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A highly efficient synthesis of 2-[3-aminopropyl]-5,6,7,8-tetrahydronaphthyridine via a double Suzuki reaction and a Chichibabin cyclization

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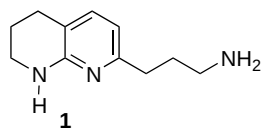
Abstract—Synthesis of 2-[3-aminopropyl]-5,6,7,8-tetrahydronaphthyridine was accomplished via a one-pot double Suzuki reaction followed by deprotection and a highly regioselective intramolecular Chichibabin cyclization. A variety of reactions conditions were screened for the Chichibabin cyclization including choice of base, solvent and reaction temperature. © 2001 Published by Elsevier Science Ltd.

Small and structurally interesting compounds that have a readily reactive functional group are new targets of synthetic organic chemistry due to the importance of these compounds in the combinatorial approach to drug discovery. One such compound, which is a key component of an investigational new drug at Merck, is 2-[3-aminopropyl]-5,6,7,8-tetrahydronaphthyridine, **1**. Accordingly, we required a rapid and efficient synthesis of **1** from readily available starting materials in order to furnish necessary quantities of our investigational drug for clinical studies.



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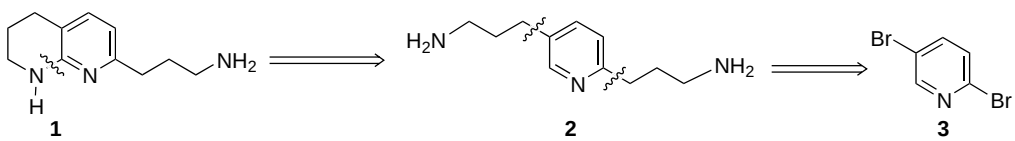
The synthesis of naphthyridine derivatives has traditionally been accomplished via a Skraup reaction or a Friedländer reaction as the key carbon–carbon bond forming reaction.[1] Unfortunately, a synthetic route of **1** comprised of either reaction as a key step would not be directly amenable to large scale development. The Skraup reaction requires harsh conditions (high reaction temperature and typically large excess of concentrated H_2SO_4), while often providing varying yields that are structurally dependent. A route based on the Friedländer reaction would most likely involve a lengthy synthetic sequence, as well as, raising regioselectivity concerns in the key Friedländer step.[2] Because of the described issues, we focused our efforts on a different, somewhat unconventional approach for the rapid and efficient synthesis of **1**.

Our retrosynthetic analysis for **1** is shown in Scheme 1. Disconnection at the C–N bond between the pyridine carbon and the secondary amine nitrogen affords the symmetrical 2,5-(3-propylyamine)pyridine **2**, which in turn is derived from the commercially available 2,5-dibromopyridine **3** via a double Pd-catalyzed coupling reaction with a common coupling partner. The success of this route relies on two key reactions with little precedent: the Chichibabin cyclization and the double Suzuki–Miyaura reaction on the dibromopyridine.



1 **2** **3**

Scheme 1.

Keywords: cyclization; amination; Suzuki–Miyaura reactions; naphthyridines.

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The Chichibabin reaction is an efficient, well documented method for the synthesis of aminopyridine derivatives.[3,4] A review of the literature reveals that most research efforts, both synthetic and mechanistic, have focused on intermolecular amination of pyridine derivatives with $NaNH_2$ or KNH_2.[6a] This may be due, in part, to the observation that increasing substitution of the nucleophilic amine typically affords a decrease in the desired product yield (NH_3>1°>aniline, 2° ≫ 3°). By comparison, reports describing the study and development of Chichibabin aminations involving alkylamines or intramolecular Chichibabin aminations are few in number, despite its potential in producing nitrogen heterocycles directly.[5,6] Nonetheless, we felt the Chichibabin cyclization of compound **2** should be feasible since it would rely on the higher reactivity of the pyridine carbon at the 6-position relative to the other carbons towards nitrogen substitution to achieve high regioselectivity, and on the favorable entropic factor to ensure an intramolecular amination.

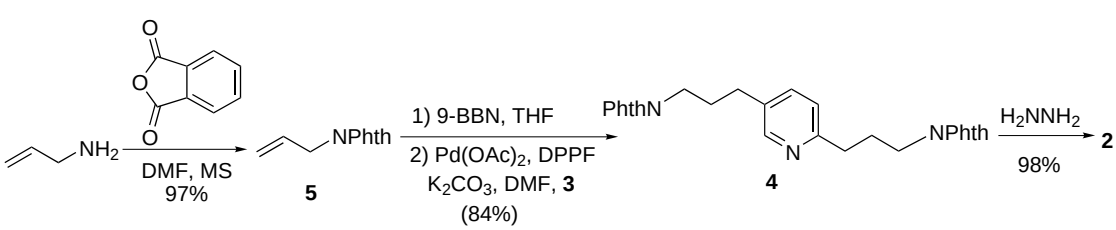
Our approach for the preparation of **2** via Pd-catalyzed cross coupling of **3** with a common partner involved investigation of three different strategies: (1) double Heck reaction with acrylonitrile followed by hydrogenation, (2) double Sonogashiro reaction with propargyl amine followed hydrogenation and (3) double Suzuki–Miyaura reaction via an in situ hydroboration of an allyl amine derivative followed by deprotection. Attempts at a double Heck reaction with acrylonitrile resulted in only low-moderate yields of the mono-Heck product (substitution at the 2-position) despite screening a variety of solvents/Pd-source/ligands. Similarly, attempts at a double Sonogashiro reaction yielded at best a 4:1 ratio of mono-Sonogashiro product (substitution at the 2-position) to starting material. By contrast, the first attempt at a double Suzuki–Miyaura reaction via 9-BBN hydroboration of a phthalimide-protected allyl amine followed by coupling resulted in a 77% yield of the desired product.[7]

As illustrated in Scheme 2, synthesis of substrate **2** was accomplished in three steps and in 80% overall yield. Reaction of allylamine with phthalic anhydride in DMF in the presence of molecular sieves afforded the crystalline phthalimide-protected allylamine **4** in 97% isolated yield. Hydroboration of **4** using 1.2 equiv. 9-BBN (0.5 M THF) resulted in complete conversion to the desired alkyl borane. This mixture was charged with 0.45 equivalents of 2,5-dibromopyridine, 2.0 equivalents K_2CO_3, and a 70°C solution of 0.045 equivalents $Pd(OAc)_2$ and 0.054 equivalents of 1,1′-bis-(diphenylphosphino)ferrocene (DPPF) in DMF. The resulting mixture was heated at 70°C for 6–10 h to provide the double Suzuki–Miyaura cross coupling product **5** in 84% isolated yield. Faster reaction rates and higher yields of the desired product were obtained when the active Pd-catalyst was generated separately via heating a solution of $Pd(OAc)_2$ and DPPF in DMF for 30 minutes compared to adding $Pd(OAc)_2$, DPPF and DMF directly to the reaction mixture. Removal of both phthalimide protecting groups in one-pot was accomplished using aqueous hydrazine in refluxing EtOH to afford **2** in 98% isolated yield.

Issues of concern in the Chichibabin cyclization of substrate **2** to the desired product **1** include regioselectivity and intramolecular versus intermolecular reactivity. A survey of the literature reveals that the carbons at the 2- and 6-position of the pyridine ring are considerably more susceptible to amination under Chichibabin conditions than the carbon at the 4-position, which in turn is significantly more reactive than the carbons at the 3-position.[6] Substrate **2** contains two primary amines with similar pK_as. However, only the primary amine connected at the 5-position of the pyridine ring can aminate at a favorable 4- or 6-position, whereas the primary amine connected at the 2-position of the pyridine ring can only aminate at the unfavorable 3-position of the pyridine ring. Finally, because of the high effective molarity of the appended amine,[8] entropic factors should favor the intramolecular reaction over the intermolecular reaction.

A variety of reaction conditions for the Chichibabin cyclization of **2** to **1** were screened. The optimization studies include choice of base, solvent, and reaction temperature. The results of these studies are shown in Table 1.

Hawes and Davis obtained a 30% isolated yield for the Chichibabin cyclization of 3-(3-pyridyl)propylamine to 1,2,3,4-tetrahydronaphthyridine using the following optimized conditions: refluxing the substrate in toluene in the presence of 2 equivalents of sodium for 72 h.[8] Using these conditions as a starting point, the cyclization of **2** to **1** was examined by heating a toluene solution of **2** in the presence of either sodium or sodium hydride. Moderate yields **1** were obtained (entries 1 and 2), with sodium hydride affording slightly higher yields. Similar to the results obtained by Hawes and Davis, long reactions times were required for complete conversion of the starting material. The use of other metal hydride reagents did not increase product yield (entries



Scheme 2.

Table 1. Results of optimization experiments for the Chichibabin cyclization of **2** to **1**

Entry	Base	Equiv. of base	Temp. (°C)[a]	Solvent	Time (h)	Assay yield (%)[b]
1	Na	3	115	Toluene	72	56
2	NaH	3	115	Toluene	72	70 (62)
3	CaH_2	3	115	Toluene	72	0
4	LiH	3	115	Toluene	72	9
5	*n*-BuLi	2	70	THF	15	66
6	EtMgBr	2	70	THF	15	<1
7	KHMDS	2	115	Toluene	15	20
8	$LiNH_2$	2	115	Toluene	15	83 (70)
9	$NaNH_2$	2	115	Toluene	15	84
10	$NaNH_2$	2	115	DMPU	15	<1
11	$NaNH_2$	2	115	Chlorobenzene	15	5
12	$NaNH_2$	2	115	DIPEA	15	59
13	$NaNH_2$	2	100	Toluene	15	84
14	$NaNH_2$	2	90	Toluene	15	92
15	$NaNH_2$	2	80	Toluene	15	83
16	$NaNH_2$	5	60	Toluene	15	0
17	$NaNH_2$	5	90	Toluene	15	99 (94)[c]

[a] Oil bath temperature in which reaction flask was immersed in.
[b] Isolated yield in parentheses.
[c] Isolated yield reported is the average of three runs.

3 and 4). Examination of strong, more soluble bases such as KHMDS, ethylmagnesium chloride, and *n*-butyl lithium were also examined, with butyl lithium affording the highest yield of the desired product. However, all reactions were characterized by HPLC as containing multiple by-products and incomplete conversion of starting material.

The use of sodium or lithium amide as base was found to be particularly effective in forming the desired heterocycle (entries 8 and 9).[9] The yields and rates of reaction were significantly better then that observed using sodium hydride or sodium metal. Reactions using sodium amide were typically faster and cleaner than reactions using lithium amide. Sodium amide is only partially soluble in refluxing toluene and, not surprisingly, faster reaction rates were observed when the sodium amide pellets were ground to a powder prior to use. Examination of other, more polar solvents which may increase the solubility of sodium amide did not improve product yields (entries 10–13). Finally, it was found that reducing the reaction temperature to 90°C and increasing the equivalents of added base increased product yield (entries 13–17).[10] Products deriving from direct amination of **2** with sodium amide or intermolecular aminations between two or more molecules of **2** were not detected.

In summary, the synthesis 2-[3-aminopropyl]-5,6,7,8-tetrahydronaphthyridine **1** was accomplished in four steps with an overall yield of 76%. The key steps of the synthesis included a double Suzuki reaction of 2,5-dibromopyridine with phthalimide protected allylamine to form two C–C bond in one-pot and an intramolecular Chichibabin reaction. The Chichibabin reaction was optimized and afforded the desired product in high yield with excellent regioselectivity, and a significant reduction in reaction times compared to literature precedence.

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10. Addition of CsCl or $MgCl_2$ to the reaction mixture did not improve product yield.