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Synthesis of 5,6-dihydrophenanthridines via *N,O*-acetal TMS ethers

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ABSTRACT

A concise and high-yielding protocol for the synthesis of 5,6-dihydrophenanthridines is disclosed. The key feature includes a sequential reduction-cyclization reaction of *N*-acylcarbamates via *N,O*-acetal TMS ethers as a stable *N*-acyliminium ion precursor.

Phenanthridine and 5,6-dihydrophenanthridine alkaloids are found throughout a wide range of natural resources, exhibiting various biological activities including antibiotic, anti-inflammatory, and anticancer activity.[1] Thus, there have been continuous endeavors to secure the classes of phenanthridines and 5,6-dihydrophenanthridines occupying biologically relevant chemical spaces. For instance, phenanthridines including aza-phenanthridines and benzophenathridines have been reported to be promising candidates for drug development and the related biological studies[2] although 5,6-dihydrophenanthridines were less explored. A recent report revealed that the natural alkaloid-based 5,6-dihydrophenanthridines possess potent inhibitory activities against acetylcholine esterase.[3] In addition, development of the 5,6-dihydrophenanthridine derivatives as bradykinin B1 antagonist has been reported.[4] 5,6-Dihydrophenanthridines as potassium channel inhibitors and as immunosuppressants were also reported.[1h] Figure 1 Notably 5,6-dihydrophenanthridines often exhibited distinct biological properties compared to the structurally related phenanthridines owing to the absence of electrophilic C=N double bond.[5]

Compared to the well developed phenanthridine syntheses,[6] only a few synthetic methods for the preparation of 5,6-dihydrophenanthridines were reported. In addition, the 5,6-dihydrophenanthridine syntheses often suffered from low yields due to the limited functional group tolerance[7] and the undesirable in situ oxidation.[8] Modified Pictet-Spengler reaction for the synthesis of 5,6-dihydrophenanthridine-6-carboxylates,[9] a sequential multicomponent reaction involving intramolecular C–H functionalization[10] and

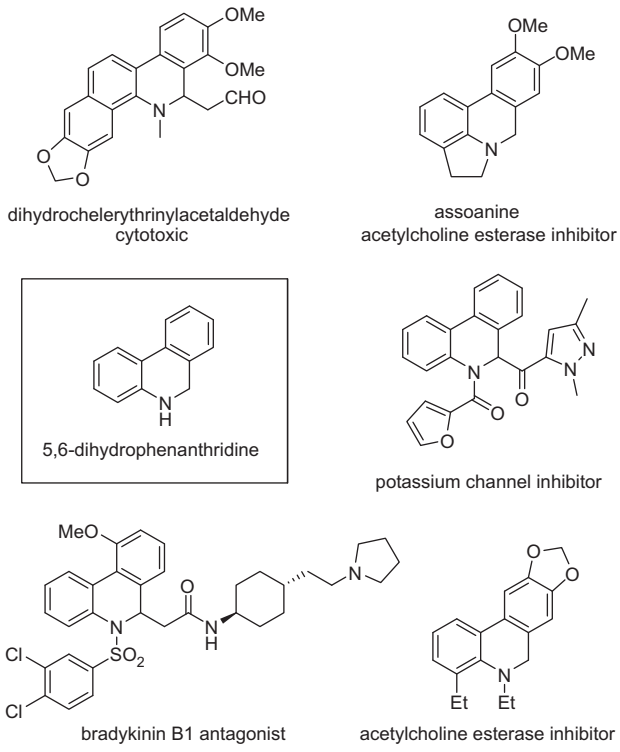

Figure 1. Selected 5,6-dihydrophenanthridines.

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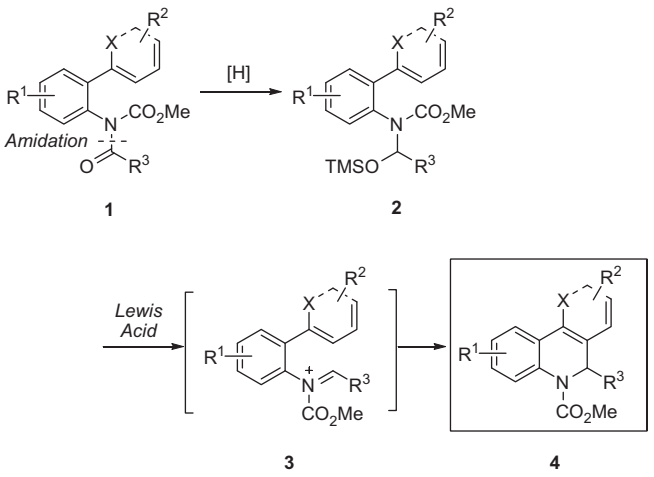
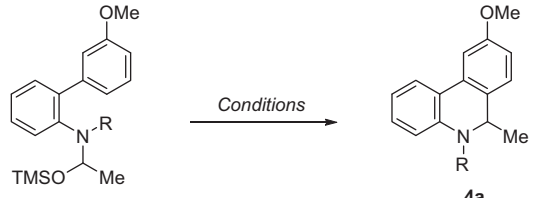


Figure 2. Synthetic strategy.

Table 1
Optimization of reaction conditions



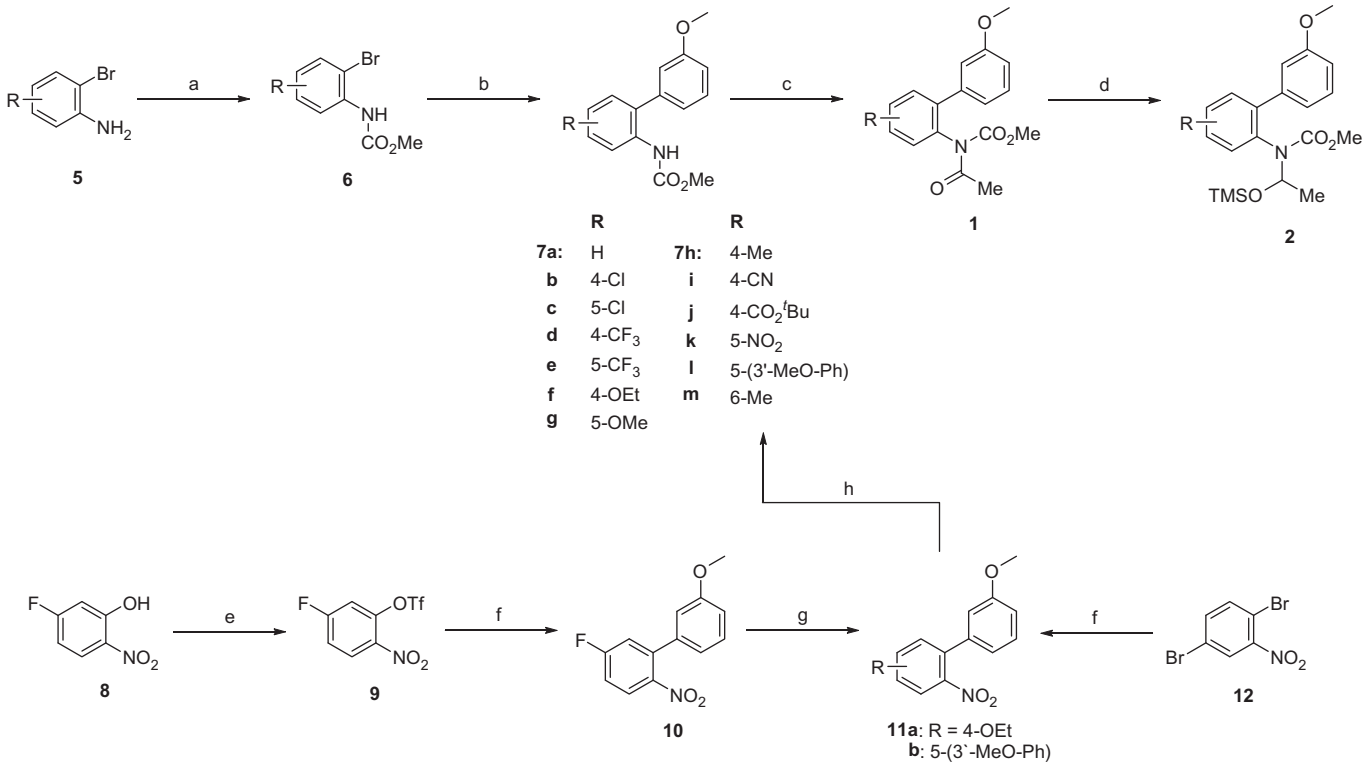
Entry	R	Lewis acid	Solvent	Temp. (°C)	Yield[a] (%)
1	CO_2Me	$TiCl_4$	CH_2Cl_2	−78	98
2	CO_2Me	$SnCl_4$	CH_2Cl_2	−30	98
3	CO_2Me	TFA	CH_2Cl_2	−30	98
4	CO_2Me	TMSOTf	CH_2Cl_2	−30	98
5	CO_2Me	$BF_3{\cdot}OEt_2$	CH_2Cl_2	−30	99
6	CO_2Me	$BF_3{\cdot}OEt_2$	Toluene	−30	97
7	CO_2Me	$BF_3{\cdot}OEt_2$	CH_3CN	−30	99
8	CO_2Me	$BF_3{\cdot}OEt_2$	THF	−30	75
9	Ts	$BF_3{\cdot}OEt_2$	CH_2Cl_2	−30	98
10	Ms	$BF_3{\cdot}OEt_2$	CH_2Cl_2	−30	99

[a] Isolated yield.

a biomimetic hydrogenation for the syntheses of 6-aryl-5,6-dihydrophenanthridines have been developed very recently.[11]

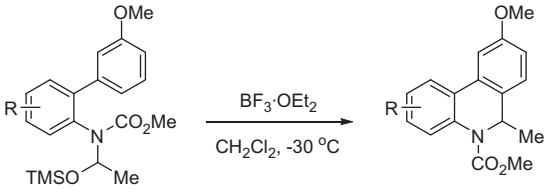
Recently, we reported an efficient synthesis of Calycotomine,[12] in which construction of the tetrahydroisoquinoline scaffold using a Pictet-Spengler type cyclization of *N,O*-acetal TMS ether was included as a key step. Kuhakarn et al. also reported synthesis of a series of 1-substituted tetrahydroisoquinoline derivatives employing a similar strategy, namely a sequential reduction-cyclization reaction of *N*-acylcarbamates.[13] Considering the limited scope of the precedent procedures to 1-substituted tetrahydroisoquinolines, the efficient and widely applicable procedures for dihydroisoquinolines are currently required. We herewith report a synthetic procedure for 5,6-dihydrophenanthridines utilizing electrophilic cyclization of *N*-acyliminium ions via *N,O*-acetal TMS ethers as stable and easily accessible precursors.[14]

As shown in Figure 2, we envisioned that 5,6-dihydrophenathridines would be easily provided from the corresponding amide precursors. The amide precursors are conveniently prepared by the standard amidation reaction. Partial reduction followed by in situ silylation of the resulting aluminum alkoxide would provide *N,O*-acetal TMS ethers. Finally, *N*-acyliminium ions are generated from



Scheme 1. Reagents and conditions: (a) $ClCO_2Me$, EtOAc, 80 °C, 92–98%; (b) 3-methoxyphenylboronic acid, $Pd(PPh_3)_4$, K_3PO_4, 1,4-dioxane, 98 °C, 75–86%; (c) LHMDS or *n*-BuLi, acetyl chloride, THF, −78 °C to rt, 88–96%; (d) DIBAL-H or $LiEt_3BH$, pyridine, TMSOTf, CH_2Cl_2, −78 °C, 56–75% except for **2i** (18%), **2j** (26%) and **2k** (15%); (e) Tf_2O, DIPEA, CH_2Cl_2, rt, 95%; (f) 3-methoxyphenylboronic acid, $Pd(PPh_3)_4$, K_3PO_4, 1,4-dioxane, 98 °C, 92% for **10**, 85% for **11b**; (g) NaOEt, EtOH, 80 °C, 85%; (h) H_2(g), Pd/C, MeOH, rt; $ClCO_2Me$, EtOAc, 80 °C, 92% for **7f**, 92% for **7l** (2 steps).

Table 2
Scope of cyclization



2a-j **4a-j**

Entry	R	Yield[a] (%)
1	H (**2a**)	99
2	4-Cl (**2b**)	98
3	5-Cl (**2c**)	98
4	4-CF_3 (**2d**)	97
5	5-CF_3 (**2e**)	97
6	4-OEt (**2f**)	99
7	5-OMe (**2g**)	99
8	4-Me (**2h**)	99
9	4-CN (**2i**)	82
10	4-$CO_2{}^t$Bu (**2j**)	98
11	5-NO_2 (**2k**)	78
12	5-(3′-Methoxy)phenyl (**2l**)	99
13	6-Me (**2m**)	98

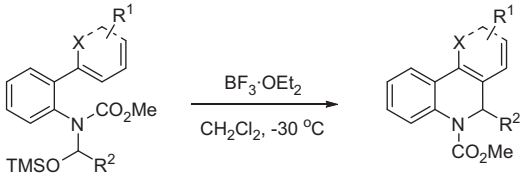
[a] Isolated yield.

N,*O*-acetal TMS ethers in the presence of appropriate Lewis acid resulting in formation of 5,6-dihydrophenanthridines via electrophilic cylcization.

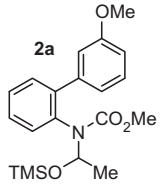
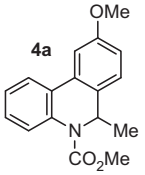
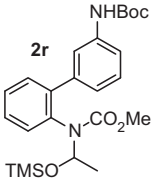
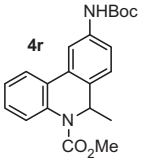
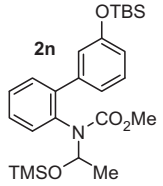
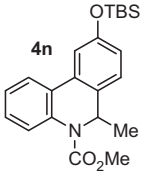
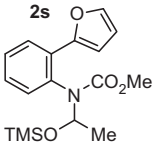
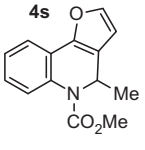
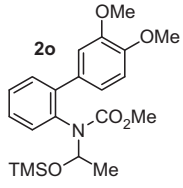
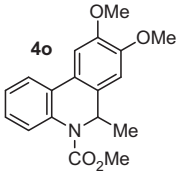
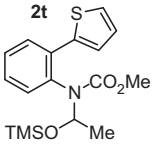
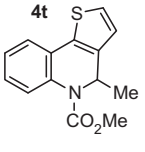
N,*O*-acetal TMS ether **2a** was prepared as shown in Scheme 1. The commercially available aniline **5a** was treated with methyl chloroformate to provide carbamate **6a**, which was coupled with 3-methoxyphenylboronic acid in the presence of $Pd(PPh_3)_4$ and then followed by the acylation of carbamate to give amide **1a**. Amide **1a** was finally reduced with DIBAL-H, and the resulting *N*,*O*-acetal was trapped with TMSOTf in situ to afford the desired *N*,*O*-acetal TMS ether **2a**. As shown in Table 1, the desired 5,6-dihydrophenanthridine **4a** was successfully obtained in high yield by treatment of *N*,*O*-acetal TMS ether **2a** with various Lewis acids at −30 °C except for $TiCl_4$. The cyclization proceeded smoothly in various solvents although THF was not appropriate in terms of chemical yield. We also found that the sulfonamide precursors could also be utilized as alternative to carbamates (entries 9, 10).[15]

Having successfully established the optimized reaction conditions,[16] we turned our attention to scope and limitation of our strategy for the synthesis of 5,6-dihydrophenanthridines. We first explored various functional groups on the benzene ring. The requisite *N*,*O*-acetal TMS ethers were prepared by analogy to the preparation of **2a** (Scheme 1). Syntheses of **7f** and **7l** required a few more steps because the corresponding *o*-bromoanilines were not commercially available. All substrates were prepared in high chemical yields except for **7i**, **7j**, and **7k**. In the preparation of *N*,*O*-acetal TMS ethers,[17] most of amides **1** showed moderate to good yields except for **7i**,[18] **7j** and **7k**[19] in which the C–N bond cleavage consistently occurred as a side reaction. Cyclization of all *N*,*O*-acetal TMS ethers successfully provided the corresponding 5,6-dihydrophenanthridines in high yields under the optimized conditions (Table 2). Substrates including both electron withdrawing and donating groups on the benzene ring system provided the desired cyclization prod-

Table 3
Scope of cyclization

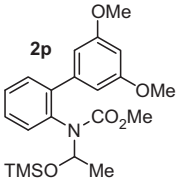
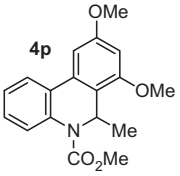
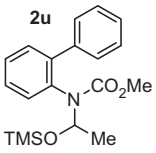
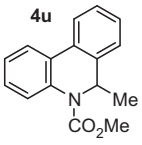
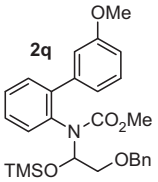
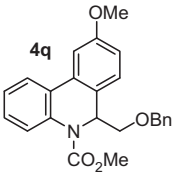
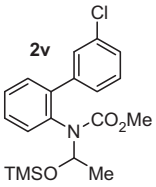
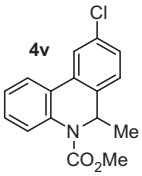


2k-p **4k-p**

Entry	Substrate	Product	Yield[a] (%)	Entry	Substrate	Product	Yield[a] (%)
1			99	6[b]			8[c]
2			98	7			95
3			98	8[d]			88[e]

(*continued on next page*)

Table 3 (*continued*)

Entry	Substrate	Product	Yield[a] (%)	Entry	Substrate	Product	Yield[a] (%)
4[b]			72[c]	9			-[e]
5			97	10			-[e]

[a] Isolated yield.
[b] *N,O*-acetal TMS ether was used as a crude mixture.
[c] Yield for two steps (*N,O*-acetal TMS ether was used as a crude mixture).
[d] TFA was used instead of $BF_3{\cdot}OEt_2$.
[e] See text.

ucts regardless of substitution position.[20] The reactions of *N,O*-acetal TMS ethers containing 4- or 5-chloro substituent required longer reaction time to be completed although they were completed within 1.5 h.

We also explored the benzene ring systems possessing various functional groups including heterocycles, which functioned as an internal nucleophile. The requisite *N,O*- acetal TMS ethers **2n**–**2v** were prepared by analogy to the previous precursors.

As shown in Table 3, all the substrates that contain activating groups on the benzene ring gave high yields. (entries 1–5) In particular, the *N,O*-acetal TMS ether **2n** possessing a *para*-siloxy group, which is readily deprotectable, provided **4p** in an excellent yield. This supports extensive synthetic utility of the protocol. The ortho- and para-disubstituted 5,6-dihydrophenanthridine **4p** was successfully provided too.[21] The *N,O*-acetal TMS ether **2q** derived from the benzyloxylacetyl amide was well tolerable and afforded the corresponding 5,6-dihydrophenanthridine as anticipated (entry 5). As shown in entry 6, effect of the protected amine substituent as an activating group was investigated. The *N,O*-acetal TMS ether **2r** was used as a crude mixture due to its instability. Effects of heterocycles such as furan (entry 7) and thiophene (entry 8) were also examined. While furan **2s** afforded the desired 5,6-dihydrophenathridine in high yield, thiophene **2t** provided poor yield under the standard conditions (<10%). However, TFA was found to be much more effective than $BF_3{\cdot}OEt_2$ after extensive efforts (entry 8). Compared to the furan moiety, higher aromatic character of thiophene is known to attribute to the lower reactivity in electrophilic substitution.[22] However, the non-substituted benzene **2u** (entry 9) and 3-chlorobenzene **2v** (entry 10) did not provide the desired 5,6-dihydrophenanthridines.

In summary, we have developed a high-yielding method for the preparation of 5,6-dihydrophenanthridines via a sequence of reduction and cyclization of *N*-acylcarbamtes. The key feature involved convenient preparation of *N,O*-acetal TMS ethers as *N*-acyliminium ion precursors, which were easily derived from amides, and efficient intramolecular aromatic substitution of *N*-acyliminium ion under mild conditions. This procedure would be widely applicable for the synthesis of 5,6-dihydrophenanthridines.

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15. The Boc or Cbz protected amides were unstable under a basic condition to give the deacylated carbamates (**7**), which were obtained as sole product after NH-silica gel chromatography.
16. *Representative procedure*: To a solution of **2a** (86 mg, 0.23 mmol) in dry CH_2Cl_2 (1 mL) at −30 °C was added $BF_3{\cdot}OEt_2$ (0.085 mL, 0.69 mmol). The reaction mixture was stirred for 1 h and quenched with triethylamine. Water was added to the organic solution, and the resulting mixture was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (EtOAc : hexane = 1:3) to afford 64.5 mg (99%) of **4a** as colorless viscous oil, FT-IR (thin film, neat) ν_{max} 3081, 3002, 2968, 2836, 1707, 1611, 1570, 1496, 1439, 1386, 1331, 1316 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 7.8, 1.3 Hz, 1H), 7.60 (br s, 1H), 7.34–7.30 (m, 1H), 7.29 (d, J = 2.5 Hz, 1H), 7.25–7.21 (m, 1H), 7.14 (d, J = 8.3 Hz, 1H), 6.85 (dd, J = 8.3, 2.5 Hz, 1H), 5.63 (m, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 1.19 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 154.3, 134.5, 131.6, 131.2, 127.9, 127.6, 126.6, 125.8, 124.9, 123.6, 113.4, 108.9, 55.4, 53.0, 51.8, 20.7; HRMS (ESI+) calcd for $C_{17}H_{17}NO_3$ (M^+) 283.1208, found 283.1203.
17. In most case, DIBAL-H gave slightly higher yield than $LiEt_3BH$.
18. $LiEt_3BH$ was used for the more elaborate control of the amount of reducing agent.
19. **7k** was prepared using only $LiEt_3BH$. When DIBAL-H was used, only C–N bond cleavage occurred.
20. In **7i** and **7k**, the yields for cyclization slightly decreased because they slowly decomposed at room temperature.
21. Because the *N*,*O*-acetal TMS ether **2p** could not be isolated with the by-product which resulted from the C–N bond cleavage, it was used as a crude mixture in cyclization reaction. On the analysis of LC-Mass data, it was judged that the cyclization reaction proceeded well. In addition, the yield for two steps was almost same to the yield of **4a** from **1a**.
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