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Aminoborohydrides 15. The First Mild and Efficient Method for Generating 2-(Dialkylamino)-pyridines from 2-Fluoropyridine

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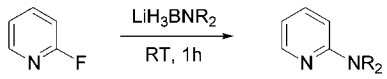
ABSTRACT



75 - 99% Yield

Lithium aminoborohydride (LAB) reagents promote the amination of 2-fluoropyridine under mild reaction conditions, providing 2-(dialkylamino)-pyridines in excellent yield and purity. Treatment of 2-fluoropyridine with 1.1 equiv of lithium aminoborohydride at room temperature affords complete conversion after 1 h. This is the first general way by which 2-(dialkylamino)pyridines may be directly obtained from fluoropyridines under ambient reaction conditions. 2-Chloropyridine can also be converted to 2-(dialkylamino)pyridine by simply increasing the number of LAB equivalents and the reaction temperature.

Aminopyridines are valuable synthetic targets with a variety of applications. They are commonly used as ligands in inorganic and organometallic chemistry[1] and as fluorescent dyes.[2] The aminopyridine moiety is present in pharmaceuticals used to help relieve the effects of multiple sclerosis,[3] botulism,[4] Alzheimer's disease,[5] spinal cord injuries,[6] malaria, and depression.[7] Aminopyridines have previously been prepared by nucleophilic aromatic substitution (S_NAr) of halopyridine substrates with free amines under high pressure[8] and/or high temperatures.[9] Phosphoramides have also been used in the amination of chloropyridines, but this method requires long reaction times, high temperatures, and the handling of toxic material.[10] Recently, Buchwald et al. have demonstrated transition metal-catalyzed cross coupling of halopyridines with amines as an efficient route to aminopyridines.[11] In this reaction, 2-, 3-, or 4-amino-substituted pyridines are obtained from the corresponding bromo- or chloropyridines treated with a palladium catalyst, ligand, and free amine. Acyclic dialkylamines such as di-*N*-butylamine, however, do not react in this system. Also, fluoropyridines are unreactive substrates in this reaction due to the strong fluorine−carbon bond, which does not allow oxidative insertion of the palladium catalyst.

We report herein the first general way by which 2-(dialkylamino)pyridines may be directly obtained from 2-fluo-

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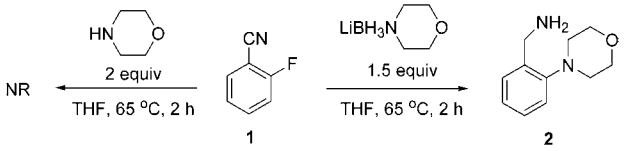
ropyridine, presumably through an S_NAr reaction mechanism. Lithium aminoborohydrides (LABs) are used as the amination reagents. This reaction is generally applicable to the introduction of a variety of secondary amines and complementary to existing synthetic methods. The activation of carbon−fluorine bonds is of importance since this reaction contributes to the fundamental understanding of the reactivity of such very stable bonds.[12]

LAB reagents are a new class of powerful yet selective reducing agents that reproduce, in air, virtually all of the transformations for which lithium aluminum hydride is used. LAB reagents are nonpyrophoric and are readily prepared from any primary or secondary amine, thus allowing precise electronic and steric control of their reactivity by substituents on the nitrogen atom. It was recently found that in some circumstances, LABs preferentially transfer their amine functionality over a hydride. During a screening of the reducing capabilities of LAB reagents, a unique tandem amination−reduction reaction between LABs and 2-halobenzonitriles was discovered.[13] During this reaction, reduction of the nitrile is accompanied by amination at the carbon bearing the halogen, and 2-aminobenzylamines (**2**) are obtained (Scheme 1). The amination capabilities of LAB

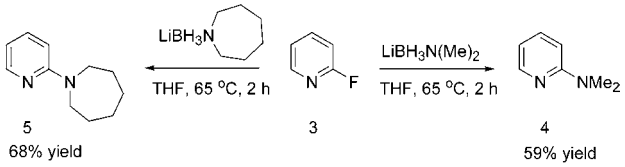
Scheme 1. LAB-Promoted Tandem Amination−Reduction



reagents have now been extended to effect the transformation of 2-fluoropyridine to 2-(dialkylamino)pyridines.

The direct amination of 2-fluoropyridine via LAB was first attempted to determine if an amination reaction analogous to that of 2-fluorobenzonitrile (**1**) was indeed possible. The same reaction conditions that had been optimized for the amination of 2-fluorobenzonitrile were employed, and 2-fluoropyridine (**3**) was treated with 1.5 equiv of lithium dimethylaminoborohydride at 65 °C for 2 h. Upon addition of 2-fluoropyridine to the LAB reagent, the colorless solution turned deep red in color. Meisenheimer complexes, the anionic intermediates formed during an S_NAr reaction, are known to form highly colored solutions. In fact, a similar, deep red color change in the S_NAr reactions of LABs with 2-halobenzonitriles had been observed. Gratifyingly, 2-(dimethylamino)pyridine (**4**) was isolated in 59% yield under these reaction conditions (Scheme 2). The same reaction was attempted with a cyclic LAB reagent to see if similar results would be obtained. When lithium homopiperidinoborohydride was used as the LAB reagent in this reaction, comparable results were observed and 2-(hexamethyleneimino)-pyridine (**5**) was isolated in 68% yield (Scheme 2).

Scheme 2. LAB-Promoted S_NAr of 2-Fluoropyridine



The progress of these reactions was monitored by TLC, which indicated complete consumption of starting material after a 2 h period. Still, the isolated product yields were only moderate. To account for the loss in yield, the reaction with lithium dimethylaminoborohydride was repeated and examined for side-product formation. It was discovered that 33% of the desired product was lost in the form of the 2-(dimethylamino)pyridine−borane complex (**6** and **7**), which remained in the neutral layer during workup. The workup procedure was thus modified accordingly. Heating the reaction mixture in acidic methanol liberates the product from the borane complex, and 2-(dimethylamino)pyridine was isolated in 85% yield after workup.

After these initial findings, attempts were made to optimize the reaction conditions further. It was discovered that elevated reaction temperatures were unnecessary and only 1.1 equiv of LAB reagent were required for the desired transformation. When 2-fluoropyridine was reacted at room temperature with 1.1 equiv of LAB reagent for 1 h, 2-(hexamethyleneimino)-pyridine was isolated in 97% yield after employing the modified workup procedure.

Table 1 lists the products obtained from reaction of various LAB reagents with 2-fluoropyridine. The optically active LAB reagent prepared from (*S*)-(+)-2-methylpiperidine (entry 9) gave the lowest yield (60%), presumably as a result of increased sterics.

It is important to note that when 2-fluoropyridine is treated with a free amine such as homopiperidine at reflux temperature, the substrate remains intact even after extended reflux. Other amines, specifically lithium amides such as LDA, do not promote amination of 2-halopyridines. Rather, these reagents result in *ortho* lithiation.[14] Clearly, the LAB reagent is essential for promoting the amination of 2-fluoropyridine.

To gain insight into the kinds of boron species that are formed during this reaction, an aliquot of the reaction mixture was analyzed by ^{11}B NMR. Among the observed signals were found two aminopyridine-borane monomers at δ −16.23 (q) and δ −12.89 (q), attributed to the pyridinoborane (**6**) and aminoborane complexes (**7**) of 2-(amino)pyridine, respectively (Figure 1). The dominant ^{11}B NMR signal is a sharp peak at δ 3 (t, J = 113 Hz). This signal may indicate that the majority of the aminopyridine product exists as an aminopyridine−borane dimer (**8**) in solution before workup.[15] Acyclic aminopyridine dimer complexes with borane are

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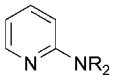
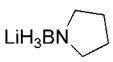
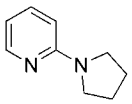
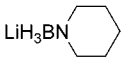
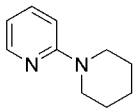
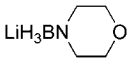
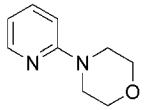
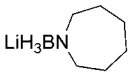
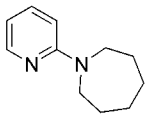
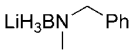
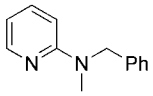
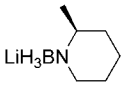
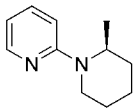
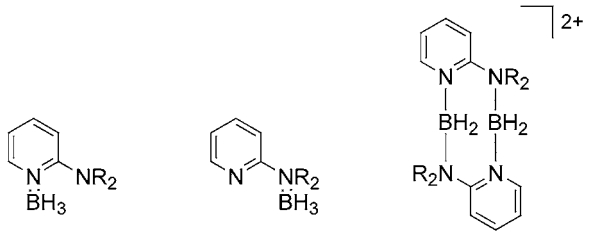
(15) BH_2 compound shown in Figure 1 may be cyclic or acyclic. The exact identity of this species is not forthcoming at this moment and is under further investigation.

Table 1. Products Obtained Using Various LAB Reagents

entry	LAB	product	yield[a]
1 2 3	LiH_3BNR_2		85 (R=Me) 76 (R=Et) 75 (R=Pr)
4			81
5			99
6			83
7			97
8			95
9			60

[a] Yields refer to crude isolated product. All products are >90% pure by ^{1}H NMR.



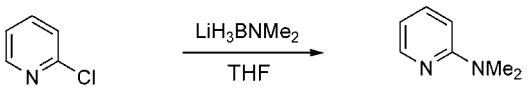
6 **7** **8**

Figure 1. Aminopyridine−borane monomers and putative dimer observed by ^{11}B NMR during reaction.

known and reported to have chemical shifts and *J*-values similar to our observed signal.[16]

In an attempt to extend this method to other substrates, 2-chloropyridine was reacted with lithium dimethylaminoborohydride under the same reaction conditions optimized for 2-fluoropyridine. The reaction was investigated by GC analysis using mesitylene as an internal standard, and yields were calculated using the internal standard and correcting for detector response. When 2-chloropyridine was treated with 1.1 equiv of lithium dimethylaminoborohydride at room temperature for 1 h, a significant amount of starting material remained. Continued stirring at room temperature for 21 h resulted in only 38% GC yield of 2-(dimethylamino)pyridine. Performing the reaction at reflux temperature in THF, a 52% yield of 2-(dimethylamino)pyridine was observed. Optimal yields were obtained after 1 h at reflux when 2.5 equiv of LAB reagent were used. These results are summarized in Table 2.

Table 2. Reaction Condition Optimization for 2-Chloropyridine



LAB equiv	temp	time	yield[a]
1.1	rt	21 h	38
1.1	65 °C	23 h	52
1.5	65 °C	3 h	63
2.5	65 °C	1 h	87

[a] Yields determined by GC using an internal standard.

Surprisingly, 2-bromopyridine was also found to undergo LAB-promoted S_NAr under these conditions. The yields, however, were lower, and 2-bromopyridine was sluggish to react. For these reasons, and because the palladium-catalyzed amination reactions are superior for the 2-bromopyridine substrate, further optimization of this reaction was not pursued.

The observed reactivity of 2-fluoropyridine, 2-chloropyridine, and 2-bromopyridine in these reactions suggest a S_NAr mechanism, as fluoride possesses the best leaving group ability, followed by chloride and bromide. Moreover, since no *cine* substitution occurs in these reactions, the involvement of a benzyne intermediate is ruled out. The amination reaction was attempted with 2-fluoropyridine-borane as the substrate to see if borane alone could promote amination with a free amine. However, even after extended reflux with pyrrolidine, the 2-fluoropyridine-borane starting material remained unchanged. In addition, lithium amides are known to promote ortho metalation, and not amination. It therefore seems reasonable to conclude that both the boron and the lithium components of the LAB reagent are needed for amination to occur.

In summary, LAB reagents containing both acyclic dialkylamines and cyclic amines have been shown to promote the amination of 2-fluoropyridine under exceedingly mild reaction conditions, providing a variety of 2-aminopyridines in excellent yield. This constitutes the only method for which 2-fluoropyridines can be converted into 2-aminopyridines under ambient conditions. The significance of this amination method lies in the way in which it complements the current synthetic methods used to produce this important class of

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compounds. Other haloheteroaromatics are currently being investigated as substrates for LAB-induced aminations.

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Supporting Information Available: General experimental details and synthetic procedures for LAB reagents, GC scale reactions of 2-chloropyridine (Table 2), and all products listed in Table 1, as well as ^{1}H NMR and ^{13}C NMR spectra and HRMS for all products listed in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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