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A Concise Synthesis of Physostigmine from Skatole and Activated Aziridine via Alkylative Cyclization

Masako Nakagawa* and Michiaki Kawahara

Faculty of Pharmaceutical Sciences, Chiba University, 1-33, Yayoi-cho, Inage-ku, Chiba-shi, 263-8522, Japan

nakagawa@p.chiba-u.ac.jp

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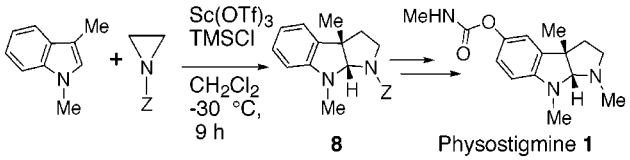
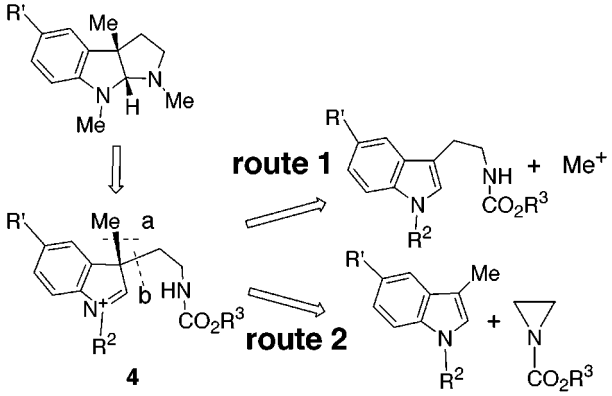
ABSTRACT



A concise synthetic route to physostigmine has been developed, where the key step relies on the alkylative cyclization of 1,3-dimethylindole with (*Z*)-aziridine catalyzed by $Sc(OTf)_3$ and TMSCl in dichloromethane at −30 °C, to give 8 in 90% yield, which, in turn, can be readily converted into physostigmine.

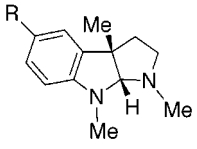
Recently, we developed an expeditious route to racemic and optically active physostigmine (**1**) from tryptamine and tryptophan derivatives by alkylative cyclization, which involves the intramolecular trapping of an indolenium species (**4**) by the amino side chain (route 1, Scheme 1).[1]

Scheme 1



As a variant of this route, we anticipated that an indolenium intermediate (**4**) could be retrosynthesized to give 1,3-dimethylindole and an aziridine derivative. To this end, we investigated the reaction of 1,3-dimethylindole with alkoxycarbonylaziridines under various conditions, which could serve as a novel and concise route to medicinally important physostigmine alkaloids,[2] which include anticholinesterase and miotic.s[3] Physostigmine (**1**) was first isolated in 1864 from Calabar beans as a principal base. Interestingly, physostigmine (**1**) was also isolated from *Streptomyces* as an insecticidal compound.[4] Furthermore, this alkaloid ring system has also been found in marine alkaloids such as the flustramines from broyoza *Flustra foliacea*.[5]

More recently, analogues of **1** have shown a promise in the treatment of Alzheimer's disease. Thus, Calabar alkaloids are very interesting biochemical tools and several syntheses of **1** have been reported.[6]



R=OCONHMe Physostigmine **1**
R=OMe Eserethole **2**
R=H Desoxyeseroline **3**

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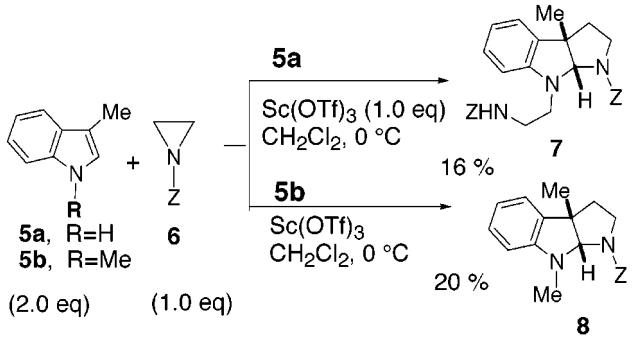
We present here our preliminary results on the synthesis of (±)-**1** via route 2 as shown in Scheme 1.

Aziridines and their ring-opened products are valuable intermediates in organic synthesis.[7] The reaction of aziridines with 3-unsubstituted indoles has been reported to give tryptophan derivatives[8] or 3-substituted indoles[9] by use of a Lewis acid.

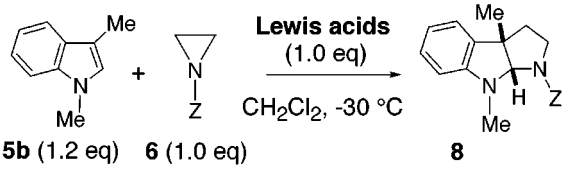
We initially examined the key reaction of *N*-benzyloxycarbonyl (*Z*)-aziridine with skatole in the presence of 1.0 equiv of $Sc(OTf)_3$. While the expected reaction took place, it was accompanied by a second alkylation on the newly formed indoline nitrogen atom of pyrroloindole to form a dialkylated compound, such as **7**. Encouraged by this result, we carried out a similar reaction of 1,3-dimethylindole **5** with **6**, and **8** was obtained in 20% yield (Scheme 2).[10]

Scheme 2



A brief optimization study involving 1,3-dimethylindole and **6** was performed using other conditions (Lewis acids, temperature). Among the Lewis acids tested, $Sc(OTf)_3$, $EtAlCl_2$, and Et_2AlCl were found to promote the reaction, but the yields were not statisfactory (Table 1).

Table 1. Effect of Lewis Acids[10]



Run	Lewis acids	%, yield	Run	Lewis acids	%, yield
1	none	0	4	$Yb(OTf)_3$	11
2	$Sc(OTf)_3$	25	5*	$EtAlCl_2$	28
3	$Sn(OTf)_2$	11	6*	Et_2AlCl	23

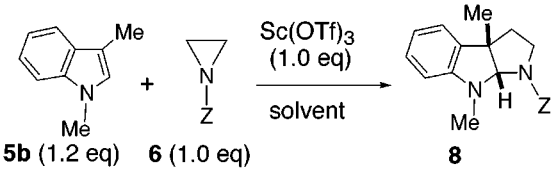
* Reaction temp. -78 °C, Lewis acid 1.5 eq

trace-----CuOTf, $Zn(OTf)_2$, AgOTf, $Sm(OTf)_3$, $Hf(OTf)_4$, $Y(OTf)_3$, $Eu(OTf)_3$, $ZnBr_2$

0 %----$La(OTf)_3$, $Zr(OiPr)_4$, YCl_3, $MgBr_2$TMSCl, TMSOTf

While the reaction proceeded in CH_2Cl_2, toluene, and CH_3CN at −30 °C, the reaction did not take place in THF (Table 2).

Table 2. Effects of Solvents and Temperature[10]



Run	Solvent	Temp. (°C)	Time (h)	%, Yield
1	CH_2Cl_2	-30	9	25
2	THF	-30	12	0
3	Toluene	-30	12	16
4	CH_3CN	-30	12	21
5	CH_2Cl_2	-78	9	0
6	CH_2Cl_2	-50	9	15
7	CH_2Cl_2	0	9	11

To facilitate the reaction, we examined the effects of Lewis acids in the presence of chlorotrimethylsilane (TMSCl) in CH_2Cl_2 (Table 3). The effect of TMSCl is notable when combined with $Sc(OTf)_3$. Addition of TMSCl enhanced the yield of **8** up to 52%.[11]

Table 4 shows the results of optimizing the quantity of $Sc(OTf)_3$. The formation of **8** was enhanced by changing

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(8) (a) Sato, K.; Kozikowski, A. P. *Tetrahedron Lett* **1989**, *30*, 4073−4076. (b) Bennani, Y. L.; Zhu, G.-D.; Freeman, J. C. *Synlett* **1998**, 754−756.

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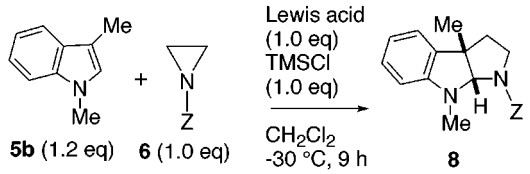
(10) Yields, shown in Scheme 2 and Tables 1−4, were calculated on the basis of **6**.

(11) Similar effects of TMSCl were observed in an imino−ene reaction. Yamanaka, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 159−161.

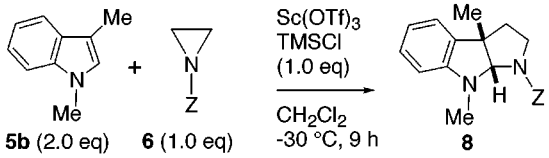
Table 3. Effect of TMSCl with Lewis Acids[10]



Run	Lewis acid	%, Yield,	% yield without TMSCl
1	None	0	NR
2	$Sc(OTf)_3$	52	25
3	$Yb(OTf)_3$	26	11
4	$EtAlCl_2$ (1.6 eq)	28	30
5	TMSOTf	—	0

the ratio of $Sc(OTf)_3$ and aziridine to 2:1, to give a maximum yield of 90%. Under these optimized conditions, 1 g of **6** could be converted to **8** in 84% yield, together with recovery of $Sc(OTf)_3$.

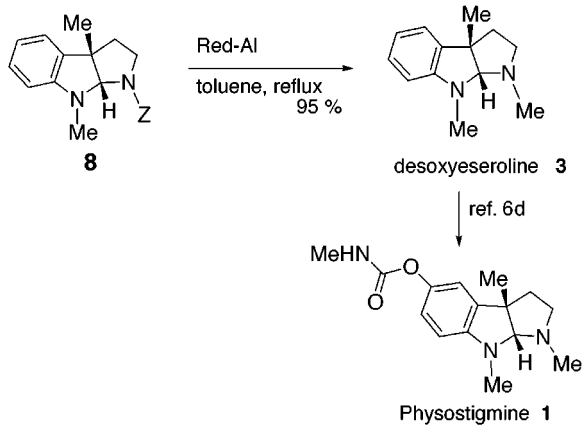
Table 4. Optimization of Catalyst Amounts[10]



Sc / Aziridine	%, Yield
0.5	19 %
1.0	60 %
2.0	90 %

Reduction of **8** with Red-Al gave desoxyeseroline (**3**), which has been previously converted to physostigmine by Fuji and co-workers (Scheme 3).[6d]

Scheme 3



In conclusion, we have reported a new and concise synthetic route to pyrrolo[2,3-*b*]indole by the reaction of 1,3-dimethylindole with activated aziridine in the presence of $Sc(OTf)_3$. Further studies are currently underway to extend the present approach to the construction of optically active physostigmine and a variety of related natural products.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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