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Route selection in the synthesis of C-4 and C-6 substituted thienopyrimidines

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ABSTRACT

Three different routes have been investigated for the preparation of 6-aryl-*N*-(1-arylethyl)thienopyrimidin-4-amines. First the possibilities of selective Suzuki reactions on 6-bromo-4-chlorothienopyrimidine were investigated. The preference for mono arylation at C-6 could be increased, in the case of $Pd(PPh_3)_4$ catalysis, by reducing the water content of the reaction, or by using less electron rich Pd-ligands. The highest selectivity was obtained with $Pd(OAc)_2$ or $Pd_2(dba)_3$, while reactions with the more electron rich $Pd(PPh_3)_4$ and especially XPhos gave a lower mono- to dicoupled product ratio. Secondly, two alternative strategies avoiding this selectivity issue were tested. Suzuki reaction on C-6 of 6-bromothienopyrimidin-4(3*H*)-one (three examples) proceeded in 70–89% yield using $Pd(PPh_3)_4$ in dioxane/water. Similar conditions on 4-amino-6-bromo-thienopyrimidine (eight examples) gave 67–95% yield. The reaction could be performed with boronic acids containing nonprotected phenolic groups in the *ortho*, *meta* and *para* positions. By prolonging the reaction time, coupling with sterically crowded arylboronic acids was also efficient. Diarylation of 6-bromo-4-chlorothienopyrimidine gave the corresponding 4,6-diarylated derivatives in 71–80% yield depending on the nature of the arylboronic acid.

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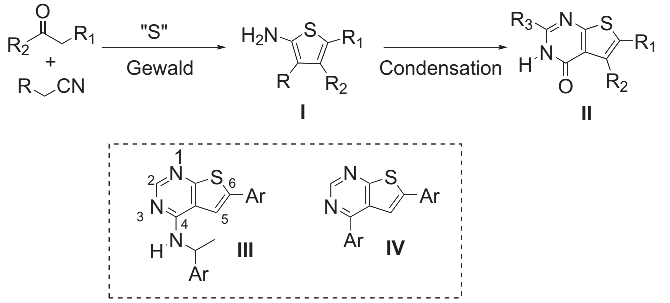
1. Introduction

Thienopyrimidines have become an interesting structural element in development of pharmaceutical compounds.[1,2] Among others, these heterocycles have been used as part of kinase inhibitors to regulate dysfunctional cell signalling in cancer cells,[3–9] as calcium receptor antagonists,[10] transglutaminase inhibitors,[11,12] as peptidase IV inhibitors[13] and against hepatitis C virus infections.[14]

A useful starting point for thienopyrimidine synthesis is the Gewald reaction,[15–18] in which an activated nitrile reacts with a carbonyl compound in the presence of a sulfur source to give substituted 2-aminothiophenes (**I**), Scheme 1. The 2-aminothiophenes (**I**) can be used to make a range of different products.[11,17,19–21] Starting with cyanoacetate esters or malonitrile, the formed 2-aminothiophenes can be condensed to give thienopyrimidines (**II**),[22,23] which we herein have used in the synthesis of a series of heterocycles like **III** and **IV**.

The preferred chemical route depends on a number of factors, most importantly being the overall cost and the space-time yield. However, in drug discovery and lead optimisation phases, the possibility of making a high number of derivatives using robust chemistry from a common precursor will reduce work effort and speed up development.



Scheme 1. Gewald reaction to give substituted 2-aminothiophenes (**I**) and condensation to give thienopyrimidines (**II**), and the target products **III** and **IV**.

The Suzuki–Miyaura reaction is very efficient for the construction of sp^2–sp^2 carbon–carbon bonds, and is ideal for creating chemical diversity due to the large array of commercially available arylboronic acids.[24,25]

A number of publications describe Suzuki cross-couplings involving thiophenes and pyrimidines, while less is published in the case of thienopyrimidines.[26,27] Regioselectivity issues in Suzuki coupling have previously been studied for chloropyrimidine,[28,29] various five-membered heterocycles,[30] pyridopyrimidines,[31] imidazopyridines,[32] and brominated thiophenes.[33]

Based on our interest in kinase inhibitors,[34] we were in need of various 6-aryl-*N*-(1-arylethyl)thienopyrimidin-4-amines **III** and

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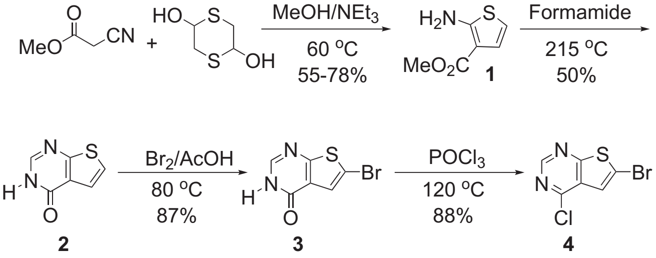
4,6-diaryl thienopyrimidines **IV**. Our aim was to prepare a series of these compounds as efficiently as possible from a late common intermediate using the Suzuki reaction as a key step.

2. Result and discussion

2.1. Starting materials

We envisioned 6-bromothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**3**) and 6-bromo-4-chlorothieno[2,3-*d*]pyrimidine (**4**) as possible late stage intermediates for making a range of 4-amino-6-aryls and 4,6-diaryl derivatives, Scheme 2.



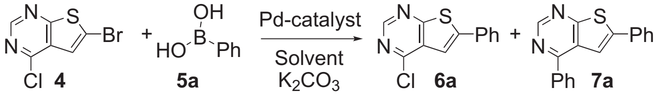
Scheme 2. Synthesis of the thienopyrimidine building blocks.

These were synthesised starting with a Gewald reaction using methyl cyanoacetate and 1,4-dithiane-2,5-diol giving the amino-ester **1**. The reaction was run thermally on a 15–100 g scale, or on a 6 g scale using microwave irradiation in sealed tubes. This gave a 55–78% yield depending on the conditions. The microwave method gave similar yields to the thermal process, but a shortening of reaction time from 3 h to minutes was achieved. The thiophene derivative **1** was then reacted with formamide at high temperature to yield thieno[2,3-*d*]pyrimidin-4(3*H*)-one (**2**). Aromatic bromination in acetic acid yielded **3** and chlorination at C-4 gave the derivative **4**. All these reactions were performed on a 15–30 g scale.

Compounds **2**–**4** were difficult to purify by chromatography due to limited solubility and by crystallisation due to co-precipitation of inorganic material. To have control of the mass balance in the Suzuki coupling steps compound **3** and **4** were purified by silica-gel filtration in gram scale. However, the following reactions were also successfully performed on semi pure materials.

2.2. Selective Suzuki coupling

We first attempted a selective Suzuki coupling on **4** at C-6 using phenylboronic acid (**5a**), Scheme 3. The building block **4** contains two reactive sites. Whereas bromo substituted positions usually reacts faster, the low electron density at C-4 in the pyrimidine unit complicates a selective reaction.[35]



Scheme 3. Attempted selective Suzuki coupling on **4**.

Employing the classical Pd(PPh$_3$)$_4$ system, the effect of reaction temperature and dioxane/water ratio on the degree of conversion and product distribution was investigated (Table 1).

With water/dioxane (50/50, v/v) as the solvent system, the reaction proceeded slowly at lower temperatures (Table 1, entries 1–3). However, at 110 °C full conversion was obtained in 6 h. Unfortunately, the reaction proceeded with poor selectivity (Table 1, entries 4–5), and traces of **3** was also observed due to hydrolysis of the starting material.

Table 1
Conversion and product distribution upon variation of reaction temperature and solvent composition in the reaction of **4** with **5a** using K$_2$CO$_3$ as base and Pd(PPh$_3$)$_4$ as Pd-source

Entry	PhB(OH)$_2$ (Eq)	Water (vol.%)	Temp (°C)	Rx time (h)	Conv. (%)[a]	**6a** (%)	**7a** (%)	Ratio **6a**/**7a**
1	1.2	50	22	6	0	0	0	—
2	1.2	50	40	24	65	52	13	4
3	1.2	50	60	24	92	61	31	2
4	1.2	50	110	6	>99	43	57	1
5	1.2	25	110	7	>99	49	51	1
6	1.0	2	110	5	92	82	10	8
7	1.0	0	110	5	86	79	7	11
8	1.0	0	110	24	95	85	10	8

[a] Conversion was measured by ^{1}H NMR spectroscopy.

To improve the ratio of mono- to diarylated product, and to supress hydrolysis of **4**, the water content and the amount of arylboronic acid was reduced (Table 1, entries 6–8). By using a low water content or pure dioxane a higher selectivity ratio was the result. A drawback however, was a decreased rate of reaction.

The rate of Suzuki-type couplings are amongst other thing dependent on the electronic properties of the catalyst. It was therefore investigated whether variation of the ligand affected the product ratio using Pd(OAc)$_2$, Pd$_2$(dba)$_3$ and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos). The less electron donating Pd(OAc)$_2$ and Pd$_2$(dba)$_3$ both gave a high ratio of **6a**/**7a** (Table 2, entries 1–5). However, complete conversion could not be obtained in 24 h. Use of the more electron rich XPhos resulted in a low ratio of **6a**/**7a** supporting the idea that electronic effects are important for selectivity.

Table 2
Conversion and product distribution using Pd(OAc)$_2$, Pd$_2$(dba)$_3$ and Pd(OAc)$_2$/XPhos in Suzuki coupling

Entry	PhB(OH)$_2$ (Eq)	Catalyst	Water (vol.%)	Rx time (h)	Conv. (%)[a]	**6a** (%)	**7a** (%)	Ratio **6**/**7**
1	1.0	Pd(OAc)$_2$	2	5	24	24	>1	>24
2	1.2	Pd(OAc)$_2$	50	5	75	71	4	17
3	1.2	Pd$_2$(dba)$_3$	50	5	81	77	4	20
4	1.2	Pd$_2$(dba)$_3$	0	24	77	74	4	20
5	1.5	Pd$_2$(dba)$_3$	0	24	80	77	3	25
6	1.5	Pd(OAc)$_2$ / XPhos	0	5	72	45	27	2

[a] Conversion was measured by ^{1}H NMR spectroscopy.

As opposed to reactions using Pd(PPh$_3$)$_4$, the ratio of mono- to diarylated products in Suzuki couplings using Pd(OAc)$_2$ and Pd$_2$(dba)$_3$ was not affected by the amount of water used.

A challenge with the reactions in pure dioxane was a low rate of reaction, leading to incomplete conversion. *N*,*N*-Dimethylformamide (DMF) has previously been used as a highly polar solvent in similar reactions,[32,36] and Suzuki coupling on **4** in DMF using Pd$_2$(dba)$_3$ gave an excellent 90/1 ratio of **6a** and the disubstituted derivatives **7a** (data not shown). However, the product could not be isolated in more than 18% yield. Degradation reactions seem to take place. This was also observed by Delia et al.[28]

In conclusion, a 25/1 ratio of mono- to dicoupled product could be obtained by changing the palladium ligand. However, the mediocre conversion complicates purification, which led to a low yield.

Diaryl coupling has been found challenging for some dihaloheterocycles.[29,37] Therefore, this transformation was tested with **4** in the synthesis of **7a**–**c**, Scheme 4.

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