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Practical routes toward the synthesis of 2-halo- and 2-alkylamino-4-pyridinecarboxaldehydes

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Abstract—We recently required an efficient synthesis of 2-halo- and 2-alkylamino-4-pyridinecarboxaldehydes. Several routes to these compounds were investigated resulting in efficient and practical procedures from readily available and inexpensive starting materials.

1. Introduction

We recently required an efficient synthesis of 2-halo- and 2-alkylamino-4-pyridinecarboxaldehydes to support an ongoing drug development program. 2,4-Disubstituted pyridines are widely used substrates that appear in compounds directed towards a range of therapeutic areas.[1] Despite this fact, general reviews that focus on the synthesis of substituted pyridine rings do not cover many examples of 2,4-disubstitution.[2] An initial survey of the literature indicated that 2-halo-4-pyridinecarboxaldehydes were typically prepared by a reduction–oxidation sequence from 2-haloisonicotinic acid[1a–c,1i] or via a $POCl_3$ reaction with a 4-substituted pyridine *N*-oxide. While these routes provide the desired materials in reasonable yields, we were challenged with discovering a more efficient procedure. In this communication, we disclose efficient syntheses of 2-halo-4-pyridinecarboxaldehydes and three separate routes towards a 2-alkylamino-4-pyridinecarboxaldeyde.

A search of commercially available 2,4-disubstituted pyridines revealed that in addition to 2-chloro-isonicotinic acid, 2-halopicolines and 4-cyanopyridine *N*-oxide were also commercially available. We set out to explore the transformation of each of these materials into the desired 2-substituted-4-pyridinecarboxaldehydes (Fig. 1).

2. 2-Halopicolines as starting materials

We initially investigated the conversion of the 2-halopicolines to the desired alkyl amino aldehyde **1**. Amination of 2-bromopicoline **2a** utilizing the Hartwig/Buchwald protocol[3] or 2-fluoropicoline **2b** by simply heating with (*S*)-α-methylbenzylamine provided the desired 2-alkylaminopicoline **3** (Scheme 1). Unfortunately, we were unable to functionalize the picolyl methyl group while the amine side chain was in place. As a result, we began looking at methods for first oxidizing the 4-methyl group to the aldehyde oxidation state, followed by amination at the 2-position. There are numerous reports for oxidation of heteroaromatic methyl groups to the aldehyde,[4] acid[5] and oxime.[6] We

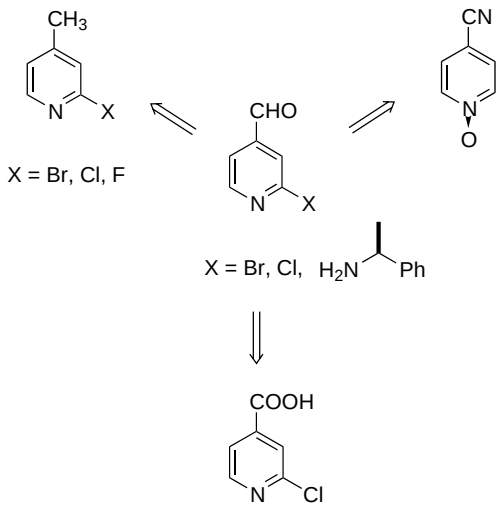

Figure 1.

Keywords: pyridine; α-methylbenzyl amine; amination.

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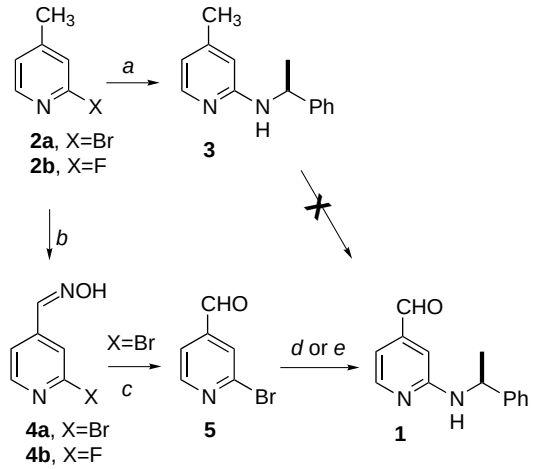
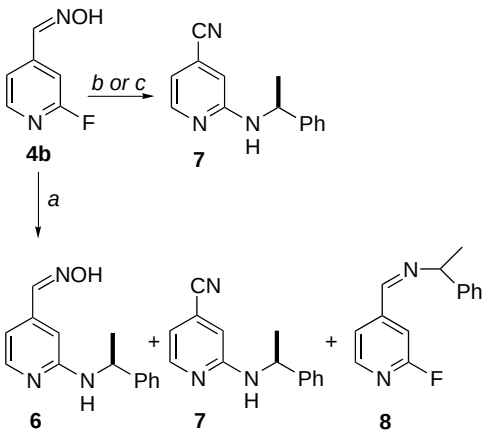


Scheme 1. *Reagents and conditions*: (a) (X = Br) $Pd(OAc)_2$, BINAP, (*S*)-α-methylbenzylamine, NaO^{t}Bu, toluene, 50°C or (X = F) (*S*)-α-methylbenzylamine, 140°C; (b) ^{t}BuONO, KO^{t}Bu, THF; (c) aq. HCl, CH_2O; (d) (i) MeOH, H_2SO_4, (ii) $Pd(OAc)_2$, BINAP, (*S*)-α-methylbenzylamine, NaO^{t}Bu, toluene, 50°C, (iii) aq. HCl; (e) (i) (*S*)-α-methylbenzylamine, toluene, (ii) CuOAc, $CsOCOCF_3$, (*S*)-α-methylbenzylamine, toluene, 110°C, (iii) aq. HCl.

were pleased to find that subjecting 2-bromo or 2-fluoro picoline to *t*-butyl nitrite in the presence of potassium *t*-butoxide provided the desired oximes **4a** and **4b** in high yield (Scheme 1).

Attempts to aminate the 2-bromo compound **4a** under standard palladium amination conditions[3] resulted in poor yields of the desired product. Presumably under strongly basic conditions the oxime undergoes deprotonation rendering the aromatic ring less reactive.[7] Instead, we chose to evaluate the amination on an aldehyde substrate. Reaction of the 2-bromo oxime **4a** with formaldehyde under acidic conditions provided the desired aldehyde **5** in 64% yield from the picoline **2a**.[8] This product is the first in the series of 2-halo-4-pyridinecarboxaldehydes required by our laboratory.



Scheme 2. *Reagents and conditions*: (a) (*S*)-α-methylbenzylamine, 140°C; (b) $Ti(O^iPr)_4$, (*S*)-α-methylbenzylamine, DMSO, 110°C; (c) (i) $SOCl_2$, THF, (ii) (*S*)-α-methylbenzylamine, 110°C, DMAC.

In order to obtain the 2-alkylamino analogue, **5** was protected as the dimethyl acetal and successfully aminated with palladium catalysis. Acidic hydrolysis of the dimethyl acetal afforded the title compound **1** (45% yield from picoline **2a**). Direct amination of the aldehyde **5**, after in situ formation of the imine from (*S*)-α-methylbenzylamine, using palladium catalysis provided **1** in only 26% yield from **5** after acidic hydrolysis. As a result, we began investigating alternative amination protocols. Ullmann-type couplings have been used for reactions of amines with aryl halides utilizing a variety of copper sources.[9] After exploring a wide range of reaction conditions, we found that the imine from **5** and (*S*)-α-methylbenzylamine could be heated with stoichiometric copper(I) acetate in the presence of cesium trifluoroacetate and excess (*S*)-α-methylbenzylamine to provide the desired product **1** after acidic hydrolysis (Scheme 1). This three-step protocol provided a 48% yield of the desired compound **1** from 2-bromopicoline **2a**. While this method has some appealing qualities, it requires the use of stoichiometric copper to effect the amination. We investigated the 2-fluoro analogue in an effort to overcome this limitation.

Chloro and bromo pyridines require metal catalysis to undergo substitution, while the corresponding fluorides often undergo displacement under thermal conditions. Amination of 2-fluoropicoline was successful in neat (*S*)-α-methylbenzylamine at 140°C. However, amination of the 2-fluoro-4-oximino compound **4b** was accompanied by some dehydration of the oxime to the nitrile. Heating **4b** in the presence of (*S*)-α-methylbenzylamine led to complex mixtures of 2-amino-4-oxime **6**, 2-amino-4-nitrile **7**, 2-fluoro-4-imine **8** and other products (Scheme 2). Interestingly, reaction of the oxime **4b** and (*S*)-α-methylbenzylamine at 110°C with $Ti(O^iPr)_4$ provided the dehydrated 2-amino-4-cyano pyridine **7** in 66% yield. Reaction of this intermediate with DIBAL provided the desired aldehyde **1** in an overall yield of 41% from the 2-fluoropicoline **2b**. Alternatively, oxime **4b** can be dehydrated with thionyl chloride, aminated by heating with (*S*)-α-methylbenzylamine in DMAC, and the nitrile reduced using DIBAL to give the desired aldehyde **1**. This is a four-step synthesis of **1** from 2-fluoro-picoline **2b** with an overall yield of 52%.

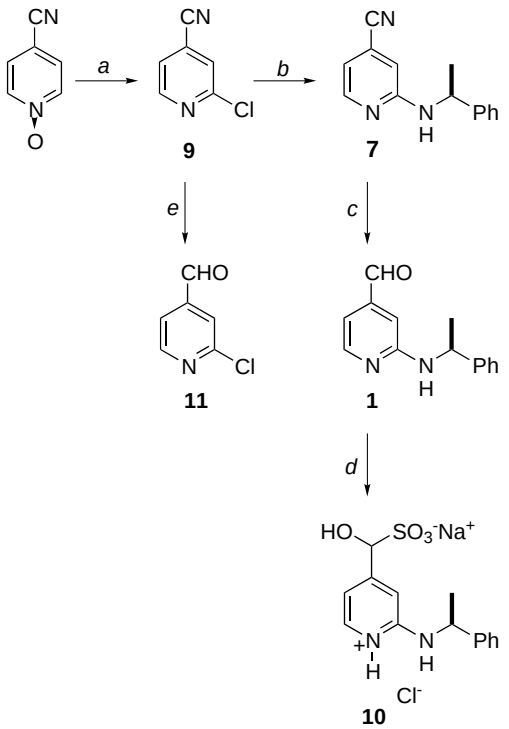
3. Pyridine *N*-oxides as starting materials

Our success reducing the nitrile to the desired aldehyde led us to investigate the 2-substituted-4-cyano pyridines as potential intermediates in the synthesis of our desired target. A search of the pertinent literature revealed two observations: 4-pyridine carboxamide *N*-oxide reacts with a mixture of $POCl_3$ and PCl_5 to give a 50% yield of 2-chloro-4-cyano pyridine,[10a] while 4-cyanopyridine *N*-oxide provides the 3-chloro-4-cyano pyridine under similar conditions.[10b] The production of the 3-chloro isomer was a curious result and we decided to reinvestigate these reactions to determine whether we could utilize them to our advantage. Interestingly, we found

that heating 4-cyanopyridine *N*-oxide with $POCl_3$,[1i] either neat or in ACN, gave the 2-chloro-4-cyanopyridine **9** as the predominant product (10:1 mixture of isomers)[11] (Scheme 3). The reaction required 24 h at 100°C to effect complete consumption of starting material, and a pH and temperature controlled work-up to safely quench the $POCl_3$, while preventing degradation of the product.[12] In this way, 2-chloro-4-cyano pyridine **9** was obtained in 69% yield.

Amination of 2-chloro-4-cyanopyridine **9** (Scheme 3) utilizing palladium catalysis[3] was initially problematic. We found that some decomposition of the nitrile occurred during the reaction, and we also observed varying amounts of a dimer (bis-arylated α-methylbenzylamine) depending on reaction conditions. These issues were overcome by slow addition of **9** to a suspension of the other reagents. At the completion of the reaction, an acetic acid wash was used to remove excess (*S*)-α-methylbenzylamine and then the product was extracted into aqueous HCl to allow for further purification. 2-Alkylamino-4-cyanopyridine **7** was crystallized from toluene–heptane in 82% yield from **9**.[13]

The DIBAL reduction of both the 2-chloro and 2-alkylamino-4-cyanopyridines proceeded very well using standard conditions (toluene, −10°C). Reduction of the 2-chloro-compound **9** gave 2-chloro-4-pyridine carboxaldehyde **11** in 80% yield. This represents an alternative synthesis of 2-chloro-4-pyridinecarboxaldehyde **11** that proceeds in 55% overall yield from 4-cyanopyridine *N*-oxide.



Scheme 3. *Reagents and conditions*: (a) $POCl_3$, 100°C; (b) $Pd(OAc)_2$, BINAP, (*S*)-α-methylbenzylamine, NaO^{t}Bu, toluene, 50°C; (c) (i) Dibal, toluene, −15°C, (ii) aq. HCl; (d) aq. $NaHSO_3$; (e) (i) Dibal, toluene, −15°C, (ii) aq. HCl.

Isolation of the 2-alkylamino compound **1** was more problematic, and as a result, the yields for this reaction varied from 60 to 90%. At the completion of the reaction it was necessary to decompose both aluminum complexes, as well as oligomers that arose from the imine intermediate. Workers at Lilly had demonstrated that a similar naphthyridine substrate could be isolated by quenching the reaction mixture into acetic acid and then extracting the product into the organic layer.[14] We found this protocol to be extremely exothermic and very difficult to control. In addition, we found that the intermediates were not completely broken down unless the pH was <4,[15] while at pH <4, all of the product was in the aqueous stream. Increasing the pH of the aqueous substrate after complete decomposition of the reaction intermediates resulted in a gel of aluminum salts.[16] As a result, we turned our attention towards isolating the aldehyde from an acidic aqueous solution. Direct crystallization of the desired compound was not successful, so we were gratified to find that adding a 20% bisulfite solution to the acidic aqueous solution of aldehyde resulted in crystallization of the bisulfite adduct **10** in 80% yield (Scheme 3). To employ the aldehyde in the subsequent steps, it was necessary to break down the bisulfite adduct at high pH. This was carried out most effectively by dissolving the solid in saturated aqueous $KHCO_3$ and extracting the resulting solution with ethyl acetate.[17] In this way the pure aldehyde **1** (obtained in 44% overall yield from 4-cyanopyridine *N*-oxide) could be isolated or used as a solution.

4. Conclusion

In summary, we have identified several routes to 2-substituted-4-pyridine carboxaldehydes from commercially available starting materials. 2-Chloro-4-pyridine-carboxaldehyde **11** was prepared from 4-cyanopyridine *N*-oxide in 55% yield, and 2-bromo-4-pyridinecarboxaldehyde **5** was prepared from 2-bromo-4-methylpyridine in 64% yield. Both of these routes offer attractive alternatives to the previously reported preparations of 2-halo-4-pyridinecarboxaldehydes. In addition, we identified three simple routes towards the 2-alkylamino-4-pyridinecarboxaldehyde **1** from 2-bromopicoline (48% overall yield), 2-fluoropicoline[18] (41%) and 4-cyanopyridine *N*-oxide (44%). When the final step is the Dibal reduction of the nitrile, isolation of **1** as the bisulfite adduct allows for easy purification and improved long term stability and handling.

Supporting information available. Includes detailed descriptions of experimental details and new compound characterization data.

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11. In addition, reaction of 4-cyanopyridine *N*-oxide with α-methylbenzyl amine in the presence of methylbenzyl isocyanate did not yield the desired 2-amino-4-cyanopyridine.
12. When **9** is aged in solutions of ACN–aq buffer, at pH 1 and at pH 11–12, the corresponding amide is slowly formed. A similar pH controlled quench was reported: Singh, B.; Lesher, G. Y.; Pennock, P. O. *J. Heterocycl. Chem.* **1990**, *27*, 1841.
13. The ee of the α-methylbenzylamine was retained in the product.
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15. The use of acetic acid and tartrate salt appeared to effectively break down the aluminum salts but not some oligomeric species, which presumably arise from trimerization of the imine intermediate. NMR studies of the reaction mixtures after these types of quenches showed complicated signals consistent with these types of intermediates.
16. Quenching the DIBAL reaction into HCl–citric acid (to break down aluminum complexes), followed by addition of NaOAc (to allow for extraction of the product out of the aqueous layer without gelling of aluminum salts) does allow for isolation of the pyridine aldehyde from toluene–heptane, but the work-up is tedious and involves several steps.
17. The higher concentration of saturated aqueous $KHCO_3$ over $NaHCO_3$ allowed for lower losses to the aqueous layer and a more efficient process.
18. Alternatively, separation of the dehydration and amination steps provides **1** in four steps and 52% overall yield from 2-fluoropicoline.