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Double nucleophilic addition. A new one-pot synthesis of 2-alkyl- and 2-phenyl-5-hydrazinopyridine from pyridine

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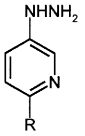
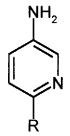
Abstract

A new method for the synthesis of 2-alkyl- and 2-phenyl-5-hydrazinopyridine has been developed. Nucleophilic addition on pyridine by alkyl or phenyl lithium reagents generated a 2-substituted dihydropyridine anion that reacts with di-*t*-butyl azodicarboxylate to form 2,5-disubstituted dihydropyridine. Conversion of the dihydropyridines to pyridines was achieved by a mild air oxidation.

The synthesis of polysubstituted pyridines has been an active research area for many years.[1] Substituted pyridines have found a number of applications, such as in biological studies,[2] anticorrosion agents,[3] insecticides,[4] mechanistic investigations,[5] and as potential drug substances.[6] The synthesis of 2-alkyl or 2-aryl-5-hydrazinopyridine (**1**) possess particular challenges, and has never been executed directly from pyridine. The reported methods involve several steps and expensive intermediates such as 2-alkyl-5-bromo or 2-alkyl-5-aminopyridine (2).[6] Recently, a synthesis of hydrazinopyridine from *para*-nitro bromopyridine by Pd catalysis has been reported, and the conditions for deprotection have also been studied.[7] We report a useful method for synthesizing 2-alkyl or 2-aryl-5-hydrazinopyridines from pyridine in one-pot.



1, R = Alkyl or aryl



2, R = Alkyl or aryl

It has been reported that nuleophilic addition of organolithium reagents toward pyridine takes place at the 2-position.[8] The reactions of this *N*-lithio-1,2-dihydropyridines with suitable electrophiles in arylalkylation,[9] alkylation,[10] hydroxyalkylation,[9,11] aminoalkylation,[9] acylation[12,13] and thiolation[14] have been reported. We envisioned that 2-alkyl or aryl-5-hydrazinopyridine could be generated by this approach if di-*t*-butyl azodicarboxylate (DBAD) were used as an electrophile, as depicted in Scheme 1.

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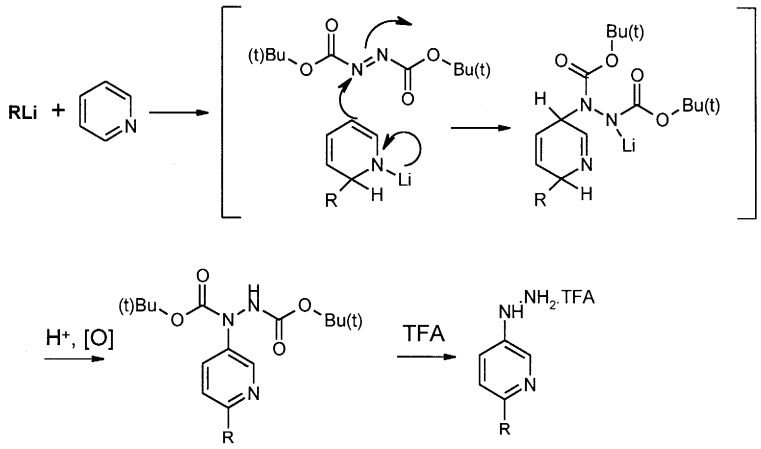


Scheme 1. Double nucleophilic addition

The results of double nucleophilic addition were illustrated in Table 1. However, the initial experiment of preparing substituted pyridohydrazine by this approach was not successful. When alkyl lithium reacts with pyridine for prolonged time, the major product was 2-alkylated pyridine **4** (Scheme 2). Formation of **4** could be caused by losing LiH or disproportionation of intermediate **3**.[15] To minimize the generation of side product **4**, it is important to add DBAD into the reaction mixture when the concentration of 2-substituted dihydropyridine **3** reaches maximum before it converts to **4**. Therefore, it is crucial to develop an analytical method to follow the progress of first nucleophilic addition.

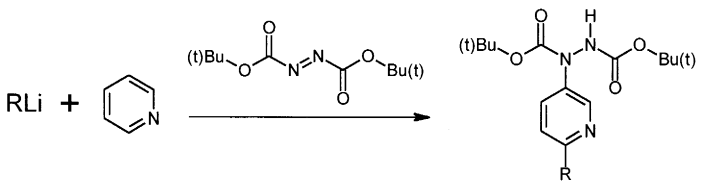
Since the lithium reagent and the active intermediate **3** formed in this reaction is highly sensitive to air and moisture, it is difficult to follow the progress of nucleophilic addition. Initial attempts of using HPLC or TLC methods failed to give any useful information. Finally, satisfactory results were obtained by using ^{1}H NMR techniques. During the reaction, a small portion of mixture was quenched by deuterated methanol. The proton signal of pyridine at 8.6 ppm, the signal of 2-substituted pyridine at 8.5 ppm, and the dihydropyridine **3** at about 5.0 ppm were integrated and analyzed. When the concentration of intermediate **3** reached maximum (its proton signal did not further increase by NMR analysis), DBAD was added to execute the second nucleophilic addition.

The first nucleophilic addition, organolithium with pyridine, took place between −10°C and 20°C. There was no reaction when the temperature was too low. At high temperature, the majority of the product was 2-substituted pyridine. The second nucleophilic addition, dihydropyridine to DBAD, was carried out initially at −70°C and then warmed to room temperature. This step was exothermic and fast, the reaction temperature was controlled by slow addition of DBAD to dihydropyridine solution.

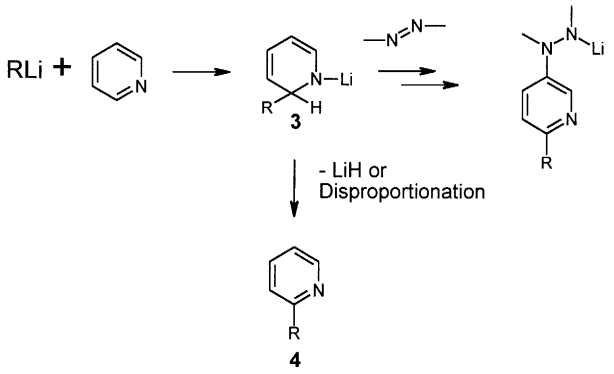
The stoichiometry of the reaction typically was one-to-one ratio of organolithium reagent to pyridine. The use of more pyridine did not enhance the yield of dihydropyridine. DBAD was used as 1.2 equiv. to organolithium reagent. Adding more DBAD did not increase the yield of products. Other azodicarboxylate reagents were also tried, such as diethyl azodicarboxylate (DEAD) and di-2,2,2-trichloroethyl azodicarboxylate. The reactions worked but the yields were not as good as in the case of DBAD. In addition, DBAD provides more readily cleavable bis-carbamate. Finally, the 2,5-substituted dihydropyridines converted into their aromatic products by stirring at room temperature in air. Removing the *t*-Boc protecting group has been executed under very mild conditions (TFA, room temperature). Some examples of this double addition are illustrated in Table 1.

In summary, a new synthesis of 2-alkyl- and 2-phenyl-5-hydrazinopyridine has been developed. The unique feature of this synthesis is to execute three chemical reactions, double nucleophilic addition and

Table 1
Results of double nucleophilic addition



Entry	RLi	Time (h)	Product	Yield (%)
1	Me–Li	6	R = CH_3	28
2	Li	4	R = *n*-Butyl	71
3	Li	6	R = *s*-Butyl	73
4	Li	8	R = *t*-Butyl	43
5	Li	6	R = *n*-Hexyl	46
6	Li	8	R = Phenyl	52



Scheme 2. Product distribution from dihydropyridine **3**

aromatizing in one-pot, which provides a very attractive route to prepare 2,5-disubstituted hydrazinopyridines.

General procedure. Pyridine (12 mmol) was added to a solution of organolithium reagent (12 mmol) at −20°C under an atmosphere of argon. The resulting mixture was stirred and allowed to warm to room temperature. The agitation was kept at room temperature for 4~8 h. Anhydrous THF (10 ml) was added and the resulting solution was cooled to −78°C. The solution of *t*-butyl azodicarboxylate (14 mmol) in anhydrous THF (15 ml) was added with syringe pump in 1.5 h. The mixture was allowed to

warm to room temperature and stirred for 2 h, followed by an additional 1 h under air (for oxidation). Saturated ammonium chloride aqueous solution (10 ml) was added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3×10 ml). The combined organic layer was dried with magnesium sulfate. The solvent was removed under reduced pressure and the crude product was purified by silica gel flash chromatography (hexane/EtOAc).

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