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# A Study of the Lithiation of 2,6-Dibromopyridine with Butyllithium, and its Application to Synthesis of L-739,010

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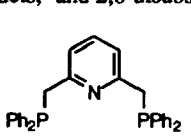
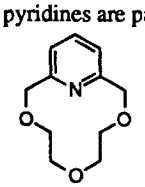
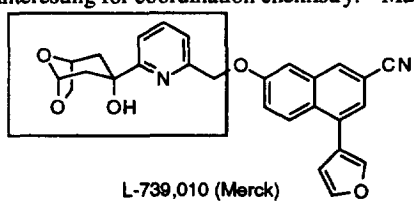
**Abstract**: Mono-lithiation of 2,6-dibromopyridine by *n*-BuLi is complicated by deprotonation of the pyridine ring by the resulting mono-lithium species. This problem can be eliminated by a reverse addition, but this causes formation of the undesired dilithio species. However, rapid lithium-halogen exchange between 2,6-dibromopyridine and 2,6-dilithiopyridine produces 2-bromo-6-lithiopyridine cleanly. Thus, using reverse addition, the mono-lithiated pyridine can be generated in 98% yield. 

Substituted pyridines are very useful building blocks for the construction of many natural and unnatural products,[1] and 2,6-disubstituted pyridines are particularly interesting for coordination chemistry.[2] Many of




L-739,010 (Merck)

these substituted pyridines have been frequently synthesized by lithiation or Grignard reaction of halogen-substituted pyridines or by the direct metalation of pyridine.[3] In the course of preparing the 5-lipoxygenase inhibitor, L-739,010,[4] we required the selective functionalization of 2,6-dibromopyridine. While the complex lithiation chemistry of several mono- and di-halogenated pyridines has been extensively examined,[3] the chemistry of 2,6-dibromopyridine has not been studied as much and the results are contradictory. In early work, Gilman reported that only 2-bromo-6-lithio-pyridine was generated from 2,6-dibromopyridine even with an excess of *n*-BuLi in diethyl ether.[5] On the other hand, Newkome later observed that 2,6-dilithiopyridine was generated when 2,6-dibromopyridine was reacted with 2 equivalents of *n*-BuLi in THF.[6] We have re-examined the reaction of 2,6-dibromopyridine with *n*-BuLi and have found the reaction to be more complex than originally anticipated, as we disclose herein. We also describe an improved way to generate the 2-bromo-6-lithiopyridine species.

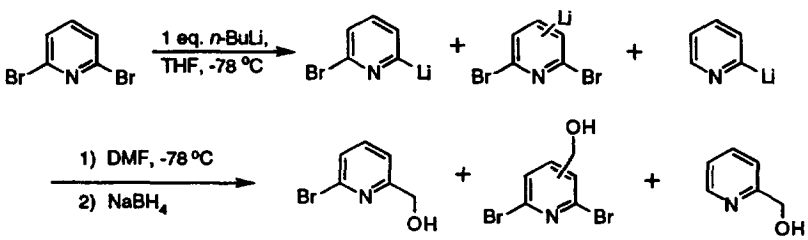
We first repeated both Gilman's and Newkome's experiments and found that Gilman's experiments could not be reproduced due to the thermal instability of the resulting 2-bromo-6-lithiopyridine species. We

found that 2-bromo-6-lithiopyridine starts to decompose at -20 °C, and the two experiments of Gilman's at -16 °C and 35 °C would therefore likely result in decomposition of either 2-bromo-6-lithiopyridine or 2,6-dilithiopyridine. In fact, in our hands, lithiation of 2,6-dibromopyridine with 2 equivalents of *n*-BuLi in ether at -40 °C resulted in formation of 56 mol % 2,6-dilithiopyridine, as evidenced by quenching with methanol, while in THF solvent, 63 mol % 2,6-dilithiopyridine was formed. While both solvents are about the same regarding the formation of di-lithiopyridine, the starting material, 2,6-dibromopyridine, is much more soluble in THF than in diethyl ether. Due to the solubility difference and for safety reasons, we decided to use THF instead of diethyl ether for further synthetic work.

We planned to prepare the 2-bromo-6-hydroxymethylpyridine intermediate via 2-bromo-6-lithiopyridine. Based on literature precedent,[7] our first approach was to slowly add 1.0 equivalent of *n*-BuLi into a solution of 2,6-dibromopyridine at -78 °C, then react the resulting mono-lithiated species with DMF, followed by quenching with methanol and subsequent reduction with $NaBH_4$. On a 10 mmol scale the reaction proceeded smoothly to provide a 75% yield of the desired product, 2-bromo-6-hydroxymethylpyridine. Unfortunately, when we conducted the reaction on a 0.5 mol scale, the desired product was obtained in only 21% yield with two major byproducts.

To probe the difference between the small scale and larger scale runs, we first studied just the lithiation step. We followed the same procedure to generate 2-bromo-6-lithiopyridine by addition of *n*-BuLi to a solution of 2,6-dibromopyridine in THF at -78 °C, then quenched with methanol and assayed the resulting mixture by HPLC. It was surprising to find that there was still a significant amount of starting material (~20%) left. Even with 50 mol% excess of *n*-BuLi, there was still about 10% starting material 2,6-dibromopyridine recovered. Interestingly, when the above reaction solution (with 1 equivalent of *n*-BuLi) was reacted with DMF followed by $NaBH_4$, no starting material (2,6-dibromopyridine) was obtained (Scheme 1), instead a mixture of 3- and 4-

Scheme 1

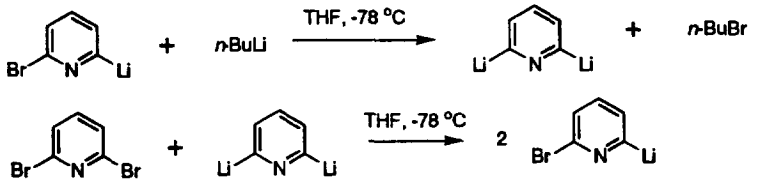



hydroxymethyl-2,6-dibromopyridine was observed, which were the same byproducts observed earlier in the 0.5 mole run. These results indicated that deprotonation of the 3 and 4 positions of 2,6-dibromopyridine occurred instead of lithium-halogen exchange. We found that the deprotonation of 2,6-dibromopyridine by 2-bromo-6-lithiopyridine readily took place even at -78 °C as evidenced by quenching with DMF followed by reduction with $NaBH_4$. The formation of 2-bromopyridine further confirmed that deprotonation was occurring by reaction with 2-bromo-6-lithiopyridine, not by reaction with *n*-BuLi.

How to selectively generate 2-bromo-6-lithiopyridine was thus problematic. When the reaction was run on a small scale, rapid addition of *n*-BuLi with vigorous stirring at -78 °C provided a relatively clean reaction. However, this halogen-lithium exchange is strongly exothermic, and to control the temperature on a larger scale reaction required a long addition time for *n*-BuLi, such that the deprotonation by 2-bromo-6-lithiopyridine

became significant. On the other hand, if reverse addition (addition of 2,6-dibromopyridine into a solution of *n*-BuLi ) was used, then the dilithiopyridine species was generated since the 2,6-dibromopyridine initially added sees a large excess of BuLi. Fortunately, *halogen-lithium exchange between 2,6-dilithiopyridine and 2,6-dibromopyridine in THF at -78 °C gave 2-bromo-6-lithiopyridine cleanly (Scheme 2).* Therefore, using the reverse addition technique, we were able to generate 2-bromo-6-lithiopyridine cleanly, and our desired product, 2-bromo-6-hydroxymethylpyridine, was isolated in 98% yield.[8]

Scheme 2




As reported in the literature,[7] 2,6-dibromopyridine can be monolithiated with *n*-BuLi relatively cleanly in diethyl ether using an improved Gilman's procedure . We believe that the success of this reaction is due to the poor solubility of 2,6-dibromopyridine in diethyl ether at low temperature (-60 °C), which makes it essentially the same as a reverse addition technique. After the addition of *n*-BuLi at -60°C, the reaction solution is warmed to -40 °C and the solid 2,6-dibromo-pyridine starts to dissolve and react with *n*-BuLi and 2,6-dilithiopyridine to generate 2-bromo-6-lithio-pyridine.

In our study, we did not observe any products derived from nucleophilic addition to the pyridine ring by either *n*-BuLi or resulting lithiopyridine species, indicating that the addition reaction is slower than deprotonation or halogen-lithium exchange in THF. In addition, no reaction of the lithiopyridine with *n*-BuBr was observed.

The reaction of 2-bromo-6-lithio-pyridine was extended to several other electrophiles, as shown in Table 1. The reaction with cyclopentanone generated the tertiary alcohol **2** in 78% yield, but reaction with the enolizable ketone β-tetralone provided only a 23% yield. Use of cerium chloride to moderate the basicity of the lithiopyridine anion resulted in a much improved reaction with a 78% yield.

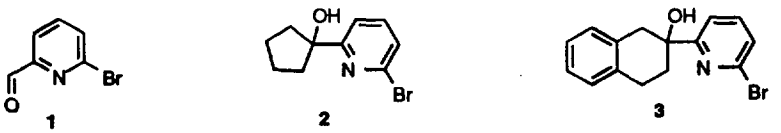


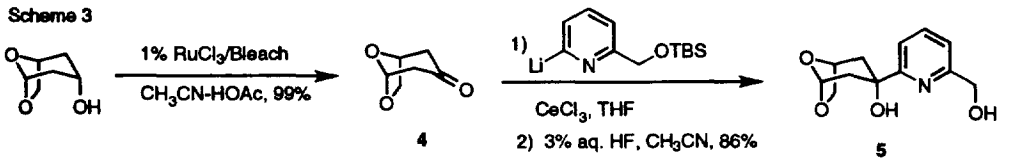

Table 1: 2-bromo-6-lithio-pyridine reactions with different electrophiles

| Entry | Reagents | Electrophiles | Product | Yield |
|---|---|---|---|---|
| 1 | 2-Br-6-Li-py | DMF | 1 | 98% |
| 2 | 2-Br-6-Li-py | $CH_3CN$ | NA | 0% |
| 3 | 2-Br-6-Li-py | Cyclopentanone | 2 | 78% |
| 4 | 2-Br-6-Li-py | β-Tetralone | 3 | 23% |
| 5 | 2-Br-6-Li-py/$CeCl_3$ | β-Tetralone | 3 | 78% |

With our understanding of lithium pyridine chemistry, we were quickly able to synthesize the left-hand fragment of L-739,010 (Scheme 3). The first step was the oxidation of 2,4-dideoxy-1,6-anhydro-D-glucose to

the bicyclic ketone **4**. Although there are many methods available for oxidation of alcohols to ketones, very few methods are acceptable for large scale process. The best method for this oxidation was to use commercial bleach with 1 mol% of $RuCl_3$ catalyst in a solution of acetonitrile and acetic acid. Acetic acid was necessary to prevent the decomposition of the ketone by the strongly basic nature of bleach. Other commonly used oxidants, such as $RuCl_3/NaIO_4$, gave poor yields, presumable due to further oxidation by $NaIO_4$. Coupling reaction of the resulting ketone **4** and the lithiopyridine species was accomplished via organocerium chemistry. Without cerium

Scheme 3

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trichloride, the coupling reaction of this readily enolizable ketone **4** only gave 24% of the desired product. Deprotection of the TBS group was carried out in 3% aqueous HF in acetonitrile, and the desired product **5** was isolated by crystallization in MTBE.

In summary, we have found a better way to generate 2-bromo-6-lithiopyridine using a reverse addition technique, and our target intermediate 2-bromo-6-hydroxymethylpyridine could be easily prepared in one vessel with 98% yield. Furthermore, lithiopyridinyl-cerium chloride reagents are strongly preferred for coupling with readily enolizable ketones.

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(8) To a solution of *n*-BuLi (50 mmol, 31.25 mL, 1.6 M in hexane) in THF (30 mL) at -75 °C was dropwise added a solution of 2,6-dibromopyridine (11.85 g, 50 mmol) in THF (70 mL), keeping the internal solution temperature below -70 °C during the addition. After the addition of 2,6-dibromopyridine, the resulting dark green solution was stirred for additional 15 min, then neat DMF (6.0 mL, 77.5 mmol) was added over a period of 30 seconds. The reaction solution was stirred at -75 °C for 15 min, then methanol (50 mL) and acetic acid (3.2 mL) were added, followed by $NaBH_4$ (1.9 g, 50 mmol ). The cooling bath was removed and the reaction solution was naturally warmed up to room temperature. The reaction solution was carefully quenched with saturated $NH_4Cl$ (150 mL), then extracted with ethyl acetate twice (200 mL, 100 mL respectively). The combined organic layer was washed with brine (100 mL), dried over $Na_2SO_4$, and concentrated to obtain the desired product, 2-bromo-6-hydroxymethyl-pyridine, as a pale yellow oil (9.25g, 98%), which has 98 wt% purity as assayed by HPLC

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