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Synthesis of a 5-alkoxypyrido[4,3-*d*]pyrimidin-4(3*H*)-one derivative via a regioselective Meisenheimer N-oxide rearrangement ☆

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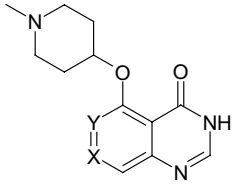
Abstract—The synthetic strategy towards a 5-alkoxypyrido[4,3-*d*]pyrimidin-4(3*H*)-one is described utilizing a selective N-oxidation and subsequent regioselective Meisenheimer N-oxide rearrangement as key steps.

In the preceding paper[1] we outlined a novel synthetic strategy to a 5-alkoxypyrido[3,4-*d*]pyrimidin-4(3*H*)-one derivative, **2**, as part of an investigation into the structure–activity relationship around a series of 5-alkoxyquinazolin-4(3*H*)-one derivatives **1**. We sought to expand these studies by synthesis of the regioisomeric 5-alkoxypyrido[4,3-*d*]pyrimidin-4(3*H*)-one derivative **3**, where C-6 of the parent quinazoline, **1** is replaced by nitrogen. Our strategy for **3** adopted similar methodology to that used for **1**, namely a nucleophilic aromatic substitution (S_NAr) of a 5-chloropyrido[3,4-*d*]pyrimidin-4(3*H*)-one with the requisite alkoxide nucleophile. Despite extensive interest in the pyrido[4,3-*d*]pyrimidin-4(3*H*)-one core from the medicinal and synthetic chemistry communities,[2–5] we are not aware of any routes available that give this specific (mono)alkoxysubstitution pattern. Herein we report our preliminary findings on the synthesis of this ring system.



1 X, Y = CH
2 X = N, Y = CH
3 X = CH, Y = N

The retrosynthetic strategy is outlined in Scheme 1. Displacement of the activated chlorine of compound **4** with an alkoxide nucleophile was expected to proceed uneventfully. Synthesis of the previously unreported 5-chloropyrido[4,3-*d*]pyrimidin-4(3*H*)-one core, as in **4**, depended critically on a regioselective Meisenheimer N-oxide rearrangement[6–9] of a suitably protected pyrido[4,3-*d*]pyrimidin-4(3*H*)-one 6-oxide, **5**. The synthesis of this key N-oxide in turn hinged upon a selective oxidation of a suitably protected analogue of the known pyrido[4,3-*d*]pyrimidin-4-one **6**, at N-6.

Quantum mechanical calculations[10] for the model compounds **A** and **B** in Figure 1 (in which the N3 protecting group has been truncated to methyl for simplicity) were used to predict the regioselectivity of the critical step of the Meisenheimer rearrangement, namely addition of chloride to the pyridine ring. The rate determining step of the reaction was assumed to be the formation of intermediates such as **A** and **B** and the Hammond postulate[11] is invoked to justify the use of these to model the regioselectivity. Model compound **A** is predicted to be significantly lower in energy than **B**. Calculated values for the energy difference (**B**−**A**) at different levels of theory are 38 kJ mol^{-1} (RHF/6-31G*[12]), 28 kJ mol^{-1} (B3LYP/6-31G*[13]) and 43 kJ mol^{-1} (MP2/6-31G*[12]). Consequently these theoretical calculations led us to expect

Keywords: Phosphorus oxychloride; Meisenheimer; Pyrido[4,3-*d*]pyrimidin-4(3*H*)-one.
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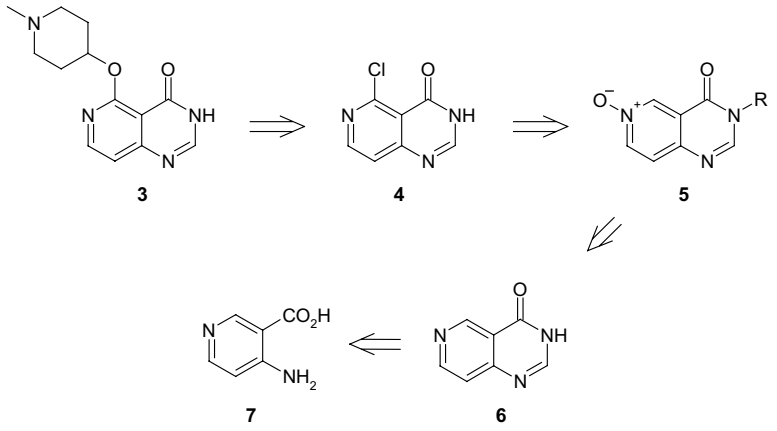


Scheme 1. Retrosynthetic strategy for assembly of the 5-alkoxypyridopyrimidinone core.

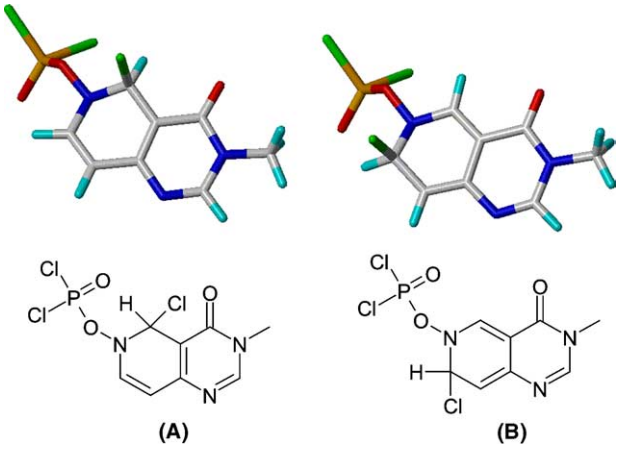
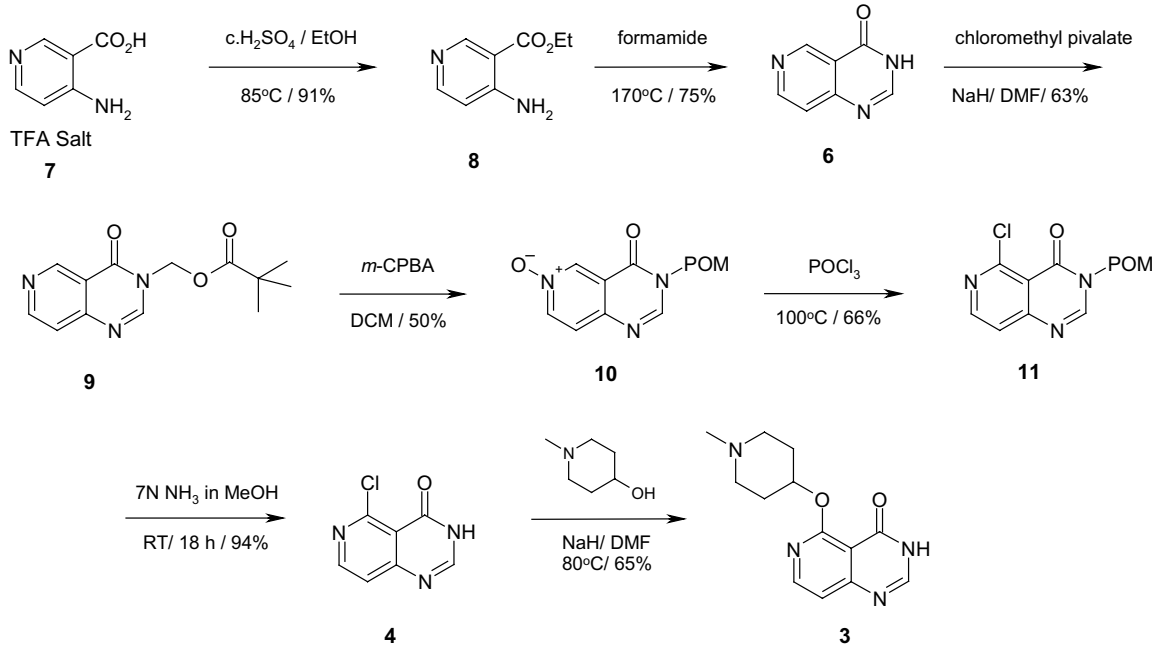


Figure 1. Lowest energy conformations of intermediates **A** (chloride addition to C5) and B (chloride addition to C7) energy-minimized at RHF/6-31G* level.

rearrangement of **5** to furnish the requisite 5-substituted product in preference to the alternative 7-substituted isomer (quinazoline ring numbering).

The sequence started with esterification of the trifluoroacetate (TFA) salt of 4-aminonicotinic acid **7**[14] (concentrated sulfuric acid, 10% (v/v)/EtOH/85 °C/18 h) to give the ethyl ester **8** in 91% yield (Scheme 2). Cyclization was achieved by heating the ester in neat formamide (170 °C/16 h) to give the pyrido[4,3-*d*]pyrimidin-4(3*H*)-one core **6** in 75% yield on a multigram scale, using an acidic ion-exchange resin catch-and-release strategy to isolate the compound from the solvent. The direct conversion of **7** to **6** with formamide was successful, but a considerable exotherm and gas evolution was noted at 150 °C that was speculated to be due to thermal decomposition of the TFA salt. Thus the two-step strategy described above was adopted. Pivaloyloxy-



Scheme 2. Synthesis of 5-alkoxypyrido[4,3-*d*]pyrimidin-4(3*H*)-one from 4-aminonicotinic acid.

methyl (POM) protection at N3 was introduced by formation of the anion with sodium hydride (1.2 equiv/DMF/0 °C) and a subsequent quench with chloromethyl pivalate (1.2 equiv/0 °C to rt/1 h) to give **9** in 63% yield. Selective oxidation of the pyridine ring nitrogen with *m*-CPBA (1.25 equiv/0 °C to rt/16 h) gave the N-oxide **10** in 50% yield. This reaction appeared to give cleanly a single regioisomer, with no evidence of oxidation at N-1 of the pyrimidone ring. Despite this, we were unable to improve the isolated yield beyond that reported here. As anticipated, the crucial Meisenheimer N-oxide rearrangement was accomplished in a regioselective manner with phosphorus oxychloride as solvent (100 °C/2 h) to give **11**, after work up with ice-cold saturated sodium carbonate solution, in 66% yield. The structure of **11** was confirmed by NMR studies.[15] Removal of the POM protecting group proceeded uneventfully by treatment with a solution of 7 N ammonia in methanol to give **4** in 94% yield. Finally, displacement of the chlorine was accomplished by in situ generation of the alkoxide nucleophile in 65% yield, in a manner analogous to that used for synthesis of **1**.[1]

In conclusion we have described the first synthesis of the 5-alkoxypyrido[4,3-*d*]pyrimidin-4(3*H*)-one ring system in seven steps from the TFA salt of 4-aminonicotinic acid in 9% overall yield. It is anticipated that a range of alkoxides and other nucleophiles could be used to introduce diversity at C-5 and that a subsequent chlorination-displacement strategy at C-4 would introduce further complexity to the molecule.

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15. NMR spectrum of compound **11** (DMSO-d_6); 1.10 (s, 9H), 5.85 (s, 2H), 7.60 (d, 1H), 8.60 (d, 1H), 8.70 (s, 1H); MS: MH^+ 296.