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

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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]

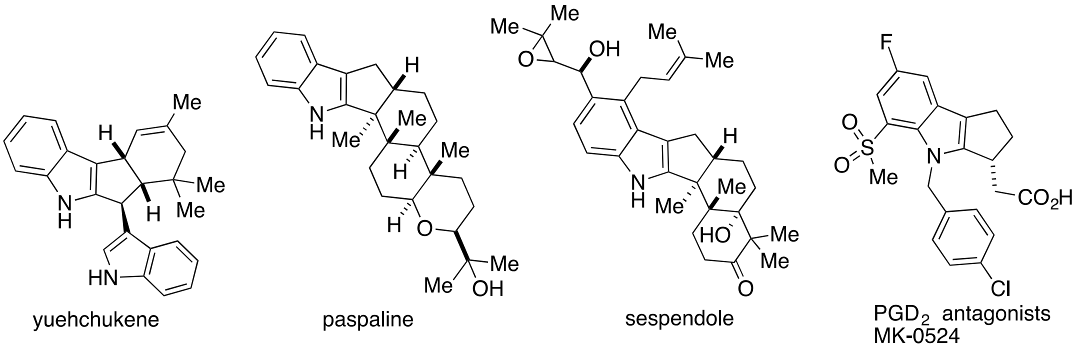
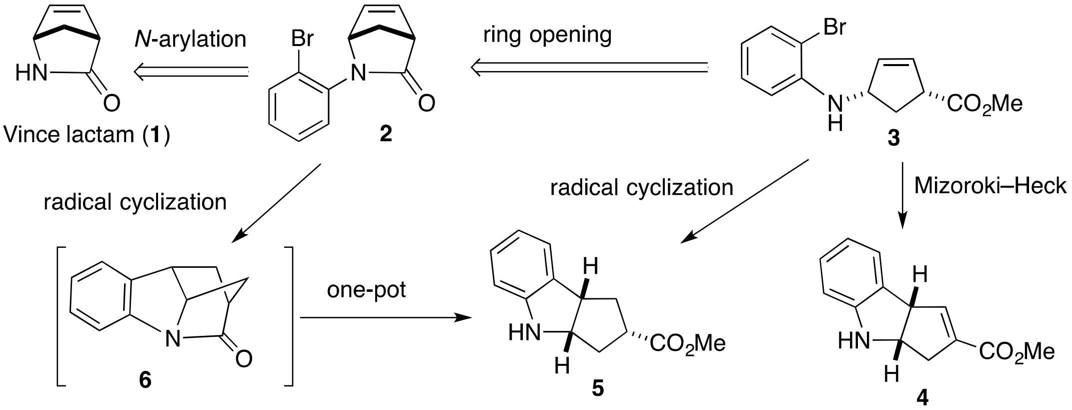


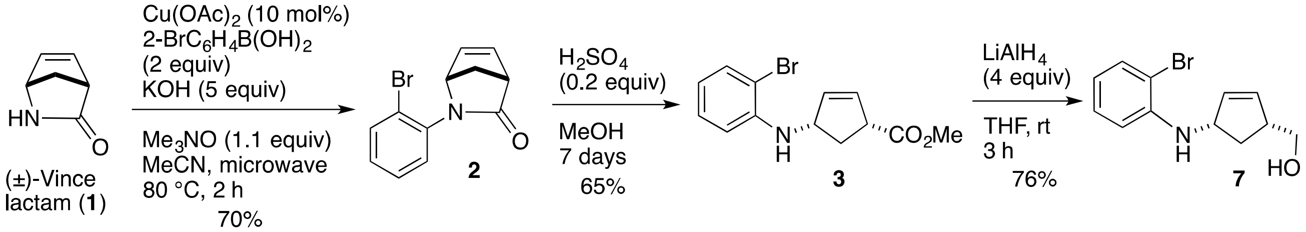
Figure 1. Biologically active compounds with a cyclopenta[*b*]indole framework

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 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 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).



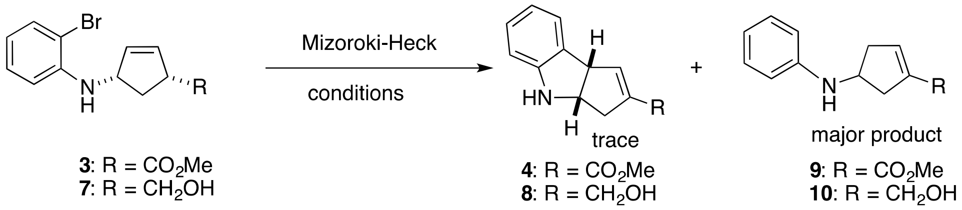
Scheme 1. Our synthetic strategies to cyclopenta[*b*]indoles



Scheme 2. Preparation of arylbromides

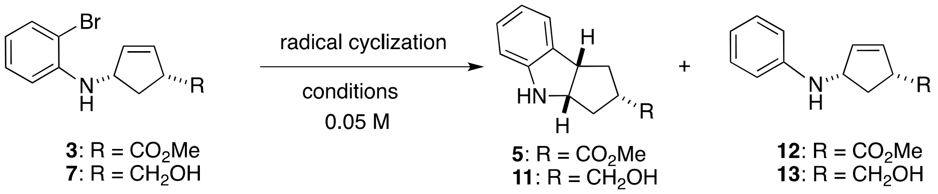
We commenced our studies by preparing aryl bromide **3** via *N*-arylation of (±)-Vince lactam (**1**) followed by ring-opening according to the our previously reported procedures,[12] which took two steps with 46% overall yield (Scheme 2). Subsequent reduction of **3** provided aryl bromide **7** in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

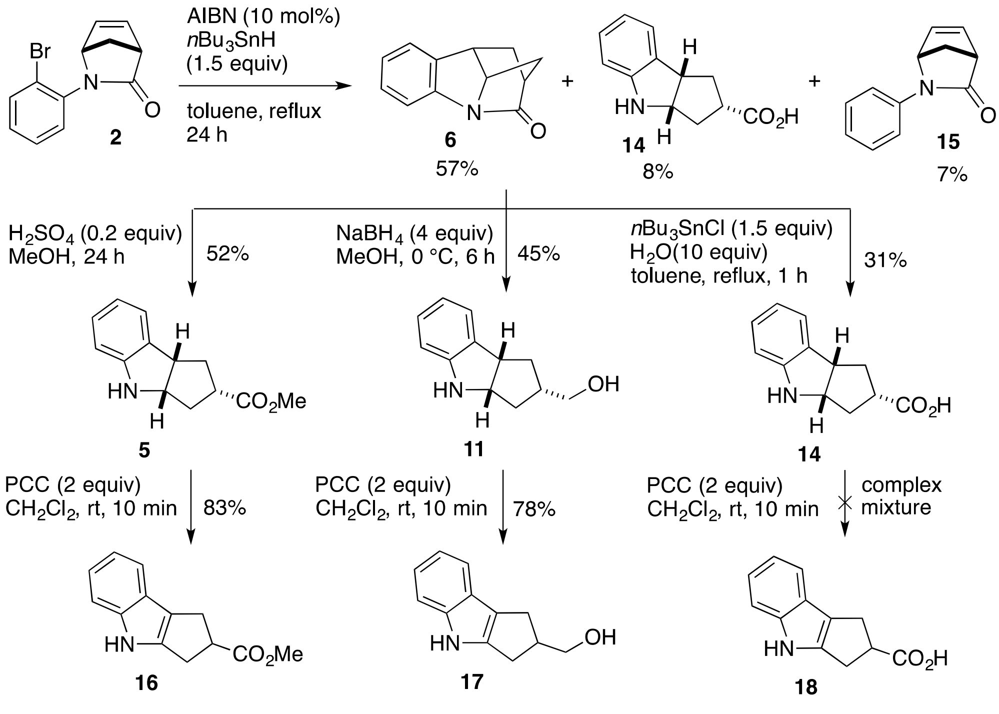


entry	**3** or **7**	conditions	% yields[a] (**5** or **11**)	 (**12** or **13**)
1	**3**	AIBN (10 mol%), *n*Bu$_3$SnH (3 equiv), benzene, reflux, 24 h	54 (**5**)	25 (**12**)
2	**3**	AIBN (10 mol%), *n*Bu$_3$SnH (3 equiv, toluene, 85 °C, 24 h	60 (**5**)	23 (**12**)
3	**3**	AIBN (10 mol%), *n*Bu$_3$SnH (3 equiv), toluene, reflux, 18 h	71 (**5**)	14 (**12**)
4	**3**	*AIBN (10 mol%), nBu$_3$SnH (1.5 equiv), toluene, reflux, 18 h*	*82* (**5**)	*6* (**12**)
5	**3**	AIBN (10 mol%), *n*Bu$_3$SnH (1.5 equiv), toluene (0.5 M), reflux, 18 h	47 (**5**)	24 (**12**)
6	**3**	AIBN (10 mol%), *n*Bu$_3$SnH (1.5 equiv), toluene (0.1 M), reflux, 18 h	70 (**5**)	9 (**12**)
7	**3**	Et$_3$B (10 mol%), *n*Bu$_3$SnH (3 equiv), air, toluene, rt, 10 h	38 (**5**)	40 (**12**)
8	**3**	Et$_3$B (10 mol%), *n*Bu$_3$SnH (3 equiv), O$_2$ (1 atm), toluene, rt, 10 h	57 (**5**)	23 (**12**)
9	**7**	AIBN (10 mol%), *n*Bu$_3$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 *n*Bu$_3$SnH in presence of catalytic amount of AIBN in refluxing benzene successfully led to 5-*exo* product **5** as a single 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 *n*Bu$_3$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 *n*Bu$_3$SnH, which promotes radical cyclization at the room temperature.[15] According to the precedents, we performed the reaction of **3** using *n*Bu$_3$SnH in presence of BEt$_3$ under air or O$_2$. Although **5** could be isolated, no improvement was (entries 7 and 8). Notably, other aryl bromide **7** also underwent the radical cyclization under the 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$_2$O in the presence of nBu$_3$SnCl afforded cyclopenta[*b*]indole **14**. Subsequents oxidation of **14** with PCC in CH$_2$Cl$_2$ 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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REFERENCES

1. a) Y.-C. Kong, K.-F. Cheng, R. C. Cambie, and P. G. Waterman, *J. Chem. Soc., Chem. Commun.*, 1985, 47; b) T. Fehr and W. Acklin, *Helv. Chim. Acta*, 1966, **49**, 1907; c) R. Uchida, Y.-P. Kim, I. Namatame, H. Tomoda, and S. Omura, *J. Antibiot.*, 2006, **59**, 93; d) C. F. Sturino, G. O'Neill, N. Lachance, M. Boyd, C. Berthelette, M. Labelle, L. Li, B. Roy, J. Scheigetz, N. Tsou, Y. Aubin, K. P. Bateman, N. Chauret, S. H. Day, J.-F. Lévesque, C. Seto, J. H. Silva, L. A. Trimble, M.-C. Carriere, D. Denis, G. Greig, S. Kargman, S. Lamontagne, M.-C. Mathieu, N. Sawyer, D. Slipetz, W. M. Abraham, T. Jones, M. McAuliffe, H. Piechuta, D. A. Nicoll-Griffith, Z. Wang, R. Zamboni, R. Young, and K. M. Metters, *J. Med. Chem.*, 2007, **50**, 794.
2. a) B. A. Haag, Z.-G. Zhang, J.-S. Li, and P. Knochel, *Angew. Chem. Int. Ed.*, 2010, **49**, 9513; b) A. G. K. Reddy and G. Satyanarayana, *Synthesis*, 2015, **47**, 1269.
3. a) J. A. Malona, J. M. Colbourne, and A. J. Frontier, *Org. Lett.*, 2006, **8**, 5661; b) N. S. Sheikh, *Org. Biomol. Chem.*, 2015, **13**, 10774.
4. A. Ekebergh, I. Karlsson, R. Mete, Y. Pan, A. Börje, and J. Mårtensson, *Org. Lett.*, 2011, **13**, 4458.
5. a) B. Xu, Z.-L. Guo, W.-Y. Jin, Z.-P. Wang, Y.-G. Peng, and Q.-X. Guo, *Angew. Chem. Int. Ed.*, **51**, 1059; b) T. Yokosawa, H. Nakayama, T. Nemoto, and Y. Hamada, *Org. Lett.*, 2013, **15**, 2978; c) Dhiman and S. S. V. Ramasastry, *Chem. Commun.*, 2015, **51**, 557; d) M. S. Santos, D. C. Fernandes, M. T. Rodrigues Jr., T. Regiani, A. D. Andricopulo, A. L. T. G. Ruiz, D. B. Vendramini-Costa, J. E. Carvalho, M. N. Eberlin, and F. Coelho, *J. Org. Chem.*, 2016, **81**, 6626.
6. a) H. Li, R. P. Hughes, and J. Wu, *J. Am. Chem. Soc.*, 2014, **136**, 6288; b) W. Tan, X. Li, Y.-X. M. D. Ge, and F. Shi, *Chem. Commun.*, 2014, **50**, 15901; c) J. Liu, M. Chen, L. Zhang, and Y. Liu, *Chem. Eur. J.*, 2015, **21**, 1009.
7. O. Miyata, Y. Kimura, and T. Naito, *Chem. Commun.*, 1999, 2429.
8. W. Zi, H. Wu, and F. D. Toste, *J. Am. Chem. Soc.*, 2015, **137**, 3225.
9. a) W. Zhang, *Tetrahedron*, 2001, **57**, 7237; b) H. Yi, G. Zhang, H. Wang, Z. Huang, J. Wang, A. K. Singh, and A. Lei, *Chem. Rev.*, 2017, **117**, 9016; c) S. Bommezijin, C. G. Martin, A. R. Kennedy, D. Lizos, and J. A. Murphy, *Org. Lett.*, 2001, **3**, 3405; d) S. J. Gharpure, P. Niranjana, and S. K. Porwal, *Org. Lett.*, 2012, **14**, 5476.
10. C. Jing, Q.-Q. Cheng, Y. Deng, H. Arman, and M. P. Doyle, *Org. Lett.*, 2016, **18**, 4550.

11. R. Singh and R. Vince, *Chem. Rev.*, 2012, **112**, 4642.
12. a) H. Abe and T. Harayama, *Heterocycles*, 2008, **75**, 2931; b) T. Abe, H. Takeda, K. Yamada, and M. Ishikura, *Heterocycles*, 2008, **76**, 133; c) T. Abe, H. Takeda, Y. Takahashi, Y. Miwa, K. Yamada, M. Ishikura, *Eur. J. Org. Chem.*, 2010, 3281.
13. T. Abe, H. Komatsu, T. Ikeda, N. Hatae, E. Toyota, and M. Ishikura, *Heterocycles*, 2012, **86**, 505.
14. A. Wetzel, J. Bergman, P. Brandt, M. Larhed, and J. Brånalt, *Org. Lett.*, 2017, **19**, 1602.
15. a) K. Nozaki, K. Ohshima, and K. Uchimoto, *J. Am. Chem. Soc.*, 1987, **109**, 2547; b) M. Inoue, T. and M. Hirama, *J. Am. Chem. Soc.*, 2003, **125**, 10772; c) C. Olliver and P. Renaud, *Chem. Rev.*, 2001, **101**, 3415.