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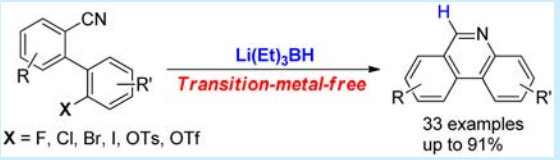
Hydride-Induced Anionic Cyclization: An Efficient Method for the Synthesis of 6-*H*-Phenanthridines via a Transition-Metal-Free Process

Wei-Lin Chen, Chun-Yuan Chen, Yan-Fu Chen, and Jen-Chieh Hsieh*

Department of Chemistry, Tamkang University, New Taipei City, 25137, Taiwan

Supporting Information

ABSTRACT: A novel procedure for hydride-induced anionic cyclization has been developed. It includes the reduction of a biaryl bromonitrile with a nucleophilic aromatic substitution (S_NAr). A range of polysubstituted 6-*H*-phenanthridines were so obtained in moderate to good yield with good substrate tolerance. This method involves a concise transition-metal-free process and was applied to synthesize natural alkaloids.



Phenanthridines, particularly those of the 6-*H*-phenanthridine variety (Figure 1), are important structural motifs of many bioactive natural alkaloids[1] and medically relevant compounds.[2] 6-*H*-Phenanthridine derivatives often exhibit good inhibition of DNA topoisomerase I and are of potential value to antitumor therapy.[3] Although numerous methods have been developed to access phenanthridine derivatives,[4] specific routes to 6-*H*-phenanthridines are still limited to photolysis,[5] microwave-assisted cyclization,[6] oxidation of 5,6-dihydrophenanthridine,[7] and intramolecular condensation.[8] In addition, most of these synthetic methods can only be applied to prepare products with a narrow scope of structural diversity. Therefore, a novel method that provides a general route to many different 6-*H*-phenanthridines is still desired.

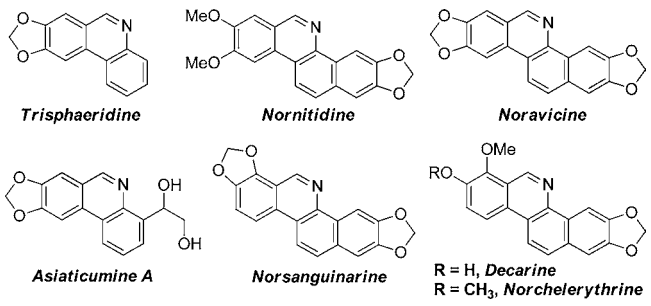


Figure 1. Examples of 6-*H*-phenanthridine alkaloids.

We have recently developed a method for the synthesis of 6-alkyl/aryl/acetyl-phenanthridines via a Cu(I/III) catalytic cycle involving the transformation of a nitrile.[9] This, with the success of our previous works involving transition-metal-catalyzed coupling reactions of nitriles,[10] motivated us to further investigate the possibility of synthesizing 6-*H*-phenanthridines by an annulation that is more environmentally friendly and efficient.

Transition-metal-free reactions are an important research target in organic synthesis, especially in the pharmaceutical industry. The standard limit for the metal content of drugs is in general ppm. Thus, the loading amount and the metal removal in each single synthetic step are crucial. Anionic ring closure reactions can potentially proceed without transition metals,[11] but are rarely reported for the construction of poly aromatic compounds via nucleophilic aromatic substitution (S_NAr).[12] In S_NAr reactions, an electron-deficient group activating the Csp^2–X bond is generally required.[13] Among all the examples, the Csp^2–F has the fastest reaction rate in S_NAr reactions,[14] and most of the reports involve the cleavage of C–F bonds.[15] Other Csp^2–X bonds such as C–Cl, C–Br and C–I are more commonly activated by an oxidative addition with late transition-metal complexes.[16] These reasons make the preloading of a fluoride in substrate important for application to the S_NAr reaction. However, the fluorination of aromatic compounds[17] is still developing and not as easy to perform as the well developed bromination. Herein, we report the first example of an efficient synthesis of 6-*H*-phenanthridines involving hydride-induced anionic cyclization by an S_NAr reaction, with the cleavage of the C–Br bond, and not requiring transition metals.

We used 2′-bromo-[1,1′-biphenyl]-2-carbonitrile (**1a**) as a model substrate (Table 1, entry 1) for our initial studies, which was treated with 1.5 equiv of $LiAlH_4$ in 0.5 mL of benzene at 100 °C for 36 h; the corresponding 6-*H*-phenanthridine (**2a**) was obtained in only 11% NMR yield. Product **2a** was confirmed by the ^1H NMR, ^{13}C NMR, and HRMS analysis. After working up the reactions we obtained messy crude NMR spectra, and the starting substrate that remained was observed with the desired product and several unidentified byproducts.

To optimize the reaction conditions, the effect of solvents, hydride sources, and reaction temperatures was investigated (Table 1). We first evaluated the effect of solvent on this reaction (entries 1–8) and found that it was significant. When aromatic solvents such as toluene, *o*-xylene, and 1,2-dichlorobenzene were used, the reaction proceeded but gave

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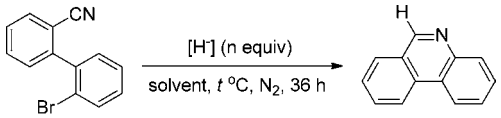
Table 1. Optimization of Reaction Conditions[a]



1a (1.0 equiv) **2a**

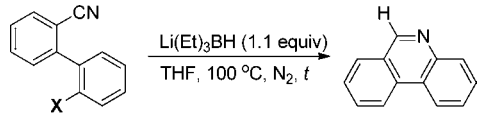
entry	[H⁻]	*n*	solvent	temp (°C)	yield (%)[b]
1	$LiAlH_4$	1.5	benzene	100	11
2	$LiAlH_4$	1.5	aromatic solvents[c]	100	9–12
3	$LiAlH_4$	1.5	pentane	100	27
4	$LiAlH_4$	1.5	hexane	100	16
5	$LiAlH_4$	1.5	ethers[d]	100	12–17
6	$LiAlH_4$	1.5	THF	100	31
7	$LiAlH_4$	1.5	*t*BuOH	100	0
8	$LiAlH_4$	1.5	polar solvents[e]	100	0
9	$NaAlH_4$	1.5	THF	100	38
10	DIBAL-H	1.5	THF	100	43
11	$LiAlH(OtBu)_3$	1.5	THF	100	37
12	MBH_4[f]	1.5	THF	100	0
13	$Li(Et)_3BH$	1.5	THF	100	69
14	$LiBH(secBu)_3$	1.5	THF	100	52
15	NaH	3.0	THF	100	17
16	$Li(Et)_3BH$ (0.5)/NaH (3.0)		THF	100	74
17	$Li(Et)_3BH$	1.5	THF	120	78
18	$Li(Et)_3BH$	1.5	THF	80	54
19[g]	$Li(Et)_3BH$	1.1	THF	100	92 (87)[h]
20[i]	$Li(Et)_3BH$	1.1	THF	100	58

[a]Reactions were carried out using 0.1 mmol (1.0 equiv) of 2′-bromo-[1,1′-biphenyl]-2-carbonitrile (**1a**) with a hydride source (*n* equiv) in 0.5 mL of solvent at *t* °C for 36 h. [b]^{1}H NMR yield based on internal standard mesitylene. [c]Toluene, *o*-xylene, and 1,2-dichlorobenzene were used. [d]Et_2O, 1,4-dioxane, and DME were used. [e]DMF, DMSO, and NMP were used. [f]M = Na, Li, K. [g]48 h. [h]Isolated yield in 0.4 mmol scale. [i]Under air.

the product in very low yields (entry 2). Better yields were obtained in nonpolar solvents, such as pentane and hexane (entries 3, 4). Ether-type solvents, such as 1,4-dioxane, DME, and Et_2O, slightly improved the yield of **2a** (entry 5). Among all the tests, THF provided the best yield for this reaction (entry 6). It was found that the reaction is unable to proceed in protic and highly polar solvents (entries 7, 8). The hydride source is also crucial for this reaction. Different aluminum hydrides afforded similar results for this reaction (entries 9–11). $NaBH_4$, $LiBH_4$, and KBH_4 were functionless (entry 12). But $Li(Et)_3BH$, a so-called "***Super Hydride***," effectively improved the yield of **2a** to 69% (entry 13). Interestingly, an excess amount of **NaH** also induced the reaction (entry 15), and the combination of $Li(Et)_3BH$ (0.5 equiv of H^-) with **NaH** afforded an even better yield of the desired product (entry 16). The reaction proceeded smoothly at 80 to 120 °C (entries 17, 18). When the reaction was conducted at 120 °C, higher yields of **2a** were observed; however, overreaction occurred as well. We thus reduced the amount of hydride and increased the reaction time to avoid this, and got a very good yield of the desired product **2a** (entry 19). The hydride-induced anionic cyclization could also proceed under air in a lower yield (entry 20). This is due to the moisture interference in this reaction.

After optimizing the reaction conditions, the capacity of this hydride-induced cyclization reaction to work with different halides and pseudohalides was then investigated (Table 2). It

Table 2. Reaction for the Substrates with Different Halides and Pseudohalides[a]



1 (1.0 equiv) **2a**

entry	X	*t* (h)	yield (%)[b]
1	F	48	91
2	Cl	48	87
3	Br	48	92
4	I	48	34
5	OTf	48	46
6	OTs	48	43
7	OMe	48	3
8	F	24	82
9	Cl	24	56
10	Br	24	53
11	I	24	31

[a]Reactions were carried out using 0.1 mmol (1.0 equiv) of substrate **1** with 1.1 equiv of $Li(Et)_3BH$ in 0.5 mL of THF at 100 °C for *t* h. [b]^{1}H NMR yield based on internal standard mesitylene.

was found that, with a 48 h reaction time, reactions for all the different substrates were completed. The performance for a fluoride and bromide as leaving groups is similar, slightly better than that of a chloride. When an iodo-substrate was introduced into the reaction, the crude spectrum was messy and a much lower yield of **2a** was detected. By GC-MS analysis, the major side reaction was confirmed as protonation of the iodide. Pseudohalides such as triflate and tosylate also worked, but in lower yields. A methoxy group in this reaction did not work well and provided **2a** in only 3% NMR yield. Almost all of the substrate remained. It is noteworthy that when the reaction time was 24 h (entries 8–11), the fluoro-substrate afforded **2a** in the highest yield, and only the reaction of iodo-substrate was completed.

Our hydride-induced anionic cyclization reaction was successfully extended to various bromo-substrates **1**, and the results are listed in Scheme 1. In most cases, the reaction required at least 48 h to fully consume the substrates (**1**). However, longer reaction times were occasionally associated with overreacting of the hydride and reduction of the 6-*H*-phenanthridines to 5,6-dihydrophenanthridines. Investigations into the effect of electron density then were made. As indicated, these reactions worked very well for both electron-withdrawing (**2b–2e**) and electron-donating groups (**2f**, **2g**) on the benzonitrile moiety. Reaction of the substrate with a methyl group on the *para* position of nitrile (**2f**) gave a lower yield, which might be caused by the abstraction of a proton on the methyl group. Substituents *ortho* to the nitrile group did not impede the addition of hydride and provided the corresponding products **2h** and **2i** in good yields. The electron density on the moiety of the aryl bromide (**2j–2n**) also did not significantly influence the reaction. However, when the substrates with the benzodiozole subunit were used in the reaction, some undefined side products were observed alongside the desired products (**2n**, **2A**, **2B**, and **2J**). For a substrate with a naphthalene subunit, the reaction proceeded smoothly and provided the corresponding product **2o** in good yield. Heteroaromatic compounds such as pyridine (**2p**) and quinoline (**2q**) were tolerated as well. However, some side

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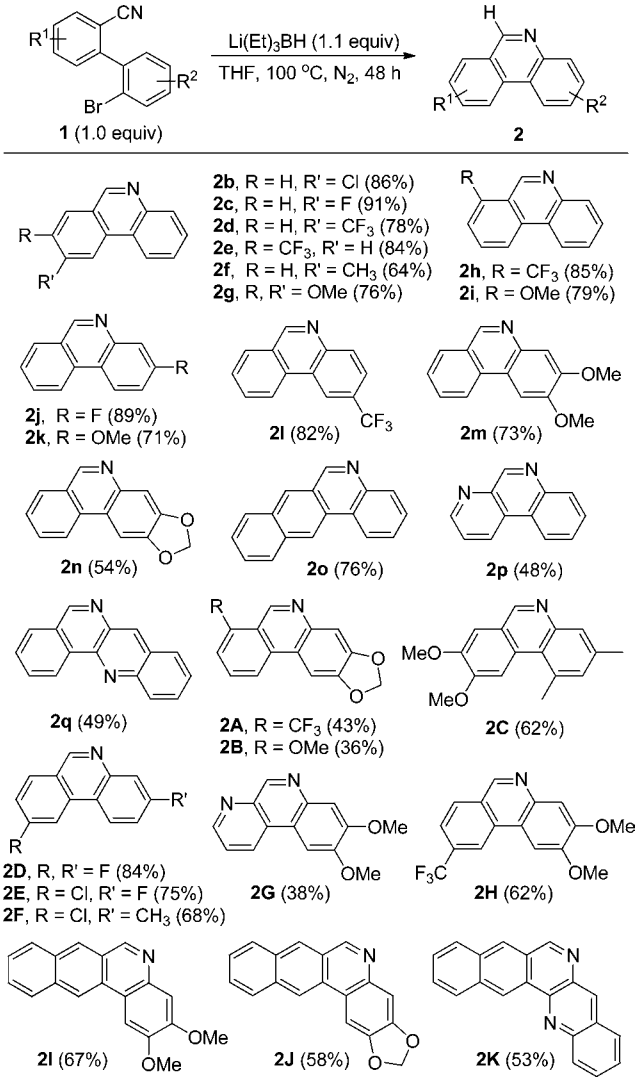
Scheme 1. Scope of 6-*H*-Phenanthridines[a,b]

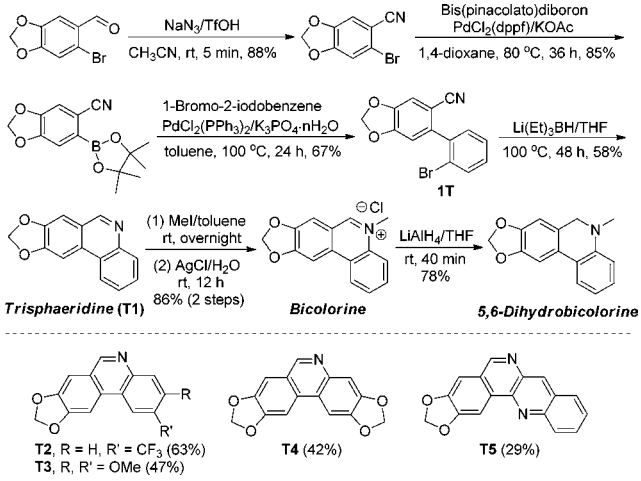


[a]Reactions were carried out using 0.4 mmol (1.0 equiv) of substrate **1** with 1.1 equiv of $Li(Et)_3BH$ in 2.0 mL of THF at 100 °C for 48 h. [b]Isolated yield.

products were observed and the desired products were isolated only in moderate yields. The combination of various subunits to establish polysubstituted 6-*H*-phenanthridines (**2A**–**2I**) and polyaromatic compounds (**2J**, **2K**) was also easily achieved in moderate to good yields by the present methodology.

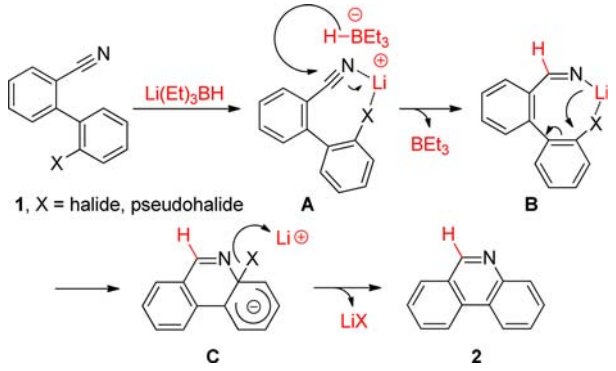
Our standard procedure was also applied to the synthesis of natural alkaloid trisphaeridine[18] (**T1**, Scheme 2), which represents the basic skeleton of the *Amaryllideceae* alkaloids[19] and appears in a wide range of natural alkaloids and bioactive compounds. The further *N*-methylation and reduction afforded two other alkaloids, bicolorine and 5,6-dihydrobicolorine.[20] Both of these two alkaloids were isolated from the bulbs of *Narcissus bicolor*, and the bicolorine even exhibits a high anticancer effect.[3a] Our synthetic process provides trisphaeridine in 29% overall yield in four steps from the commercial source, bicolorine in 25% (six steps) and 5,6-dihydrobicolorine in 20% (seven steps). In addition, the analogues of trisphaeridine (**T2**–**T5**) could be also obtained in moderate yields. This demonstrated the high convenience of this method for use in medicinal chemistry.[3]

Scheme 2. Syntheses of Trisphaeridine, Bicolorine, 5,6-Dihydrobicolorine, and the Analogues of Trispharidine



Based on previous reports[9,10,12−15] and the above results, a tentative reaction pathway can be proposed as below (Scheme 3). The reaction is likely to be initiated by the chelating of

Scheme 3. Proposed Reaction Pathway



compound **1** to lithium (complex **A**). Subsequent addition of hydride to nitrile provides the iminyl lithium complex (complex **B**). A subsequent nucleophilic aromatic substitution then takes place to generate the anionic intermediate **C**. Elimination of halide or pseudohalide affords desired product **2** and precipitate LiX.

In conclusion, we have developed a novel method for hydride-induced anionic ring closure to obtain 6-*H*-phenanthridines in moderate to good yields with tolerance of a wide variety of substrates. In addition, the present procedure can be applied to the syntheses of the three natural alkaloids, trisphaeridine, bicolorine, and 5,6-dihydrobicolorine. Further studies to explore other applications are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization, spectral data, and copies of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jchsieh@mail.tku.edu.tw.

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Notes

The authors declare no competing financial interest.

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