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Revisiting the Chichibabin reaction: C2-amination of pyridines with a NaH-iodide composite

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Abstract: The NaH-iodide composite was found capable of mediating the Chichibabin amination under milder reaction conditions, allowing for an efficient access to a range of 2-aminopyridines and their derivatives.

In 1914, Chichibabin reported synthesis of 2-aminopyridines by treatment of pyridine with sodium amide (Scheme 1A).^[1] This reaction is now known as the Chichibabin reaction (amination), capable of installing a primary amino group (-NH₂) at the C2 position of pyridines and their derivatives. On the other hand, only a few successful examples have been reported for the Chichibabin amination with primary alkyl amines^[2-4] probably due to inaccessibility of the corresponding alkyl metal amides.^[5] We have recently discovered that sodium hydride (NaH) can be performed as an enhanced Brønsted base in the presence of NaI or LiI, enabling nucleophilic amination of methoxyarenes.^[6] During the course of the study on nucleophilic amination of 3-methoxypyridine (**1**) with *n*-butylamine (**2**), we observed that the reaction provided not only 3-butylaminopyridine (**3**) in 61% yield but also 2-butylamino-3-methoxypyridine (**4**) in 7% yield via the Chichibabin amination (Scheme 1B).^{6a} The formation of C2-aminated pyridine **4** stimulated us to further investigate the possibility to develop a new protocol of the Chichibabin amination by the NaH-iodide composite, that could be implemented with a range of primary alkylamines under milder reaction conditions.

A. Chichibabin amination

B. Nucleophilic amination of 3-methoxypyridines

Scheme 1. Chichibabin amination reactions.

We commenced our study to optimize the reaction settings using pyridine (**5**) with 2 equiv of *n*-butylamine (**2**) (Table 1). We found that the reaction with NaH (3 equiv) and LiI (2 equiv) at 65 °C is

completed within 18 h to provide *N*-butylpyridin-2-amine (**6**) in 95% yield (entry 1). It should be noted that the reaction is not facilitated well solely by NaH (entry 2), emphasizing the importance of the dissolving iodide additive to enhance the Brønsted basicity of NaH. We found that higher temperature of 85 °C under sealed conditions could accelerate the conversion to form **6** in 93% yield within 7 h (entry 3), whereas use of NaI instead of LiI rendered the process sluggish (entry 4). It should be noted that LiH showed poorer reactivity for the present process (entry 5).

Table 1. Optimization of the reaction conditions^[a]

entry	additive	Temp [°C]	Time [h]	Yields [%] ^[b]
1	LiI	65	18	95
2	none	65	18	21
3	LiI	85 ^[c]	7	93
4	NaI	85 ^[c]	24	75
5 ^[d]	LiI	85 ^[c]	24	7 ^[e]

[a] The reactions were carried out using 0.5 mmol of pyridine (**5**) with *n*-butylamine (**2**) (2 equiv) in the presence of 3 equiv of NaH and 2 equiv of additive in THF (0.5 mL). [b] Isolated yields. [c] The reactions were conducted in the sealed conditions. [d] LiH (3 equiv) was used instead of NaH. [e] ¹H NMR yield.

With the optimized reaction conditions with the NaH-LiI system (Table 1, entry 3), we investigated the substrate scope for the Chichibabin amination (Scheme 2). As for substituent R¹ on primary amines (Scheme 2A), several primary alkyl groups having phenyl (for **7** and **8**), methoxy (for **9**), and dimethylamino (for **11**) groups could be introduced onto pyridine (**5**) smoothly in good yields. Optically active (-)-*cis*-myrtanylamine could also be used to afford **12**. Installation of amines having secondary alkyl groups such as cyclopentylamine (for **14**) and *exo*-2-aminonorbomane (for **15**) needs longer reaction time probably due to the steric hindrance. It is worthy to note that the reaction with optically active (*R*)-cyclohexylethylamine (94.5% ee) provided the corresponding 2-aminopyridine **16** in 60% yield without loss of the enantiomeric excess (93% ee) at α to the

nitrogen. Next, the effect of substituent R^2 on the pyridine ring was examined using *n*-butylamine (**2**) as a nucleophile (Scheme 2B). The process allowed for the use of 2-, 3-, and 4-phenylpyridines without any detrimental effect (for **17–19**). It should be noted that the amination of 3-phenylpyridine occurs regioselectively at less sterically hindered C6 site (marked in red) over C2 (marked in green).^[7] The reactions of 4-*t*-butylpyridine (for **20**) as well as quinoline (for **21**) worked well.

A. Scope of amines with pyridine (**5**)

B. Scope of pyridines and their derivatives with butylamine (**2**)

Scheme 2. Substrate scope. [a] Unless otherwise noted, the reactions were conducted using 0.5 mmol of pyridines and 1 mmol amines in the presence of 3 equiv of NaH and 2 equiv of Lil in THF (0.5 mL: 1 M) at 85 °C under sealed conditions. [b] Isolated yields based on pyridines were recorded above. [c] The reactions were conducted using 5 equiv of NaH and 2 equiv of Lil. [d] The isolated yields from the reaction with 3 equiv of pyridine (**5**) to the amines. [e] The reaction was carried out using 3 equiv of (*R*)-(-)-cyclohexylethylamine (94.5% ee) with 4 equiv of NaH and 3 equiv of Lil.

To validate versatility of the present method, we next performed double amination. The reaction of 1,3-propanediamine with 2.1 equiv of pyridine (**5**) afforded bispyridine adduct **22** in 79% yield (Scheme 3).

Scheme 3. Double amination of 1,3-propanediamine.

This protocol was found capable in double amination of commercially available 2,2'-bipyridines for the straightforward access to 6,6'-diamino-2,2'-bipyridines, the conventional synthesis of which requires multiple steps including C2-halogenation.^[8] Direct and concise incorporation of *n*-butylamine (for **23** and **24**), 3-methoxypropylamine (for **25**) and (-)-*cis*-myrtanylamine (for **26**) onto 2,2'-bipyridines was successfully attained (Scheme 4A). The method was proven scalable in 20 mmol scale maintaining good process efficiency (Scheme 4B).^[9] The resulting products should be of potential use for a ligand of transition metal catalysis.^[10]

A. Double amination of 2,2'-bipyridines

B. Double amination in 20 mmol scale

Scheme 4. Double amination of 2,2'-bipyridines. [a] Unless otherwise noted, the reactions were conducted using 1 mmol of 2,2'-bipyridines and 6 equiv of amines in the presence of 7 equiv of NaH and 4 equiv of Lil in THF (1 mL: 1 M) at 85 °C under sealed conditions. [b] Isolated yields based on 2,2'-bipyridines were recorded above. [c] The reactions were conducted using 0.5 mmol of 2,2'-bipyridines and 8 equiv of amine with 10 equiv of NaH and 7 equiv of Lil. [d] The reaction was conducted using 20 mmol of 2,2'-bipyridine and 6 equiv of *n*-butylamine in the presence of 7 equiv of NaH and 4 equiv of Lil in THF (25 mL: 0.8 M) under reflux conditions.

Double amination of 4,4'- and 2,4'-bipyridines was also demonstrated using *n*-butylamine (**2**), resulting in successful formation of **27** and **28**, respectively, in good yields (Scheme 5A and B). In amination of 2,4'-bipyridine, a small amount of 5,2'-

diaminated bipyridine **28'** was formed as a minor product (Scheme 5B).

A. Double amination of 4,4'-bipyridine

B. Double amination of 2,4'-bipyridine

Scheme 5. Double amination of 4,4'- and 2,4'-bipyridines.

This work demonstrated convenient use of the NaH-LiI composite to offer a user-friendly protocol of the Chichibabin amination for synthesis of 2-aminopyridine derivatives in an efficient way. Application of the newly synthesized C2-aminopyridine derivatives in catalysis is currently under investigation in our laboratory.

Experimental Section

A typical procedure: To a 10 mL sealed tube containing pyridine (**5**) (38.9 mg, 0.492 mmol), NaH (61.7 mg, 1.54 mmol), and LiI (136 mg, 1.02 mmol) in THF (500 μ L) was added *n*-butylamine (**2**) (98.8 μ L, 1.00 mmol) at room temperature under a N₂ atmosphere. The tube was sealed and the reaction mixture was stirred at 85 $^\circ$ C (bath temperature) for 7 h. The reaction mixture was quenched with ice-cold water at 0 $^\circ$ C and the organic materials were extracted thrice with CH₂Cl₂. The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (hexane : EtOAc = 4:1) to yield *N*-butylpyridin-2-amine (**6**) (68.5 mg, 0.456 mmol) in 93% yield as a pale yellow oil.

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Keywords: Chichibabin amination • pyridines • sodium hydride • lithium iodide • C-H functionalization

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