2-Chloro-4-tetrafluorophenoxypyrimidine: a versatile reagent for *C-2* prior to *C-4* functionalizations

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2-Chloro-4-tetrafluorophenoxypyrimidine: a versatile reagent for *C-2* prior to *C-4* functionalizations

Abstract:

A novel synthetic route to 2,4-functionalized pyrimidines is reported. The approach uses 2-chloro-4-tetrafluorophenoxypyrimidine, that enables sequential palladium catalyzed functionalization at the pyrimidine *C-2* position, followed by S_NAr displacement with diverse amines at *C-4*. The broad utility of this '*C-2* then *C-4*' functionalization sequence has been demonstrated with a range of cross-coupling partners and amines.

1. Introduction

The pyrimidine nucleus is found in many natural products and has been used as a core scaffold in numerous drug discovery programmes,[1-7] some leading to marketed drugs such as Imatinib (Glivec),[8] Nilotinib (Tasigna),[9] Radotinib (Supect),[10] or lately Osimertinib (Tagrisso).[11]
In an attempt to provide an array of receptor antagonists, we sought a versatile approach that would install an aryl or an alkyl group at the pyrimidine *C-2* position and then allow simple exploration of the *C-4* position with a diverse range of amines. 2,4-Dihalopyrimidines have provided useful building blocks for parallel synthesis routes. However, due to the higher electrophilicity of the *C-4* position, these dihalopyrimidines are not the most suitable starting points in cases where the objective is the simple variation at position 4. For such an approach, 4-chloropyrimidines with an aryl/alkyl group already installed at the *C-2* position are preferred; one of the standard methods for the preparation of 2-aryl/alkyl -4-chloropyrimidines involves the condensation of an appropriate aryl/alkyl amidine with a ketoester and further treatment with $POCl_3$.[12-14] While this sequence can be high yielding, the scope is limited by the variety of commercial amidines, the difficulty in their syntheses and the fact that the resultant hydroxypyrimidine may not react favorably with phosphorus oxychloride. An alternative method is the derivatisation of 2-chloro-4-methoxypyrimidine via metal assisted cross-coupling methodology.[15,16] Once again, the harsh conditions required for further elaboration limits the scope.
Previously, we have shown that 2-chloro-4-tetrafluorophenoxypyrimidine **1** (Fig. 1) displays reverse regiochemistry to that of 2,4-dichloropyrimidine, when subjected to sequential S_NAr substitutions with amines.[17] In the current paper, we assessed (a) the potential of readily available pyrimidine **1** to react regiospecifically at the *C-2* position with various coupling partners, under

palladium catalysis (Suzuki, Negishi and Sonogashira), and (b) the ability of the tetrafluorophenoxy group to be subsequently displaced with a range of amines without recourse to an intermediate step.

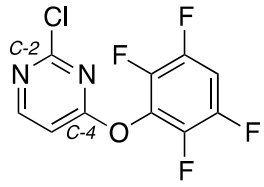
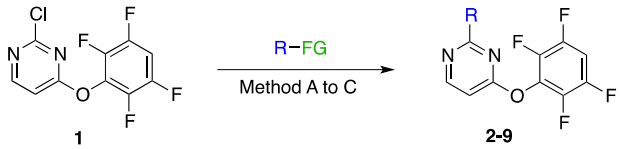


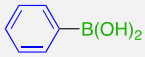
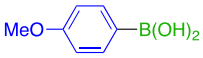
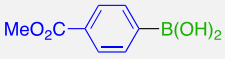
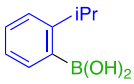
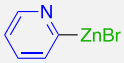
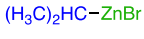
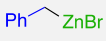
Figure 1: Structure of **1**

2. Results and discussion

2-Chloro-4-tetrafluorophenoxypyrimidine **1** was readily obtained in high yield (84%) and complete *C-4* regioselectivity,[17] from the reaction of 2,4-dichloropyrimidine and one equivalent of tetrafluorophenol in the presence of DIPEA. Compound **1** reacted smoothly with a variety of aryl boronic acids, under Suzuki coupling conditions to afford the *C-2* aryl adducts in excellent yields and complete regioselectivity (Table 1, Entries 1-4). Electronic effects (Entries 2-3) and steric hindrance (Entry 4) of the arylboronic acid had no bearing on the outcome of the coupling reactions. The best results were obtained using $Pd(OAc)_2$/SPhos as catalyst in dioxane/water, with lithium hydroxide as a base,[18] although good yields were also observed using $Pd(PPh_3)_4$ and Na_2CO_3 in dioxane/water. Cross-coupling reactions with zincate partners, under Negishi conditions using $Pd(OAc)_2$/CPhos as a catalyst in THF, equally afforded the desired *C-2* adducts in high yields and regioselectivity (Table 1, Entries 5-7), allowing access to an alkyl group at the *C-2* position (Entries 6,7). Alkyl zincates underwent coupling at room temperature whilst the reaction of 2-pyridylzincate required warming to 50°C for full conversion. Sonogashira coupling with phenylacetylene, using $PdCl_2(MeCN)_2$/ X-Phos as catalyst in THF provided alkyne **9** in good yield. Note that, the Sonogashira cross-coupling reaction proceeded poorly under standard conditions using CuI/$Pd(PPh_3)_4$ and was much improved under copper free conditions.

Table 1. C-2 Regioselective Suzuki, Negishi and Sonogashira cross-coupling reactions of **1**

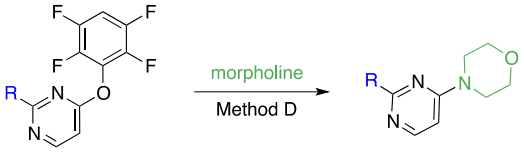


Entry	R-FG	Method[a]	Product	Yield[b]
1		A	**2**	75%
2		A	**3**	79%
3		A	**4**	78%
4		A	**5**	75%
5		B	**6**	77%
6		B	**7**	83%
7		B	**8**	82%
8		C	**9**	64%

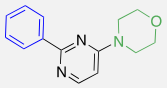
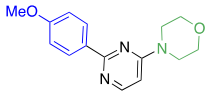
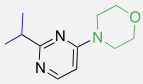
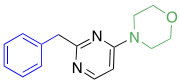
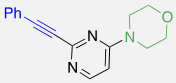
(a) Method A: $ArB(OH)_2$ (1.2 eq), LiOH (4 eq), $Pd(OAc)_2$ (5 mol%), S-Phos (10 mol%), dioxane/water, 80 °C, 2 h; Method B: RZnBr (1.2 eq), $Pd(OAc)_2$ (5 mol%), C-Phos (10 mol%), THF, rt or 50 °C, 12 h; Method C: alkyne (1.5 eq), $PdCl_2(MeCN)_2$ (5 mol%), X-Phos (7.5 mol%), THF, 60 °C, 2 h
(b) Isolated yields

We then needed to assess the potential of 2,3,5,6-tetrafluorophenoxide as a leaving group at the *C-4* position, in the presence of various substituents at position 2. In this study, we selected representative substrates from Table 1 and subjected them to treatment with morpholine/Et_3N/NMP (Table 2). In all cases, the products were obtained in high yields, demonstrating the versatility of this displacement in the presence of functional groups such as aryl, alkyl or alkynyl. Solvents other than NMP were successfully used, including DMF (at 120 °C) and acetonitrile (at reflux), although longer reaction times were required in the latter case. DIPEA or DBU could also be utilized as bases in these displacements, with similar results.

Table 2. S_NAr reaction of 4-tetrafluorophenoxypyrimidines with morpholine



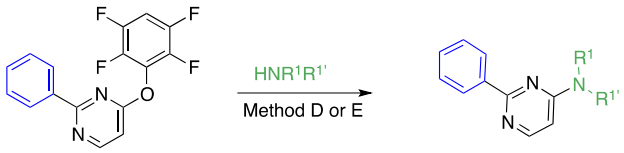
2, 3, 7-9 **10-14**

Entry	Substrate	Product		Yield[b]
1	**2**	**10**		82%
2	**3**	**11**		79%
3	**7**	**12**		84%
4	**8**	**13**		74%
5	**9**	**14**		76%

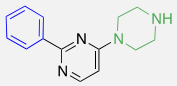
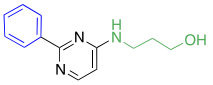
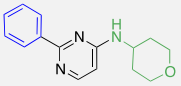
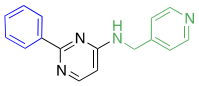
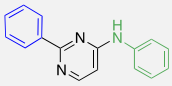
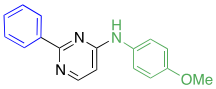
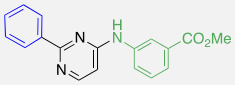
(a) Method D: 4-tetrafluoropyrimidine (0.50 mmol), morpholine (0.55 mmol), Et_3N (0.55 mmol), NMP (1 mL), 120 °C, 12 h
(b) Isolated yields

The variety of the amines that can be used to substitute the 2,3,5,6-tetrafluorophenoxy group at *C-4* was then investigated by reacting compound **2** with a range of aliphatic and aromatic amines (Table 3). Treatment of **2** with a slight excess of aliphatic amine in NMP, in the presence of triethylamine, afforded the desired products in high yields (Table 3, Entries 1-4). The S_NAr reaction with a set of aromatic amines under a range of base-catalysed conditions (DMF/DIPEA or DMSO/lutidine or MeCN/K_2CO_3) were unsuccessful and only trace amounts of the desired products, even at temperatures up to 100 °C, were obtained, whilst microwave irradiation at 110 °C improved the outcome and moderate yields (typically 20-30%) of the desired products could be obtained from the resultant complex reaction mixtures. The reaction of **2** with the same set of aromatic amines under acid-catalysed conditions proved to be more successful; the use of catalytic HCl in EtOH/water resulted in clean reaction profiles and provided good yields of the desired 4-substituted products (Table 3, Entries 5-7).

Table 3. S_NAr reaction of 4-tetrafluorophenoxypyrimidine **2** with diverse amines



2 **15-21**

Entry	Method	Product	Yield[b]
1	**D**	**15** 	89%
2	**D**	**16** 	86%
3	**D**	**17** 	71%
4	**D**	**18** 	73%
5	**E**	**19** 	84%
6	**E**	**20** 	80%
7	**E**	**21** 	77%

(a) Method D: 4-tetrafluoropyrimidine (0.50 mmol), amine (0.55 mmol), Et_3N (0.55 mmol), NMP (5 mL), 120 °C, 12 h; Method E: HCl, EtOH/water, 90 °C
(b) Isolated yields

In summary, we have described a versatile synthetic route for the sequential '*C-2* then *C-4*' functionalization of pyrimidines using readily available 2-chloro-4-tetrafluorophenoxy pyrimidine **1**. The route enables functionalization at the *C-2* position of pyrimidines, using palladium catalyzed cross-coupling conditions, followed by S_NAr amination at *C-4*. This general method therefore allows facile derivatisation at the *C-4* position of the pyrimidine nucleus with no restrictions due to functional group incompatibility. We have shown that compound **1** affords the opposite regiochemistry compared to that obtained with commonly used dihalopyrimidines, therefore offering a complementary tool for the synthesis of pyrimidine-containing compounds.

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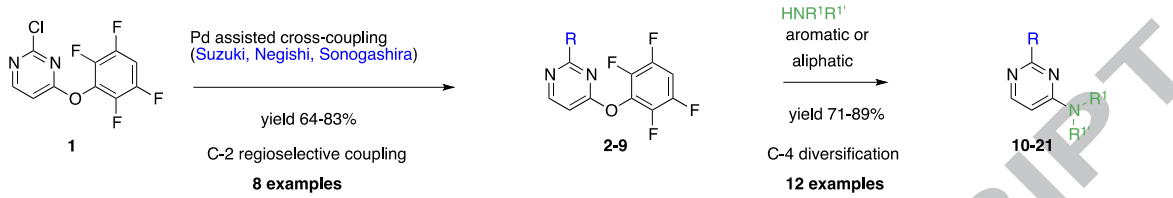
Graphical abstract



Highlights

- **Description of uses of 2-chloro-4-tetrafluorophenoxypyrimidine**
- **Description of its reactivity for the preparation of 2,4-disubstituted pyrimidines**
- **First functionalization occurs at C-2, under metal-catalysed cross-coupling reactions**
- **Second functionalization occurs at C-4, with aliphatic or aromatic amines**
- **Approach offers complementary tool for the synthesis of pyrimidine-containing compounds**