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Synthesis of a 5-alkoxypyrido[3,4-*d*]pyrimidin-4(3*H*)-one derivative via directed *ortho*-metallation of a pyridine analogue

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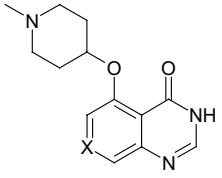
Abstract—The synthetic strategy towards a 5-alkoxypyrido[3,4-*d*]pyrimidin-4(3*H*)-one is described, utilizing palladium catalyzed amination of a bromopyridine, and subsequent directed *ortho*-metallation/carboxylation as the key steps.

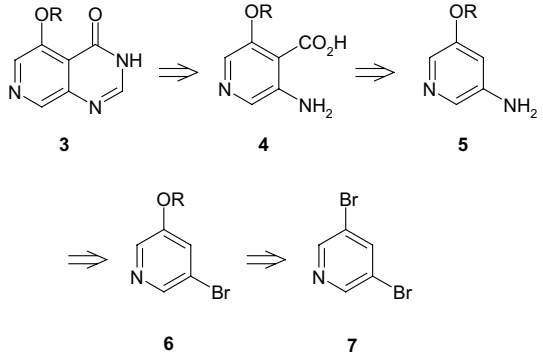
As part of an ongoing research programme, we sought to investigate the structure–activity relationships around a series of 5-alkoxyquinazolin-4(3*H*)-one derivatives as exemplified by **1**. These compounds were readily accessible to us via nucleophilic aromatic substitution (S_NAr) of commercially available 5-fluoroquinazolin-4(3*H*)-one, with alkoxide nucleophiles formed in situ by sodium hydride deprotonation of the appropriate alcohols. As part of these studies we became interested in the effects of substitution of nitrogen into the ring at C-7, to give the 5-alkoxypyrido[3,4-*d*]pyrimidin-4(3*H*)-one as exemplified by **2**. Despite extensive interest in the pyrido[3,4-*d*]pyrimidin-4(3*H*)-one core from the medicinal and synthetic chemistry communities,[1–8] we are not aware of any routes available that give this specific (mono)substitution pattern. Herein we report our preliminary findings on the synthesis of this ring system.



1 X = CH
2 X = N

We envisaged that the pyrido[3,4-*d*]pyrimidin-4(3*H*)-one core **3** could be efficiently assembled in a manner analogous to the quinazolin-4(3*H*)-one ring system.[9–16] Thus, the C-2 and N-3 atoms would be introduced as a formamide equivalent into a suitably substituted amino isonicotinic acid **4**, itself prepared by a directed *ortho*-metallation/carboxylation strategy applied to the amino pyridine **5**.[17] This should be accessible by a palladium-catalyzed amination of a bromopyridine **6**. Commercially available dibromopyridine **7** would be utilized as starting material (Scheme 1).

The sequence commenced with the treatment of 3,5-dibromopyridine **7** with sodium methoxide (1.5 equiv/DMF/40 °C/20 h) to give the methoxypyridine derivative **8** in 72% yield (Scheme 2). Palladium-catalyzed amination of **8** with *tert*-butyl carbamate, following the



3 **4** **5**

6 **7**

Scheme 1. Retrosynthetic strategy for assembly of the 5-alkoxypyridopyrimidinone core.

Keywords: Amination; DoM; Pyridopyrimidine.
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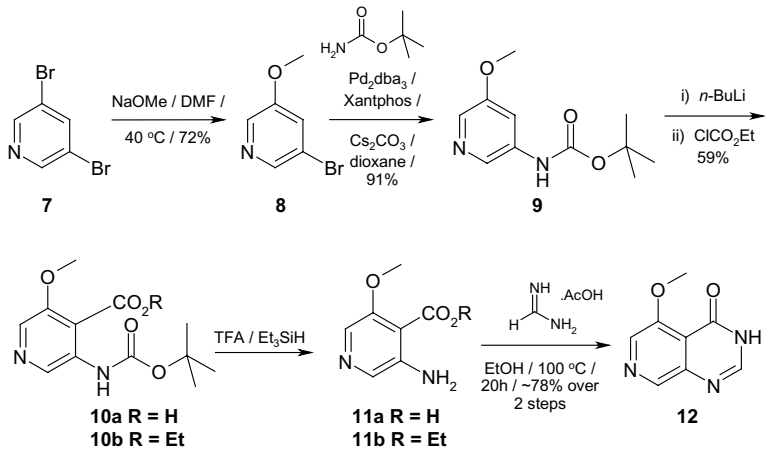
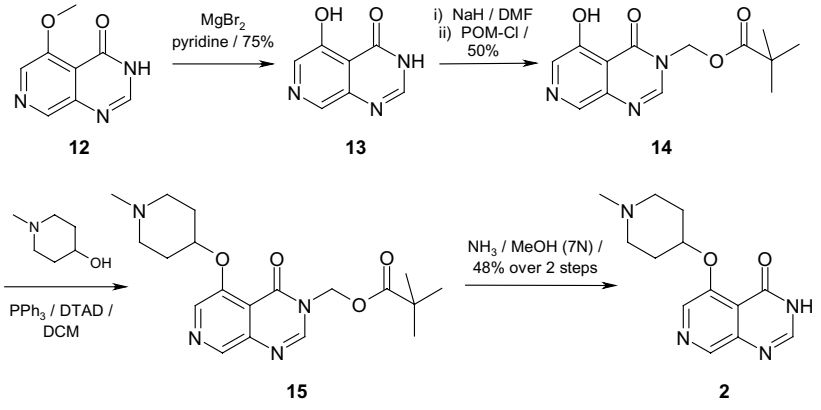


Scheme 2. Synthesis of the pyridopyrimidinone core.

procedure described by Yin and Buchwald[18] (Pd_2dba_3/Xantphos/Cs_2CO_3/dioxane/90 °C/48 h) gave the carbamate **9** in 91% yield on a multi-gram scale. Gratifyingly, early attempts to introduce a carboxylate function at position C-4 of the pyridine, by metallation with *n*-butyllithium and quenching with solid carbon dioxide were successful.[19] However, the subsequent cyclization of the deprotected amino acid **11a** with formamidine acetate to give the pyrido[3,4-*d*]pyrimidin-4(3*H*)-one **12** proved problematic due to the insolubility of the starting material. This problem was circumvented by metallation of the pyridine **9** with *n*-butyllithium (2.5 equiv/ $-78 \rightarrow 10$ °C/THF) and quenching with ethyl chloroformate (1 equiv/-78 °C) to give the ethyl ester **10b** in 59% overall yield. Removal of the protecting group with trifluoroacetic acid provided the amino ester **11b**. The improved solubility of this material in ethanol under reflux ensured an efficient cyclization with formamidine acetate to afford the pyrido[3,4-*d*]pyrimidin-4(3*H*)-one **12**, which precipitated from the reaction mixture in 78% yield from the carbamate **10b**.

With the bicyclic core now assembled, the pendant 4-hydroxy-*N*-methylpiperidine could be attached (Scheme 3). The 5-hydroxy function was revealed by treatment of the methyl ether **12** with magnesium bromide (1 equiv) in pyridine at reflux for 2 h. An aqueous work-up afforded the hydroxypyridine derivative **13** in 75% yield. Protection of the pyrimidinone portion as an *N*-pivaloyloxymethylamide by sequential treatment with sodium hydride (1.1 equiv) in DMF, followed by *N*-pivaloyloxymethyl chloride (POM-Cl) (1.2 equiv) provided the substrate **14** required for a Mitsunobu reaction in only 50% yield. Attempts to improve on this yield were unrewarded. This alcohol was partnered with 4-hydroxy-*N*-methylpiperidine (1.25 equiv) under Mitsunobu conditions (di-*tert*-butyl azodicarboxylate (DTAD), PPh_3, CH_2Cl_2) to afford the crude ether **15**. This was stirred in 7 N ammonia in methanol for 24 h to give, after silica-gel chromatography, the 5-alkoxypyrido[3,4-*d*]pyrimidin-4(3*H*)-one **2** in 48% yield over two steps.

In conclusion we have described the first synthesis of the 5-alkoxypyrido[3,4-*d*]pyrimidin-4(3*H*)-one ring system in nine steps from commercially available starting material in 5% overall yield. It is anticipated that further molecular complexity can be introduced at C-4 via a chlorination-displacement strategy, and that a diverse set of alcohols be coupled to the C-5 hydroxy group.



Scheme 3. Introduction of the *N*-methylpiperidin-4-yloxy side-chain.

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