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Regioselective cross-coupling reactions and nucleophilic aromatic substitutions on a 5,7-dichloro-pyrido[4,3-*d*]pyrimidine scaffold

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Abstract—The synthesis of a 5,7-dichloropyrido[4,3-*d*]pyrimidine scaffold is described. The chlorine at position 5 can selectively be displaced by different palladium-catalyzed cross-coupling reactions and nucleophilic aromatic substitutions. In the subsequent step, the chlorine at position 7 can be further derivatized. The described synthetic sequence allows for the construction of a diverse pyrido[4,3-*d*]pyrimidine library with structural variations at positions 5 and 7.

The pyridopyrimidine scaffold (Fig. 1) is a well-known pharmacophore in drug design and it is associated with a wide range of biological properties. Pyrido[3,2-*d*]-pyrimidines have been described as tyrosine kinase inhibitors and as dihydrofolate reductase inhibitors.[1] Pyrido[2,3-*d*]pyrimidines possess dihydrofolate reductase inhibiting and antitumour activity.[2] Pyrido[3,4-*d*]-pyrimidines are well known to be potent tyrosine kinase inhibitors and matrix metalloproteinase-13 inhibitors.[3] Pyrido[4,3-*d*]pyrimidines are also known to be inhibitors of tyrosine kinases of the epidermal growth factor receptor family.[4]

As part of a structure–activity study on immunosuppressive agents, we were interested in synthetic schemes to introduce a variety of substituents at positions 5 and 7 of the pyrido[4,3-*d*]pyrimidine scaffold that can be used in high-throughput medicinal chemistry. An ideal key intermediate to elaborate this type of chemistry is 5,7-dichloropyrido[4,3-*d*]pyrimidine. Both chlorine atoms are ideal substrates for nucleophilic aromatic substitutions (SNAr) and palladium-catalyzed cross-coupling reactions. Regioselective cross-coupling reactions of multiple halogenated heterocycles have recently been reviewed.[5] However, as far as we know, regioselective cross-coupling reactions on a pyrido[4,3-*d*]pyrimidine scaffold have not been reported before.

We envisioned to synthesize the pyrido[4,3-*d*]pyrimidine scaffold from an appropriately substituted pyridine analogue, that is, 4-amino-2,6-dichloronicotinic acid **4**. However, much to our surprise, the synthesis of this compound is not described in the literature. Therefore, we worked out the synthesis of compound **4** from the commercially available 4-amino-2,6-dichloropyridine **1** (Scheme 1). The amino group was protected as a

Figure 1.

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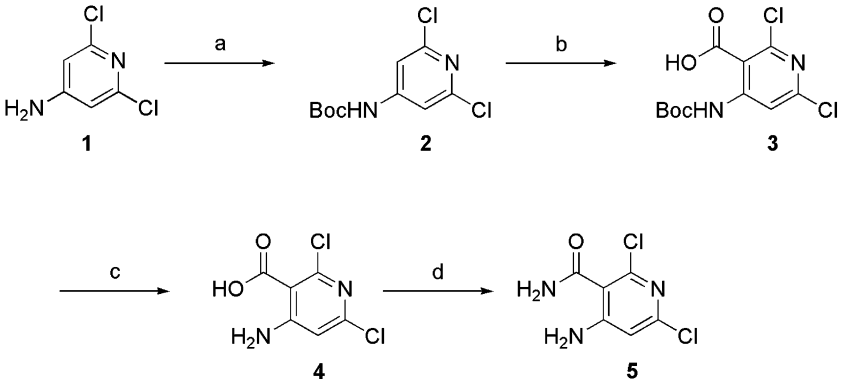
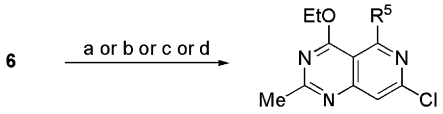


Scheme 1. Reagents and conditions: (a) $(Boc)_2O$, NaHMDS, THF, rt, 3 h; (b) *n*-BuLi, CO_2, diethyl ether, −78 °C, 4 h then rt overnight; (c) TFA, CH_2Cl_2, rt, 12; (d) $SOCl_2$, 1,2-dichloroethane, reflux, 3 h then NH_3(aq), diethyl ether, 0 °C, 20 min.

tert-butoxycarbonyl group (Boc). The formation of a carbanion by treatment with *n*-butyllithium (*n*-BuLi), in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), and quenching by the addition of anhydrous carbon dioxide gas led to the formation of the nicotinic acid derivative **3**. The Boc group was cleaved off under acidic conditions, yielding pyridine analogue **4**. By refluxing compound **4** in thionylchloride, the carboxylic acid was converted to its corresponding acid chloride, which was subsequently treated with ammonia, affording amide **5**.

In order to construct the pyrido[4,3-*d*]pyrimidine bicycle, 4-amino-2,6-dichloronicotinamide **5** was condensed with triethylorthoacetate. Only 4-ethoxy analogue **6** could be isolated in a 38% yield, whereas the 4-hydroxy derivative could not be detected. However, the 4-ethoxy congener offers some advantages compared to the hydroxy compound such as better solubility in common organic solvents and hence, easier handling and purification. In addition, the ethoxy compound could be easily converted to its 4-hydroxy analogue by acidic or basic hydrolysis. Alternatively, compound **7** could also be prepared by heating compound **5** in triethylorthoformate (Scheme 2).

2-Methyl-4-ethoxy-5,7-dichloropyrido[4,3-*d*]pyrimidine **6** was considered as an ideal starting material to study the regioselectivity of nucleophilic aromatic substitutions and palladium-catalyzed cross-coupling reactions (Scheme 3). The treatment of compound **6** with 1 equiv of morpholine leads exclusively to the monosubstituted compound **8**. A Suzuki coupling, a Stille coupling and a Sonagashira reaction were chosen as representatives for palladium-catalyzed cross-coupling reactions. The Suzuki reaction (step (d)) was performed with 3,4-dimethoxyphenylboronic acid under standard reaction conditions: potassium carbonate as a base and

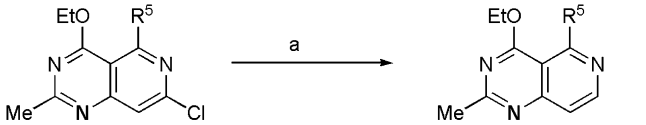


8: R^5 = morpholinyl (procedure a)
9: R^5 = 3-hydroxypropynyl (procedure b)
10: R^5 = phenyl (procedure c)
11: R^5 = 3,4-dimethoxyphenyl (procedure d)

Scheme 3. Reagents and conditions: (a) morpholine, NEt_3, dioxane, 80 °C, N_2, 24 h; (b) propargyl alcohol, NEt_3, $Pd(OAc)_2(PPh_3)_2$, dioxane, reflux, N_2, 24 h; (c) tributylphenyltin, $Pd(PPh_3)_4$, dioxane, reflux, N_2, 1 h; (d) 3,4-dimethoxyphenylboronic acid, K_2CO_3, $Pd(PPh_3)_4$, dioxane/H_2O, reflux, N_2, 2 h.

tetrakistriphenylphosphine as the catalyst.[6] For the coupling with propargyl alcohol, a copper free version of the Sonagashira reaction (step (b)) was carried out using bis(triphenylphosphine)palladium(II)acetate as the catalyst and triethylamine as the base.[7] The Stille coupling (step (c)) was done with tributylphenyl stannane and tetrakis(triphenylphosphine)palladium(0) as the catalyst.[8]

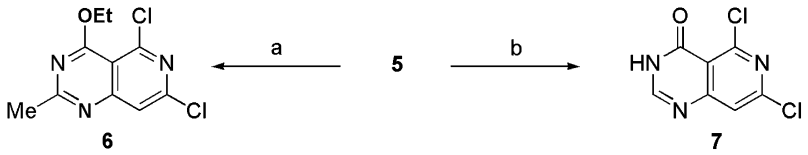
For all the above mentioned reactions, only one single isomer was isolated.[9] The regiochemistry of the isolated compounds could easily be elucidated by 2D NMR studies (NOESY and HMBC spectra). For compound



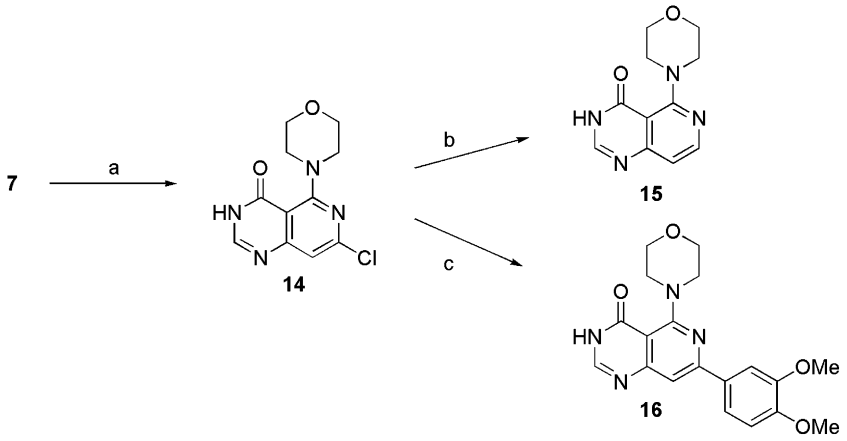
8 : R^5 = morpholinyl
10 : R^5 = phenyl

12 : R^5 = morpholinyl
13 : R^5 = phenyl

Scheme 4. Reagents and conditions: (a) H_2, KOAc, 10% Pd/ C, THF/MeOH (2:1), rt, 4 h.



Scheme 2. Reagents and conditions: (a) triethyl orthoacetate, reflux, 12 h; (b) triethyl orthoformate, reflux, 3 h.



Scheme 5. Reagents and conditions: (a) morpholine, NEt_3, dioxane, 80 °C, N_2, 24 h; (b) H_2, KOAc, Pd/C, THF/MeOH (2:1), rt; (c) 3,4-dimethoxyphenylboronic acid, K_2CO_3, $Pd(PPh_3)_4$, dioxane/H_2O, reflux, N_2, 2 h.

8, a clear NOE contact was observed between the ethoxy protons and the protons on the morpholino ring. In addition, a clear HMBC cross-peak was seen between C(5) of the pyrido[4,3-*d*]pyrimidine scaffold and the morpholino protons. For compounds **10** and **11**, we observed clear HMBC correlations between the protons on the phenyl ring and C(5) of the pyrido[4,3-*d*]pyrimidine moiety, whereas no HMBC cross-peak was detected between the proton on C(8) and the phenyl protons. For the Sonogashira derived coupling product **9**, a clear HMBC connectivity was observed between the CH_2 protons adjacent to the triple bond and C(5) of the pyrido[4,3-*d*]pyrimidine core structure. All these findings indicate that the chlorine at position 5 was displaced, whereas the chlorine at position 7 was still intact.

Alternatively, the regiochemistry could also be proven unambiguously through chemical conversion (Scheme 4).[10] The remaining chlorine of compounds **8** and **10** was reduced off by catalytic hydrogenation over palladium, giving rise in the ^{1}H NMR spectrum to two doublets, arising from the protons at positions 7 and 8. If the remaining chlorine would be present at position 5, only a singlet (from the proton at position 5) would be observed in the ^{1}H NMR spectrum, after reductive removal of the chlorine.

The remaining chlorine at position 7 can be used for a subsequent SNAr or palladium-catalyzed cross-coupling reaction, as exemplified in Scheme 5. The treatment of compound **7** with morpholine furnished 5-morpholino derivative **14**. The regiochemistry of this compound was proven by the reductive dehalogenation of chlorine, yielding compound **15**. In the subsequent step, chlorine at position 7 was used for a Suzuki-type of coupling with 3,4-dimethoxyphenyl boronic acid, yielding the 5,7-disubstituted pyrido[4,3-*d*]pyrimidine analogue **16**.

In summary, we developed an efficient approach which makes sequential palladium-catalyzed cross-coupling reactions or nucleophilic aromatic substitutions possible and will allow for the construction of a diverse pyrido[4,3-*d*]pyrimidine library, with structural variations at positions 5 and 7 of the scaffold.

References and notes

1. (a) Smaill, J. B.; Palmer, B. D.; Rewcastle, G. R.; Denny, W. A.; McNamara, D. J.; Dobrusin, E. M.; Bridges, A. J.; Zhou, H.; Hollis Showalter, H. D.; Winters, R. T.; Leopold, W. R.; Fry, D. W.; Nelson, J. M.; Slintak, V.; Elliott, W. L.; Roberts, B. J.; Vincent, P. W.; Patmore, S. J. *J. Med. Chem.* **1999**, *42*, 1803–1815; (b) Gangjee, A.; Zhu, Y.; Queener, S. F. *J. Med. Chem.* **1998**, *41*, 4533–4541.
2. Gangjee, A.; Adair, O.; Queener, S. F. *J. Med. Chem.* **1999**, *42*, 2447–2455.
3. (a) Rewcastle, G. W.; Murray, D. K.; Elliott, W. L.; Fry, D. W.; Howard, C. T.; Nelson, J. M.; Roberts, B. J.; Vincent, P. W.; Showalter, H. D. H.; Winters, R. T.; Denny, W. A. *J. Med. Chem.* **1998**, *41*, 742–751; (b) Bunker, A.; Picard, J.; Lodaya, R.; Waldo, M.; Marlatt, M. WO 2005/016926.
4. Bridges, A. J.; Denny, W. A.; Fry, D.; Kraker, A.; Meyer, R. F.; Rewcastle, G. W.; Thompson, A. M. US 5654307.
5. Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245–2267.
6. Schomaker, J. M.; Delia, T. J. *J. Org. Chem.* **2001**, *66*, 7125–7128.
7. Li, J.; Zhang, X.; Xie, Y. *Eur. J. Org. Chem.* **2005**, *20*, 4256–4259.
8. Schnute, M. E.; Cudahy, M. M.; Brideau, R. J.; Homa, F. L.; Hopkins, T. A.; Knechtel, M. L.; Oien, N. L.; Pitts, T. W.; Poorman, R. A.; Wathen, M. W.; Wieber, J. L. *J. Med. Chem.* **1999**, *42*, 2447–2455.
9. Compound **8**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.06$ (s, 1H, H-8), 4.63 (q, $J = 7.15$ Hz, 2H, OCH_2CH_3), 3.86 (t, $J = 4.55$ Hz, 4H, $O(CH_2)_2$), 3.51 (t, $J = 4.55$ Hz, 4H, $N(CH_2)_2$), 2.62 (s, 3H, 2-CH_3), 1.50 (t, $J = 7.15$ Hz, 3H, OCH_2CH_3). Compound **9**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.62$ (s, 1H, H-8), 4.63 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 4.62 (s, 2H, CH_2OH), 2.69 (s, 3H, 2-CH_3), 1.55 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3). Compound **10**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.67$ (s, 1H, H-8), 7.46–7.42 (m, 5H, ArH), 4.31 (q, $J = 6.9$ Hz, 2H, OCH_2CH_3), 2.70 (s, 3H, 2-CH_3), 0.96 (t, $J = 6.9$ Hz, 3H, OCH_2CH_3). Compound **11**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.64$ (s, 1H, H-8), 7.06–7.04 (m, 2H, ArH), 6.93 (d, $J = 8.75$ Hz, 1H, ArH), 4.36 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 3.95 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 2.70 (s, 3H, 2-CH_3), 1.05 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3).
10. *General procedure for the reductive removal of chlorine*: A solution of compound **8** or **10** (0.04 mmol), KOAc (6 mg)

and 10% Pd/C (2 mg) in THF/MeOH (2:1, 1 ml) was stirred for 4 h at room temperature under a H_2 atmosphere. The mixture was filtered over Celite and the solvents were evaporated in vacuo. The solid was redissolved in dilute HCl and the pH was adjusted to 10, by the addition of a 2 M NaOH solution. The mixture was extracted with CH_2Cl_2, washed with water and brine and dried over $MgSO_4$. After concentration under reduced pressure, the crude residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH 30:1), yielding the pure compounds **12** and **13** (in yields varying from 45% to 60%).