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RADICAL CYCLIZATIONS OF ARYL BROMIDES FOR SYNTHESIS OF CYCLOPENTA[*b*]INDOLES FROM VINCE LACTAM

Takumi Abe,* Tsuyoshi Morita, and Koji Yamada

Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan. E-mail; abe-t@hoku-iryo-u.ac.jp

Abstract – Radical cyclizations of aryl bromides, synthesized in two steps from Vince lactam, afforded cyclopenta[*b*]indoles in good yields. Furthermore, an unprecedented method for constructing cyclopenta[*b*]indoles utilizing tricyclic intermediate was also explored.

Cyclopenta[*b*]indole framework is a key structural motif in a series of medicinal natural products and biologically active materials, such as yuehchukene,[1a] paspaline,[1b] sespendole,[1c] and MK-0524[1d] (Figure 1). Therefore, several methodologies have been developed for constructing this attractive heterocycles. Reported protocols involve Fischer indolization,[2] Nazarov cyclization,[3] Heck-Suzuki cascade,[4] Friedel-Crafts reaction,[5] [3 + 2]cycloaddition,[6] [3.3]sigmatropic rearrangement,[7] and Rautenstrauch rearrangement.[8] However, methods to construct cyclopenta[*b*]indole frameworks through a radical cyclization have been scarce.[9] In spite of the great progress that has been disclosed, further exploration of efficient methods for their synthesis are still in great demand.[10]

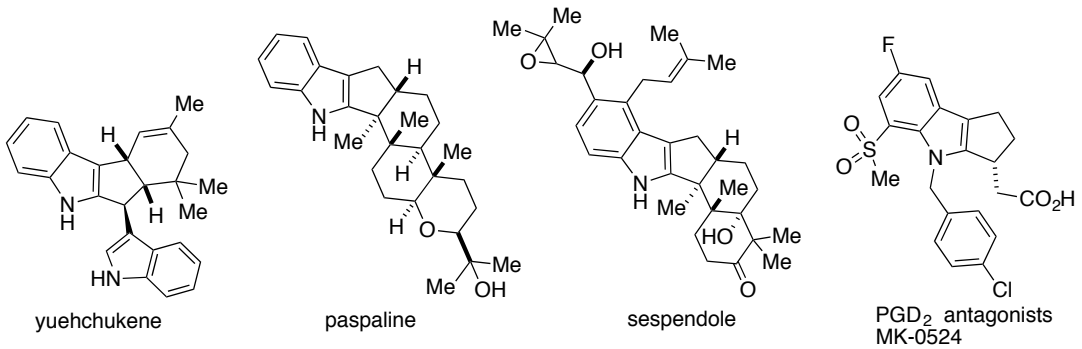
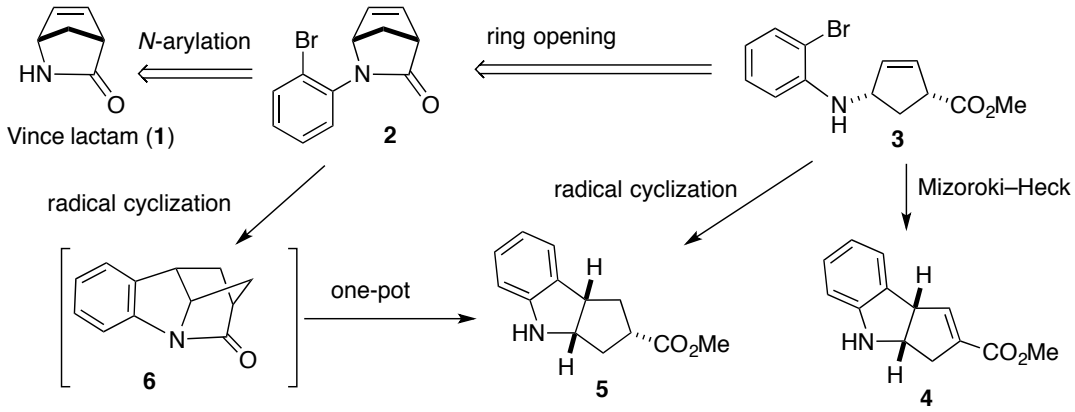


Figure 1. Biologically active compounds with a cyclopenta[*b*]indole framework

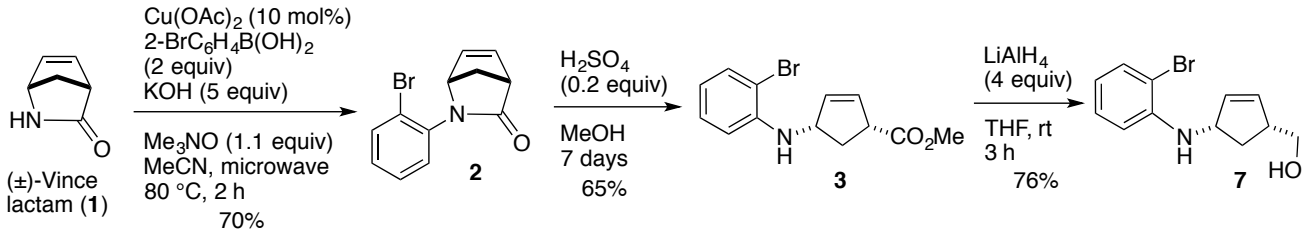
Vince lactam (2-azabicyclo[2.2.1]hept-5-en-3-one) **1** is commercially available and has been utilized as a versatile synthetic intermediates in medicinal chemistry including marketed drugs.[11] In our previous work, we focused on the arylation of Vince lactam to afford *C*- or *N*-arylated Vince lactams.[12] In the arylation

program, we found a procedure for introduction of 2-bromobenzene by *N*-arylation between **1** and 2-bromoiodobenzene under microwave irradiation, which was easily applicable to 20-gram scale synthesis. Using this as a springboard, we explored the construction of cyclopenta[*b*]indoles. Herein, we report a concise synthesis of cyclopenta[*b*]indoles through radical cyclization of aryl bromides, prepared in two steps from Vince lactam.[1]

As part of our synthetic application of **1**[12] and cyclopenta[*b*]indole alkaloid synthesis,[13] we envisioned that β,γ-unsaturated cyclopentene ester **3**, which is readily available from *N*-arylated Vince lactam **2**, could allow Mizoroki–Heck reaction or radical cyclization, to afford cyclopenta[*b*]indole **4** or **5** in a stereoselective manner. We also hoped to occur 5-*exo* cyclization of *N*-arylated Vince lactam **2** via a tetracyclic intermediate **6** leading to cyclopenta[*b*]indole **5** in one-pot operation (Scheme 1).



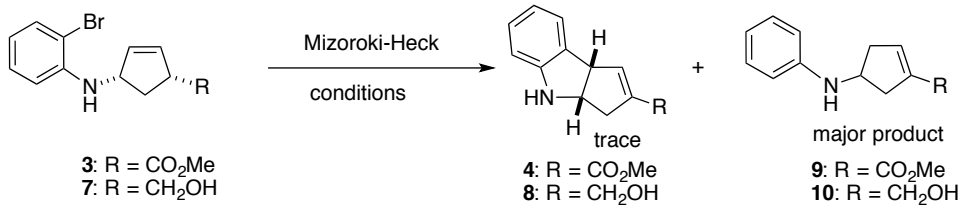
Scheme 1. Our synthetic strategies to cyclopenta[*b*]indoles



Scheme 2. Preparation of arylbromides

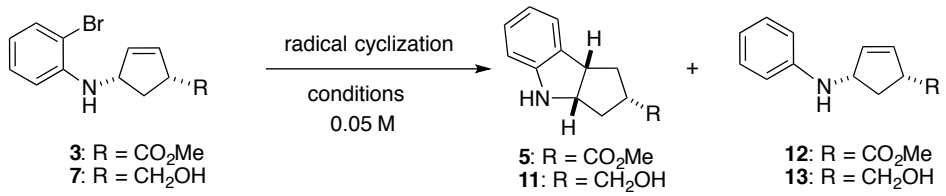
We commenced our studies by preparing aryl bromide **3** via *N*-arylation of (±)-Vince lactam (**1**) followed by ring-opening according to the our previously reported procedures,[12] which took two steps with 46% overall yield (Scheme 2). Subsequent reduction of **3** provided aryl bromide **7** in 76% yield. The *cis*-configuration of **3** and **7** was confirmed by NOE experiment and 2D-NMR techniques.

With aryl bromides **3** and **7** in hand, Mizoroki-Heck reaction was conducted under various conditions (Scheme 3). However, in most cases, the dehalogenated and olefin isomerized byproducts were mainly isolated together with the desired cyclopenta[*b*]indole **4**. This is in agreement with the previously reported olefin isomerization of the rigid cyclic γ-amino acids in the presence of a base.[14]



Scheme 3. Attempts at Mizoroki-Heck reaction

Table 1. Radical cyclization of aryl bromides **3** and **7**



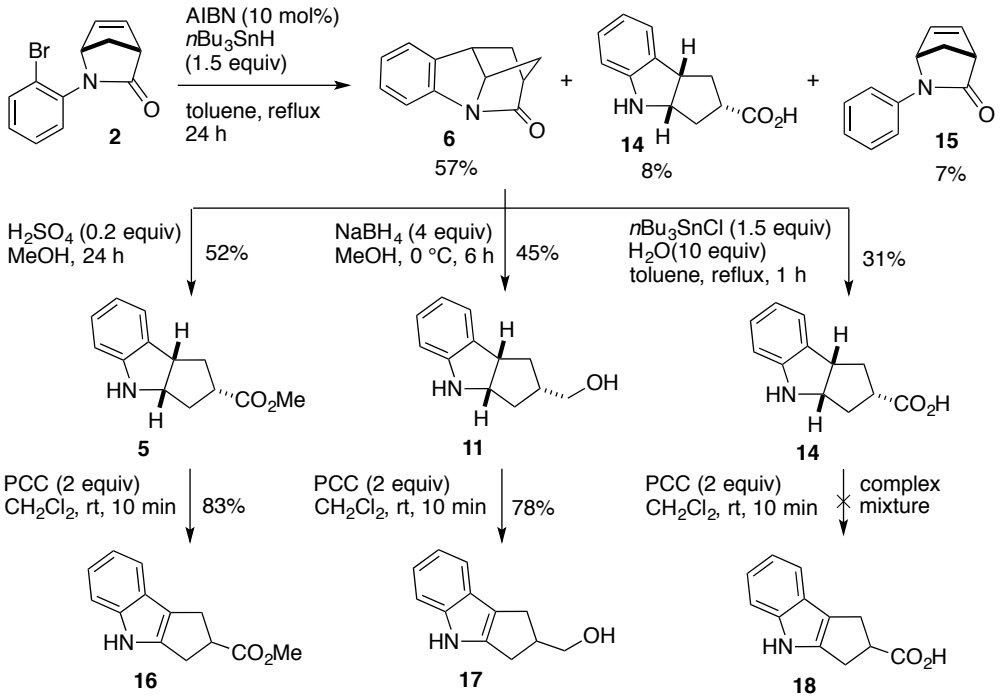
entry	**3** or **7**	conditions	% yields[a] (**5** or **11**)	% yields[a] (**12** or **13**)
1	**3**	AIBN (10 mol%), nBu$_3$SnH (3 equiv), benzene, reflux, 24 h	54 (**5**)	25 (**12**)
2	**3**	AIBN (10 mol%), nBu$_3$SnH (3 equiv, toluene, 85 °C, 24 h	60 (**5**)	23 (**12**)
3	**3**	AIBN (10 mol%), nBu$_3$SnH (3 equiv), toluene, reflux, 18 h	71 (**5**)	14 (**12**)
4	***3***	*AIBN (10 mol%), nBu_3SnH (1.5 equiv), toluene, reflux, 18 h*	*82* (**5**)	*6* (**12**)
5	**3**	AIBN (10 mol%), nBu$_3$SnH (1.5 equiv), toluene (0.5 M), reflux, 18 h	47 (**5**)	24 (**12**)
6	**3**	AIBN (10 mol%), nBu$_3$SnH (1.5 equiv), toluene (0.1 M), reflux, 18 h	70 (**5**)	9 (**12**)
7	**3**	Et$_3$B (10 mol%), nBu$_3$SnH (3 equiv), air, toluene, rt, 10 h	38 (**5**)	40 (**12**)
8	**3**	Et$_3$B (10 mol%), nBu$_3$SnH (3 equiv), O$_2$ (1 atm), toluene, rt, 10 h	57 (**5**)	23 (**12**)
9	**7**	AIBN (10 mol%), nBu$_3$SnH (1.5 equiv), toluene, reflux, 18 h	52 (**11**)	36 (**13**)

[a] Isolated yield.

To overcome this structural limitation, we switched to a radical cyclization in the absence of a base and further investigated to yield cyclopenta[*b*]indole **5** (Table 1). Treatment of **3** with nBu$_3$SnH in presence of a catalytic amount of AIBN in refluxing benzene successfully led to 5-*exo* product **5** as a single diastereomer along with dehalogenated byproduct **12** (entry 1). The stereochemistry of **5** was confirmed by NOE experiment and coupling constants. When the reaction was performed in toluene, the yield of **5** slightly increased up to 71% yield (entries 2 and 3), and the best result was obtained by reducing the amount of nBu$_3$SnH (entry 4). But, the results with subjecting at higher concentration than 0.05 M were less satisfactory due to formation of byproducts from an intermolecular reaction (entries 5 and 6). Lewis acid such as BEt$_3$ was found to be mild radical initiator in combination with nBu$_3$SnH, which promotes radical cyclization at the room temperature.[15] According to the precedents, we performed the reaction of **3** using nBu$_3$SnH in presence of BEt$_3$ under air or O$_2$. Although **5** could be isolated, no improvement was observed (entries 7 and 8). Notably, other aryl bromide **7** also underwent the radical cyclization under the optimized reaction conditions to give the desired 5-*exo* product **11** and byproduct **13** in 52% and 36% yields, respectively (entriy 9). The stereochemistry of **11** was assigned by NOE experiment and coupling

constants.

To broaden the synthetic utility of this strategy, we next turned our attention to feasibility of the radical cyclization of *N*-arylated Vince lactam **2** for the construction of the cyclopenta[*b*]indole frameworks in a one-pot process. As demonstrated in Scheme 4, a variety of cyclopenta[*b*]indole derivatives were synthesized. Upon radical cyclization, **2** afforded small amounts of cyclopenta[*b*]indole **14** along with tricyclic compound **6** and dehalogenated product **15** in 57% and 7% yields, respectively. The stereochemistry of **6** and **14** was confirmed by NOE experiment and coupling constants. Attempts to increase the yield of **14** were unsuccessful because **6** was sensitive to the high temperatures. Remarkably **6** could be subjected to further transformations to yield various cyclopenta[*b*]indole derivatives. Acid-promoted methanolysis of **6** gave cyclopenta[*b*]indole **5** in 52% yield, whereas $NaBH_4$ reduction provided cyclopenta[*b*]indole **11**. Moreover, treatment of **6** with H_2O in the presence of nBu$_3$SnCl afforded cyclopenta[*b*]indole **14**. Subsequents oxidation of **14** with PCC in CH_2Cl_2 resulted in a complex mixture, whereas **5** and **11** could be successfully oxidized into indoles **16** and **17**, respectively. Notably, the corresponding aldehyde did not be obtained in the PCC oxidation of **11**. Thus, this method provides an efficient access to both cyclopentane-fused indolines and indoles, which are valuable building blocks in medicinal chemistry.



Scheme 4. Exploration of synthetic utilities

In conclusion, we have developed a new methodology for the concise synthesis of cyclopenta[*b*]indoles from Vince lactam through *N*-arylation of Vince lactam and radical cyclization of cyclopentenes. Furthermore, an unprecedented method for constructing cyclopenta[*b*]indoles utilizing tricyclic

intermediate was also explored.

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