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Development of a Concise Scaleable Synthesis of 2-Chloro-5-(pyridin-2-yl) Pyrimidine via a Negishi Cross-Coupling

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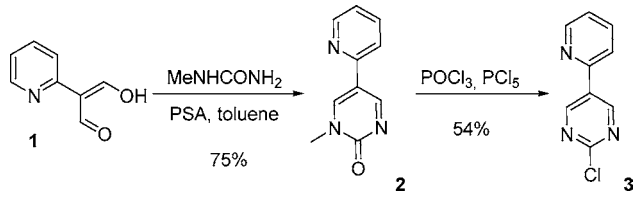
Abstract:

A practical and scaleable synthesis of 2-chloro-5-(pyridin-2-yl) pyrimidine, an intermediate in the synthesis of a selective PDE-V inhibitor, was developed. A Negishi cross-coupling between the in situ prepared 2-pyridylzinc chloride and 5-iodo-2-chloropyrimidine catalyzed by $Pd(PPh_3)_4$ afforded the product in one step. Development of a convenient purification did away with the necessity of chromatography, allowing the preparation of the product on kilogram scale.

Introduction

During our program for the development and scaling up of a selective PDE-V inhibitor, a short and efficient synthesis of the 2-chloro-5-(pyridin-2-yl) pyrimidine, **3**, was required. This was a key intermediate in the last step of our convergent synthetic strategy.[1] The medicinal chemistry route involved the condensation of the 2-pyridyl malonaldehyde **1** with methylurea followed by demethylation/chlorination with a mixture of $POCl_3$ and PCl_5 (Scheme 1) to give **3** in a overall 40% yield.[2] This synthetic route proved unsuitable for scaling-up due to the difficulties to prepare **1** in bulk quantities. Therefore, it was decided to explore a synthetic approach using a cross-coupling between the two heterocyclic rings (Figure 1).

Scheme 1. **Medicinal chemistry route**



Results and Discussion

Classical and well-established cross-coupling methods mediated by Pd or Ni include the Stille,[3] Suzuki−Miyaura,[4]

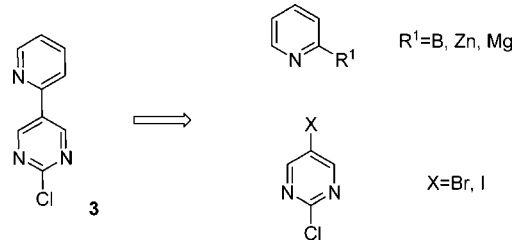


Figure 1. **Cross-coupling approach.**

Kumada,[5] and Negishi[6] couplings. Due to the toxicity of tin, the Stille coupling was not considered as a valuable alternative. By far, the preferred cross-coupling in process development is the Suzuki−Miyaura coupling, since the boronic acids are thermally stable compounds and the reaction does not require anhydrous conditions. However, there are only few examples of the scaling-up of the Kumada[7] or Negishi[8] cross-couplings.

The pyridine fragment was selected for the preparation of the organometallic partner. 5-Bromo-2-chloropyrimidine, **6**, and 5-iodo-2-chloropyrimidine, **8**, were prepared from the 2-hydroxypyrimidine hydrochloride in two steps (Scheme 2). In the case of the bromo derivative, the bromination was carried out with Br_2 in concentrated aqueous HCl to afford 5-bromo-2-hydroxypyrimidine, **5**, subsequent chlorination with $POCl_3$ in the presence of *N*,*N*-dimethylaniline gave **6** in a 65% overall yield. The iodo derivative was prepared by iodination of **4** with ICl in H_2O−AcOH, followed by chlorination with $POCl_3$. With acetonitrile as cosolvent only 1 equiv of $POCl_3$ was needed for the chlorination, making the workup easier. Following this procedure **8** was prepared in multikilogram scale.[9]

In order to perform the Suzuki−Miyaura coupling, we tried the synthesis of the 2-pyridylboronic acid. Unfortu-

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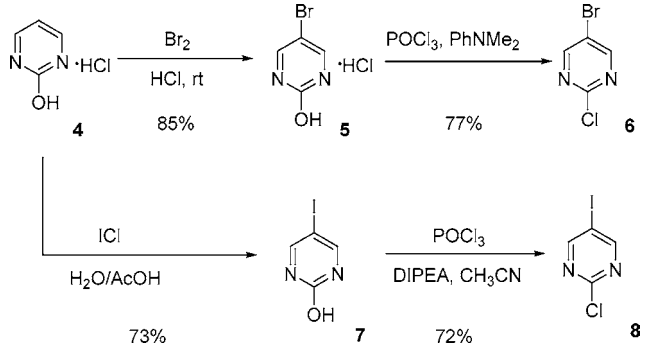
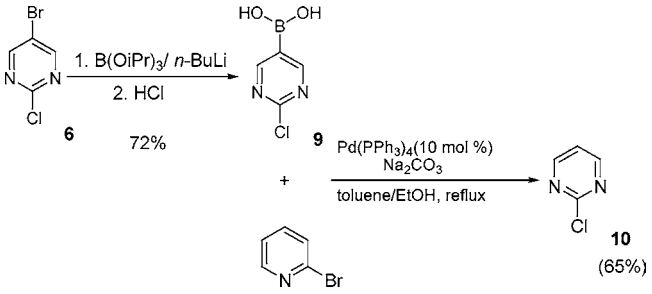
Scheme 2. **Preparation of 5-halo-2-chloropyrimidines**



nately, transmetallation between triisopropylborane and 2-pyridyllithium, followed by hydrolysis with HCl, afforded the 2-pyridylboronic acid in low yields after a difficult isolation, indicating that this synthetic pathway was not amenable to kilogram scale. Conversely, the 5-(2-chloro)pyrimidyl boronic acid **9** was efficiently prepared (72% yield) from **6** following the standard procedure (Scheme 3).[10] The cross-coupling between the boronic acid **9** and the 2-bromopyridine under classical Suzuki conditions did not afford the expected product **3**. The deboronated product **10** was the major compound, besides other degradation products. Other attempts with $Pd(PPh_3)_4$ and different bases and solvent systems gave complex mixtures, in which the adduct **3** could not be identified. Kumada coupling between 2-pyridylmagnesium bromide and 5-iodo- or 5-bromo-2-chloropyrimidine in the presence of $Ni(Cl_2)$dppf failed to afford the adduct **3**. The unreacted pyrimidines, besides degradation products, were found.

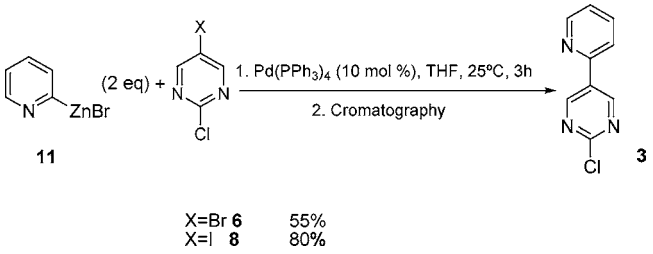
Scheme 3



Finally, the Negishi coupling between the 2-pyridylzinc bromide, **11**, and pyrimidines **6** and **8**, in the presence of a catalytic amount of $Pd(PPh_3)_4$, was tried. We were delighted to observe that the 2-chloro-5-(pyridin-2-yl) pyrimidine, **3**, was obtained in 80% yield from the iodo derivative and in 55% yield from the bromo derivative (Scheme 4). On the basis of the previous results, the Negishi coupling between 2-pyridylzinc bromide, **11**, and 5-iodo-2-chloropyrimidine, **8**, was selected for further development and scale-up.

Now that a scaleable synthesis of **8** was developed successfully, the synthesis of the organozinc partner was considered. At the bench, **11** was prepared from 2-bromo pyridine by Li/Br exchange with *n*-BuLi in THF at −78 °C, followed by transmetallation of the 2-pyridyllithium inter-

Scheme 4. **Negishi coupling**



mediate to the corresponding 2-pyridylzinc with $ZnBr_2$. In an effort to avoid the use of deep cooling, some other approaches to **11** were considered. The insertion of metallic zinc into the C−Br bond of the 2-bromo pyridine failed, even when the zinc was activated with 1,2-dibromoethane or TMSCl. Instead of using the 2-pyridyllithium as intermediate for subsequent transmetallation to zinc, the use of the 2-pyridylmagnesium bromide was explored. 2-Pyridylmagnesium bromide was easily prepared from 2-bromo pyridine and magnesium. Unfortunately, the addition of $ZnBr_2$ to a THF solution of 2-pyridylmagnesium bromide gave an unstirrable mixture. Finally it was decided to adapt the original route via the 2-pyridyllithium to pilot-plant requirements (Scheme 5). For safety and environmental reasons, *n*-BuLi was replaced by HexLi.[11] It was observed that the temperature for a successful Br/Li exchange could be increased to −60 °C, which implied a significant saving of energy and cooling time. $ZnBr_2$ was substituted by $ZnCl_2$ which resulted in several advantages. (1) The solubility in THF is higher for $ZnCl_2$ than for $ZnBr_2$, consequently peak volumes of solvent were reduced. (2) The addition of $ZnCl_2$ to THF was less exothermic than the addition of $ZnBr_2$, contributing to a safer process. (3) It was observed that the cross-coupling between 2-pyridylzinc chloride, **13**, and **8** was faster as compared to the 2-pryridylzinc bromide. (4) With $ZnCl_2$ less foaming was observed during the aqueous workup.

In order to have a better control of the temperature during the Br/Li exchange, 2-bromopyridine was added to a cooled solution of HexLi in THF, instead of the common addition of HexLi to the 2-bromopyridine solution. Further optimization of the reaction conditions included a considerable reduction of the amount of $Pd(PPh_3)_4$, from 10 to 2 mol %. However, the amount of **13** could not be decreased. The use of less than 2 equiv of **13** had a deleterious effect on the yield of the reaction. Under these conditions the yields of **3**, determined in the crude reaction mixture by quantitative HPLC, were 80−90%. Another important issue to be solved was the residual metal content in **3**. As **3** was used in the final coupling step, the residual metal content in this intermediate should not exceed the upper limitation of 20 ppm. After some experimentation, the best results were obtained using a multistep workup. The crude reaction mixture was first washed with an aqueous EDTA·3Na

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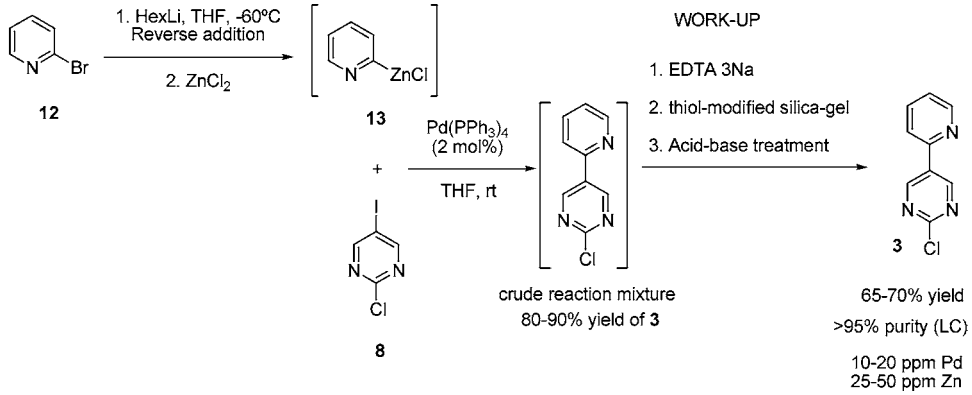
(11) The hexane produced by hydrolysis of HexLi is maintained in the reaction mixture, whereas *n*-BuLi has to address the safety and environmental aspects of potential butane emision. See: Baenziger, M.; Mak, C. P.; Muehle, H.; Nobs, F.; Prokoszovich, W.; Reber, J. L.; Sunay, U. *Org. Process Res. Dev.* **1997**, *1*, 395.

Scheme 5. **Optimized Negishi coupling**



solution. It was found that the trisodium salt of EDTA had a higher solubility in water and better coordinating properties than the normal EDTA. Most of the zinc, coordinated to EDTA, was removed in this step. After separation of layers, the THF was removed under reduced pressure and replaced by CH_2Cl_2. The resulting solution was stirred with a mixture of silica gel 60 (16.5 g/mol Pd) and thiol-modified silica gel (1.5 g/mol Pd), in order to trap palladium and zinc that had not been removed by the EDTA treatment. After filtration, the solution was treated with 2 N HCl. The product, as hydrochloride, was dissolved into the aqueous layer, while triphenylphosphine and other organic byproducts remained in the organic layer. The aqueous layer was then stirred with activated charcoal,[12] with the aim to further reduce the content in metals. It was expected that the hydrochloride form of **3** would have poorer coordinative capabilities than neutral **3**, facilitating the removal of Pd and Zn. Subsequent filtration afforded a clear aqueous solution that was neutralized with concentrated ammonia, causing the precipitation of **3** out of the solution. At the end of this procedure, 2-chloro-5-(pyridin-2-yl) pyrimidine **3** was obtained in 65−70% yield, the purity was higher than 95% (determined by quantitative HPLC), and the Pd and Zn contents were respectively in the range of 10−20 ppm and 25−50 ppm. Although higher than the previous set threshold of 20 ppm, these levels of Pd and Zn in this intermediate were judged acceptable as they were further reduced to below 5 ppm in the final coupling and purification step.

Six batches were finally run in a mini-plant on a 29 mol scale (165-L Hastelloy reactor). At the mini-plant scale, however, the yields dropped to 40−48%. Although the purity (95−99%) and the levels of Pd (12−40 ppm) were comparable to those of the lab results, the Zn content was surprisingly high (200−500 ppm). The lower yield obtained on the mini-plant scale might be attributed to the lumping of the precipitate formed after the addition of the $ZnCl_2$ solution, although this phenomenon was not observed on the lab scale. To minimize this risk the temperature at which the $ZnCl_2$ solution was added was raised to −45 °C, which, on the contrary, resulted in the formation of more impurities. However, the high Zn content proved not to be a problem as the workup of the final coupling and subsequent purification further reduced the Pd and Zn content to below 5 ppm each in the API. Thus, despite the lack of robustness of the process, 16 kg of **3** were prepared.

(12) Norit A Supra.

Conclusion

In conclusion, a process was developed that has been used on a mini-plant scale to produce 16 kg of 2-chloro-5-(pyridin-2-yl) pyrimidine, **3** (Scheme 5). This intermediate had an acceptable quality, and also Pd and Zn content proved to be acceptable for the production of its derived API. We have demonstrated the feasibility of the Negishi cross-coupling reaction which on mini-plant scale is rarely used.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were measured on a Bruker AV600 spectrometer in DMSO-d_6. The chemical purities were determined by quantitative and qualitative methods on a HP 1090 series II HPLC instrument using a Hypersyl BDS-C18 column, 3 μm particle size (4.0 mm × 100 mm), and UV detector.

2-Hydroxypyrimidine Hydrochloride (4). A 10-L flask was charged successively with urea (180 g, 3 mol), 2-propanol (5 L), and 1,1,3,3-tetramethoxypropane (492 g, 3 mol). To the heterogeneous mixture, 11 N aqueous HCl (570 mL, 6.2 mol) was added dropwise. The addition was slightly exothermic, and the reaction mixture became homogeneous. After addition, the mixture was heated to 53−60 °C and stirred for 3 h during which the mixture started to crystallize. The mixture was cooled to 0 °C and stirred for another 3 h. The precipitate was filtered, washed with 2-propanol (1 L), and dried in vacuo at 50 °C yielding 290 g (73%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.81 (t, J = 5.7 Hz, 1 H) 8.74 (d, J = 5.7 Hz, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 103.8, 148.4.

2-Hydroxy-5-iodo-pyrimidine (7). A 1-L flask was charged successively with 2-hydroxypyrimidine hydrochloride (100 g, 0.75 mol), water (450 mL), and acetic acid (38 mL). The mixture was heated to 40 °C, and a 33% aqueous solution of ICl (243 mL, 0.79 mol) was added over 20 min. The mixture was stirred for another 6 h at 40 °C, and it was cooled to approx 2 °C. The precipitate was filtered off and washed with water (3 portions of 100 mL). The wet product was suspended in acetone (500 mL) and the mixture stirred for 20 min. The precipitate was filtered off and dried in vacuo at 40 °C, yielding 122 g (72.6%) of the title compound. ^{1}H

NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 2 H) 10.40 (br s, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 66.5, 154.3, 161.8.

2-Chloro-5-iodo-pyrimidine (8). A 3-L flask was charged successively with 2-hyroxy-5-iodo-pyrimidine (100 g, 0.45 mol), acetonitrile (540 mL), and phosphorous oxychloride (82.9 g, 0.54 mol). Diisopropylethylamine (29.1 g, 0.23 mol) was added dropwise. Upon addition, the mixture was heated to reflux and kept under the same heating conditions for 20 h. After the mixture was cooled to 40 °C, water (900 mL) was added over 20 min. The formed black precipitate was extracted with ethyl acetate (1130 mL). The extract was washed with an aqueous solution of sodium sulfite (150 g in 570 mL). The extract was transferred into a 2-L flask, and water (270 mL) was added. The mixture was heated to reflux, and about 600 mL of solvent was distilled off, and another portion of water (540 mL) was added. Solvent evaporation was continued until the inner temperature reached 85 °C. The mixture was cooled to approx 22 °C and filtered. The precipitate washed with water (100 mL) and dried at 40 °C in vacuo yielding 78.4 g (72%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (s, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 92.9, 159.0, 165.4.

2-Chloro-5-(pyridin-2-yl) Pyrimidine (3). A 2-L flask was charged with tetrahydrofuran (130 mL) and purged with nitrogen. The mixture was cooled to −70 °C, and a solution of hexyllithium in hexanes (175 mL 2.5molar, 0.436 mol) was added dropwise at such a rate that the inner temperature remained below −50 °C. On completion of the addition the mixture was cooled to −65 °C, and 2-bromopyridine (65.7 g, 0.416 mol) was added at such a rate that the inner temperature remained below −65 °C. Subsequently, a solution of $ZnCl_2$ (57.8 g, 0.416 mol) in tetrahydrofuran (268 mL) was added below −55 °C. Upon completion of the addition, the mixture was allowed to warm to approx 22 °C. After stirring for another 2 h, $Pd(PPh_3)_4$ (4.8 g, 0.004 mol) was added. Subsequently, a solution of 5-iodo-2-chloropyrimidine (50 g, 0.2 mol) in tetrahydrofuran (160 mL) was added at such a rate that the temperature remained below 30 °C. After stirring for another hour, a 0.39 M aqueous solution of EDTA·3Na (1 L) and dichloromethane (100 mL) were added, and the mixture was stirred vigorously for 15 min. The layers were separated, and from the organic layer the solvents were evaporated under reduced pressure, leading to a black oily residue. The residue was dissolved in dichloromethane (300 mL), and to the solution were added Kieselgel 60 (66 g) and thiol-modified silica[13] (6.1 g).The mixture was stirred for 20 min and filtered. The solid collected was washed with dichloromethane (3 aliquots of 230 mL). From the filtrate the solvents were evaporated until the residual volume reached approx 350 mL. After cooling to approx 22 °C the residue was washed with a 2 N hydrochloric acid solution (2 aliquots of 350 mL). The combined aqueous layers were treated with Norit A Supra (1.4 g). After filtration the filtrate was neutralized with aqueous ammonia (pH 6−7). The resulting precipitate was collected by filtration and dried in vacuo at 40 °C, yielding 25.6 g (67%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (dd, J = 6.8, 5.0 Hz, 1 H) 7.99 (td, J = 7.8, 1.8 Hz, 1 H) 8.13−8.17 (m, J = 8.1 Hz, 1 H) 8.73−8.76 (m, J = 4.8 Hz, 1 H) 9.40 (s, 2 H). Melting point: 114.1 °C. HRMS (ESI+) calc for $C_9H_6N_3Cl$ [M^+] 191.0250, found 191.0250. IR (neat) 3059, 3047, 1589, 1574, 1539, 1478, 1441, 1401, 1375, 1169, 1155, 1053, 989, 959, 803, 784 cm^{-1}. Anal. calcd for $C_9H_6N_3Cl$: C, 56.41; H, 3.16; N, 21.93; Cl, 18.5. Found: C, 56.07; H, 3.09; N, 21.89; Cl, 18.5.

(13) Purchased from Silicylce Inc.

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