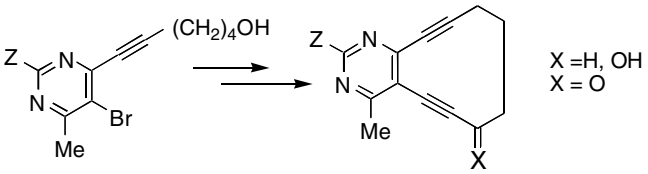

Figure 1.

Despite their biological significance, only a few methods have been reported for the synthesis of alkynyl substituted pyrimidines[11] and most of them involve the use of Sonogashira coupling of halo pyrimidines with terminal alkynes.[2–4,12] Although a variety of halo (e.g., chloro, bromo or iodo) pyrimidines have been utilized in these reactions, the use of 5-bromo-4-chloropyrimidines has not been investigated thus far.[13a-b] Over the last three decades, palladium catalyzed alkynylation (Sonogashira coupling)[13c] has become a most attractive and powerful tool for C–C bond forming reactions.[13d] Typically this reaction is carried out using a palladium catalyst [e.g., $Pd(PPh_3)_4$, $(PPh_3)_2PdCl_2$, etc.] and a copper salt as co-catalyst in the presence of an amine base. The use of Pd/C–CuI–PPh_3 as a less expensive catalyst system for efficient Sonogashira coupling has also been explored.[14] Due to our continuing interest in palladium catalyzed reactions[15] we recently reported an unprecedented synthesis of 4-alkynylthieno[2,3-*c*]pyran-7-ones.[15g] We now wish to report a regioselective synthesis of 4- and 5-alkynyl pyrimidines from the appropriate halo pyrimidines, for example, 5-bromo-4-chloro- or 4-chloro-5-iodopyrimidines using a Pd/C based methodology. These derivatives are attractive due to the synthetic potential of C-4/C-5 alkynyl fragments for use in library construction.

It was anticipated that the bromo group of 5-bromo-4-chloropyrimidine would participate preferentially in the Pd/C catalyzed alkynylation (Scheme 1, Path a)

Keywords: 4-Alkynyl-5-bromopyrimidine; Palladium catalyst; Terminal alkynes; 5-Bromo-4-chloro-6-methylpyrimidine.
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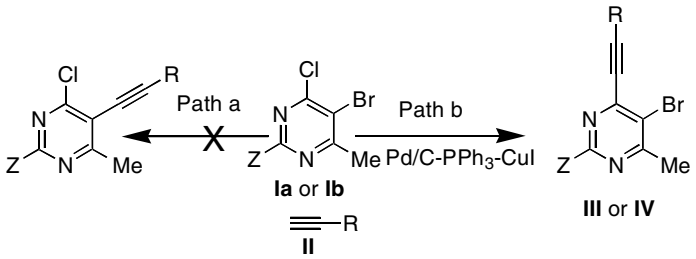
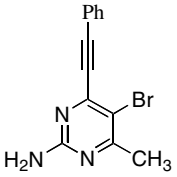
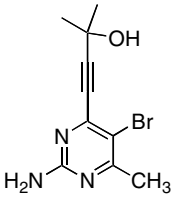
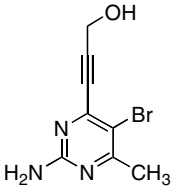
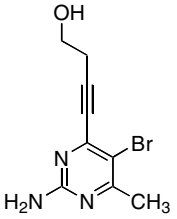
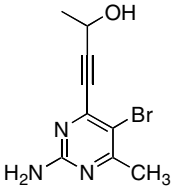
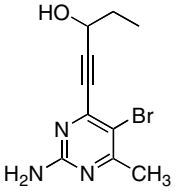


Scheme 1. Alkynylation of 5-bromo-4-chloro-6-methyl pyrimidines under Pd/C–Cu catalysis.

Table 1. Pd/C-catalyzed coupling of 5-bromo-4-chloro-6-methylpyrimidin-2-ylamine (**Ia**) with terminal alkynes[a]

Entry	Alkyne (**II**)	Time (h)	Product[b] (**III**)	Yield (%)[c]
1	≡–Ph	15		67
2	≡–C(OH)Me_2	20		92
3	≡–CH_2OH	24		66
4	≡–CH_2CH_2OH	15		70
5	≡–CH(OH)CH_3	15		66
6	≡–CH(OH)CH_2CH_3	20		60

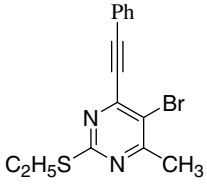
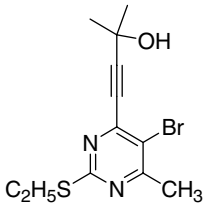
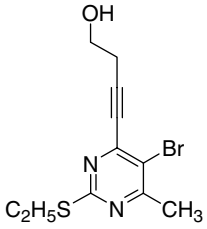
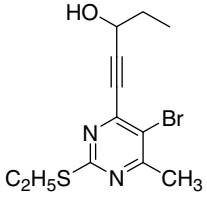
[a] All reactions were carried out using **Ia** (1.0 equiv), **II** (1.5 equiv), 10% Pd/C (0.05 equiv), PPh_3 (0.12 equiv), CuI (0.10 equiv) and Et_3N (2 equiv) in DMF at 80 °C.
[b] Identified by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy.
[c] Isolated yields.

due to the well known order of halide reactivity, that is I > Br ≫ Cl towards the palladium catalysts. However, we observed that the chloro group was replaced exclusively by an alkynyl moiety without affecting the bromo group (Scheme 1, Path b) under the palladium–copper catalysis conditions employed. Thus, when 5-bromo-4-chloro-6-methylpyrimidine [**Ia** ($Z = NH_2$) or **Ib** (SC_2H_5)][16a-b] was treated with 1.5 equiv of the terminal alkyne (**II**, R = alkyl, hydroxyalkyl, etc.)[16c] in dimethylformamide (DMF) in the presence of 10% Pd/C (0.05 equiv), PPh_3 (0.12 equiv), CuI (0.10 equiv) and triethylamine (2 equiv) under a nitrogen atmosphere, the corresponding 4-alkynyl–5-bromopyrimidine (**III** or **IV**) was obtained as the only product in good to excellent yield.[17] The unexpected and enhanced reactivity of the chloro group over the bromo group prompted us to investigate this reaction in a more detailed and systematic way.[18] The results of this study are summarized in Tables 1 and 2.

Using this palladium catalyzed reaction, a variety of terminal acetylenes (**II**) were reacted with 5-bromo-4-chloro-6-methylpyrimidin-2-ylamine (**Ia**, $Z = NH_2$) to afford 4-alkynyl pyrimidines (**III**) in good yields (Table 1). Aryl, alkyl and hydroxy groups present on the terminal alkynes were well tolerated during the course of the reaction. Replacement of the amino group on the pyrimidine ring by an ethylsulfanyl moiety was also well tolerated in the present Pd/C mediated coupling reaction. Thus the use of 5-bromo-4-chloro-6-methyl-2-ethylsulfanylpyrimidine (**Ib**, $Z = SC_2H_5$) also led to the formation of the corresponding 4-alkynyl analogues in good to excellent yields (Table 2).

We have shown that a chloro group at the C-4 on a pyrimidine ring is more reactive towards the palladium catalyzed alkynylation reaction than the C-5 bromo group. To compare the reactivity of the chloro group at C-4 with an iodo group at C-5, we investigated the reaction of 4-chloro-5-iodo-6-methylpyrimidin-2-ylamine[19] (**Ic**) with terminal alkynes. The iodo group was found to be the more reactive group under the conditions studied and the corresponding 5-alkynyl pyrimidine was isolated as the only product (Table 3). This

Table 2. Pd/C-catalyzed regioselective coupling of 5-bromo-4-chloro-6-methyl-2-ethylsulfanylpyrimidine (**Ib**) with terminal alkynes[a]

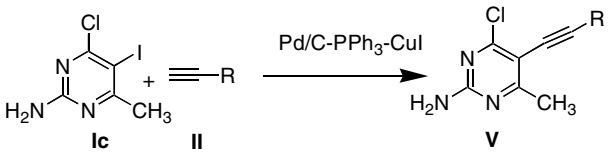
Entry	Alkyne (**II**)	Time (h)	Product[b] (**IV**)	Yield (%)[c]
1	≡–Ph	15		76
2	≡–$C(OH)Me_2$	20		96
3	≡–CH_2CH_2OH	15		93
4	≡–$CH(OH)CH_2CH_3$	15		96

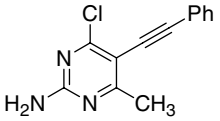
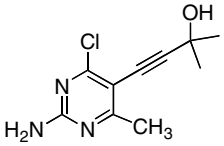
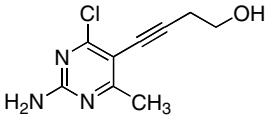
[a] All reactions were carried out using **Ib** (1.0 equiv), **II** (1.5 equiv), 10% Pd/C (0.05 equiv), PPh_3 (0.12 equiv), CuI (0.10 equiv) and Et_3N (2 equiv) in DMF at 80 °C.

[b] Identified by ^1H NMR, ^{13}C NMR, IR and mass spectroscopy.

[c] Isolated yields.

Table 3. Pd/C-catalyzed reaction of 4-chloro-5-iodo-6-methylpyrimidin-2-ylamine (**Ic**) with terminal alkynes[a]



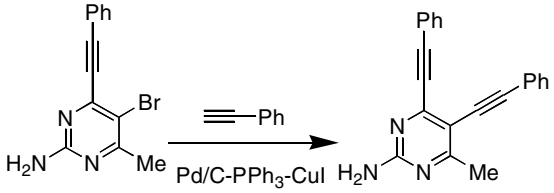
Entry	Alkyne (**II**)	Time (h)	Product[b] (**V**)	Yield (%)[c]
1	≡–Ph	15		54
2	≡–C(OH)Me_2	20		70
3	≡–CH_2CH_2OH	20		60

[a] All reactions were carried out using **Ic** (1.0 equiv), **II** (1.5 equiv), 10% Pd/C (0.05 equiv), PPh_3 (0.12 equiv), CuI (0.10 equiv) and Et_3N (2 equiv) in DMF at 80 °C.
[b] Identified by ^1H NMR, ^{13}C NMR, IR and mass spectroscopy.
[c] Isolated yields.

observation is in good agreement with that reported by Russell and co-workers[2a] and others.[18,20]

Since the synthesis of pyrimidine enediynes from **III** or **IV** requires the replacement of the bromo group by another alkynyl moiety (Fig. 1), we therefore assessed the reaction of 5-bromo-4-methyl-6-phenylethynylpyrimidin-2-ylamine with phenylacetylene using Pd/C–PPh_3–CuI as the catalyst system (Scheme 2). The reaction proceeded well affording a good yield of bis-alkynyl pyrimidine[21a] and therefore demonstrated the potential of this reaction sequence for the synthesis of novel pyrimidine enediynes. Furthermore, bis-alkynyl pyrimidines could be of interest in view of a recent study on the viability of proteins as targets for thermally and photoactivated enediynes.[21b]

In summary, we have shown that the chloro group of 5-bromo-4-chloropyrimidines can be replaced by a terminal alkyne under Pd/C–copper catalysis without affecting the bromo group. The bromo group of the resulting 4-alkynyl-5-bromopyrimidine could be utilized for further alkynylation. 4-Chloro-5-iodo-pyrimidine yielded the corresponding 5-alkynyl-4-chloropyrimidines under the same reaction conditions. The present Pd/C mediated regioselective synthesis of 4- and 5-alkynylpyrimidines does not involve the use of expensive reagents or catalysts and therefore permits a practical access to these compounds. The methodology has potential to be used for the synthesis of compounds of pharmacological interest.



Scheme 2. Synthesis of a bis-alkynylpyrimidine.

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16. Compound **Ia** was prepared by brominating 2-amino-6-methyl-3*H*-pyrimidin-4-one with bromine in acetic acid followed by the treatment with $POCl_3$ according to a procedure described in the literature, see for example: (a) Price, C. C.; Leonard, N. J.; Reitsema, R. H. *J. Am. Chem. Soc.* **1946**, *68*, 766; (For the preparation 2-amino-6-methyl-3*H*-pyrimidin-4-one, see: Jaeger, R. *Justus Liebigs Ann. Chem.* **1891**, *262*, 365); Compound **Ib** was prepared by reacting 6-methyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one with bromoethane in the presence of NaH in DMF at 80 °C for 16 h. The resulting 2-ethylsulfanyl-6-methyl-3*H*-pyrimidin-4-one was brominated in acetic acid (see: (b) Erkin, A. V.; Krutikov, V. I.; Pavlovich, N. I. *Russ. J. Gen. Chem.* **2003**, *73*, 463) and then treated with $POCl_3$ according to a similar procedure described in the litera-

ture, see for example: Curd, F. H. S.; Davis, M. I.; Owen, E. C.; Rose, F. L.; Tuey, G. A. P. *J. Chem. Soc.* **1946**, 720. (For the preparation of 6-methyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one, see: Foster, H. M.; Snyder, H. R. *Org. Synth. Coll. Vol. IV* **1963**, 638); (c) All the terminal alkynes used are commercially available.

17. *Typical procedure for the preparation of 4-(2-amino-5-bromo-6-methylpyrimidin-4-yl)-2-methylbut-3-yn-2-ol* (Table 1, entry 2): a mixture of **Ia** (0.2 g, 0.89 mmol), 10% Pd/C (48 mg, 0.045 mmol), PPh_3 (28 mg, 0.10 mmol), CuI (17 mg, 0.089 mmol) and triethylamine (0.18 g, 1.8 mmol) in dry DMF (5 mL) was stirred for 1.5 h under a nitrogen atmosphere. To this mixture was added dimethylpropargyl alcohol (0.11 g, 1.30 mmol) slowly and the mixture was stirred at 80 °C for 15 h. The mixture was then cooled to room temperature and filtered through celite. The filtrate was diluted with water (30 mL) and extracted with EtOAc (3×15 mL). The organic layers were collected, combined, washed with water (2×15 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue thus obtained was purified by column chromatography using EtOAc–petroleum ether to afford the title compound as an ash coloured powder. Mp 196–198 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36 (br s, 2H), 5.07 (br s, 1H), 2.49 (s, 3H, CH_3), 1.65 (s, 6H, $2CH_3$); IR (KBr, cm^{-1}) 3435, 3314, 2239; Mass (*m*/*z*) 272 (M+2, 97), 270 (M^+, 100), 254 (M^+-16); ^{13}C NMR (50 MHz, DMSO-d_6) 166.4, 161.6, 149.8, 107.8, 101.6, 78.4, 63.6, 31.0 (2C, $2CH_3$), 24.6; HPLC 97.8%, Inertsil ODS 3V (250×4.6 mm), 0.01 M KH_2PO_4 (pH = 5.5)/CH_3CN 0/30, 5/30, 30/80, 40/80, 45/30, 50/30, 1.0 mL/min, 235 nm; retention time 11.5 min.
18. The greater reactivity of a halogen attached to the azomethine carbon of a pyrimidine ring under palladium catalysis has been reported earlier, see Refs. 12t and 13a. See also: Kondo, Y.; Watanabe, R.; Sakamoto, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1989**, *37*, 2814.
19. Compound **Ic** was prepared by iodinating 2-amino-6-methyl-3*H*-pyrimidin-4-one with iodine in aqueous NaOH at 80 °C for 12–15 h followed by the treatment with $POCl_3$.
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