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Selective bifunctionalization of pyrido[2,3-*d*]pyrimidines in positions 2 and 4 by SN_{Ar} and palladium-catalyzed coupling reactions

G. Lavecchia, S. Berteina-Raboin* and G. Guillaumet

Institut de Chimie Organique et Analytique, UMR CNRS 6005, Université d'Orléans, BP 6759, 45067 ORLEANS Cedex 2, France

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Abstract—Selective disubstitution of 2,4-dichloropyrido[2,3-*d*]pyrimidine with various nucleophiles was investigated. Suzuki and Stille cross-coupling reactions on monosubstituted compound 4-*tert*-butylamino-2-chloro-pyrido[2,3-*d*]pyrimidine were performed in high yields.

Pyrido[2,3-*d*]pyrimidines are known to be pharmacophoric elements in numerous active compounds such as anticancer,[1–3] anti-viral,[4,5] and anti-inflammatory agents.[6]

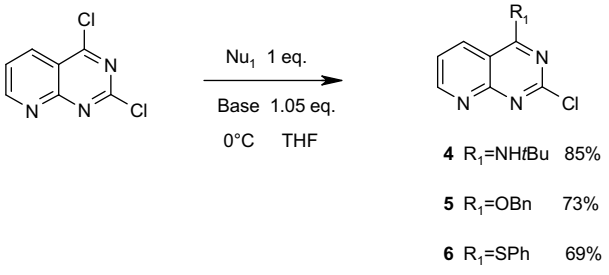
Many publications are devoted to the synthesis of polysubstituted[7,8] and fused pyrido[2,3-*d*]pyrimidine[9,10] system, most whose involve substitution on a pyridine ring.[11,12] Prior exploration on the reactivity of pyrimidine moiety has shown that substitution essentially occurred at position 4.[13]

Aiming to extend pyrido[2,3-*d*]pyrimidine libraries, a useful pathway has been developed to obtain pyrido[2,3-*d*]pyrimidines, that are selectively substituted in positions 2 and 4 with various nucleophiles.

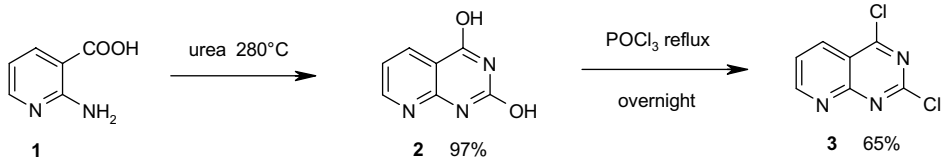
We also describe two types of palladium-mediated cross-coupling reactions (Suzuki and Stille) in position 4, leading to new dissymmetrical species.

Starting material: 2,4-dichloropyrido[2,3-*d*]pyrimidine **3** was prepared from 2-aminonicotinic acid **1** via 2,4-dihydroxypyrido[2,3-*d*]pyrimidine **2** following Robin and Hitchings method[14] (Scheme 1).

Compound **3** was easily substituted at position 4 with different nucleophiles[15] (Scheme 2). This position was more reactive than position 2, as in simple pyrimidinic systems.[16] The structures were confirmed by NOESY studies.



Scheme 2.



Scheme 1. Previous synthesis of 2,4-dichloropyrido[2,3-*d*]pyrimidine **3**.

Keywords: Suzuki reaction; Stille reaction; Cross-coupling; Palladium; SN_{Ar}; Pyrido[2,3-*d*]pyrimidine.
* Corresponding author. Tel.: +33 023 849 4856; fax: +33 023 841 7281; e-mail: sabine.berteina@univ-orleans.fr

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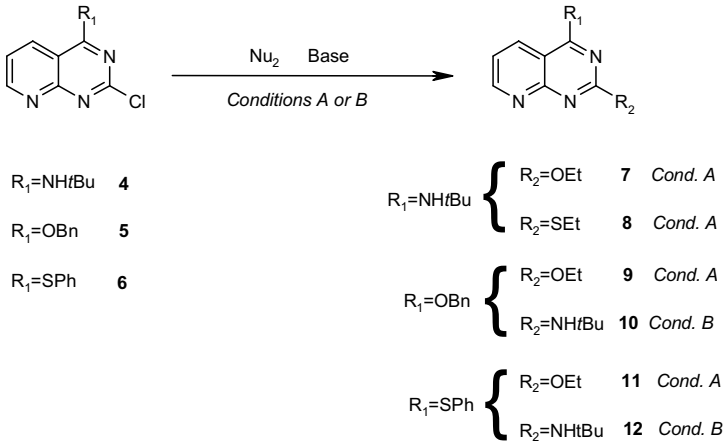


Scheme 3. Reagents and conditions: (A) 1 equiv nucleophile, 1.05 equiv NaH, THF, 0 °C; (B) large excess *tert*-butylamine, THF, reflux overnight.

The reactions proceeded in good yield with high selectivity for position 4, without an isomer in position 2.

The chlorine at position 2 of monosubstituted compounds **4**–**6** could be substituted with several other nucleophiles[17] to give products **7**–**12** as shown in Scheme 3.

The introduction of a *tert*-butylamino-group required harsher conditions than for other nucleophiles such as sodium ethoxide or sodium ethanethiolate, although expected products were obtained in high yield (Table 1).

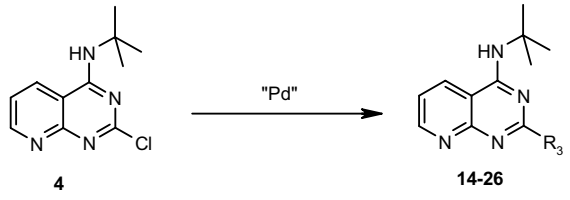
We also found that compounds **9** and **11** were easily substituted at position 4 by sodium ethoxide under very mild conditions, affording **13**[18] (Scheme 4). It should be noted that compound **7** (*tert*-butylamino-group in position 4) did not react even under stringent conditions.

Table 1. Nucleophilic substitutions at position 4

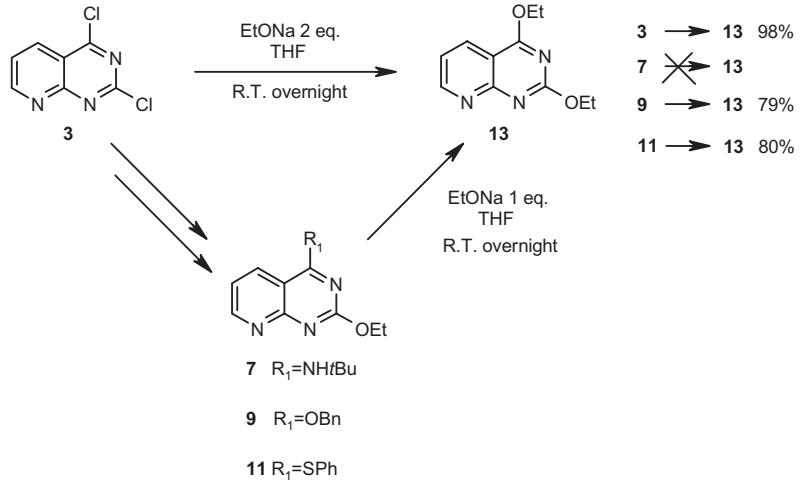
R_1	R_2	Yield (%)
NH-*t*-Bu	OEt	78
	SEt	75
OBn	NH-*t*-Bu	81
	OEt	72
SPh	NH-*t*-Bu	83
	OEt	77

A similar reactivity was already observed with the pyrido[4,3-*d*]pyrimidine system, as methylsulfanyl- or anilino-groups in position 4 were also displaced by nucleophiles.[13]

Position 2 was also functionalized using palladium-promoted cross-coupling reactions performed on compound **4**. Suzuki[19] and Stille[20] conditions were applied (Scheme 5). Unfortunately, the chlorine in position



Scheme 5. Suzuki conditions: boronic acid 1.05 equiv, $Pd(PPh_3)_4$ 5 mol%, Na_2CO_3 2 equiv, DME/H_2O, 75 °C. Stille conditions: tin derivative 1.25 equiv, $Pd(PPh_3)_4$ 5 mol%, toluene reflux then TBAF 1 M/THF.



Scheme 4.