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Synthesis of substituted 3-iodopyrroles by electrophilic cyclization of propargylic aziridines

Masahiro Yoshida *, Mohammad Al-Amin, Kozo Shishido

Graduate School of Pharmaceutical Sciences, The University of Tokushima, 1-78-1 Sho-machi, Tokushima 770-8505, Japan

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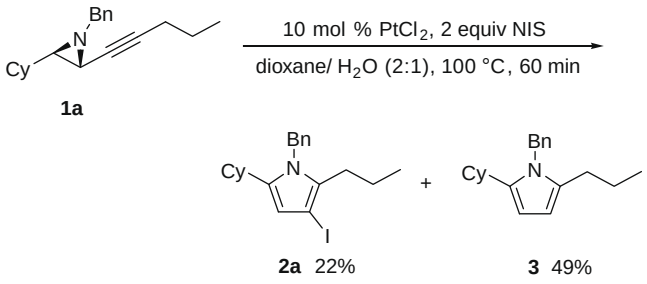
ABSTRACT

The electrophilic cyclization of propargylic aziridines is described. 3-Iodopyrroles having a variety of substituents were conveniently synthesized by the reaction of propargylic aziridines with iodine. The resulting substituted 3-iodopyrrole was further functionalized to the tri-substituted pyrroles with high efficiency.

Substituted pyrroles are an important class of heteroaromatic molecules which are components in a variety of biologically active natural products and industrially useful compounds.[1] They are also extensively utilized as synthetic intermediates for heterocyclic compounds in organic synthesis.[2] For these reasons, considerable effort has been devoted toward finding an efficient synthesis of substituted pyrroles.[3] Among them, transition metal-catalyzed cycloisomerization of propargylic aziridines is one of the useful methodologies for the synthesis of substituted pyrroles. Recently, the example about the gold-catalyzed synthesis of pyrroles has been reported independently by Davies[4] and Hou.[5] We have also found that platinum acts as a catalyst for the cycloisomerization of propargylic aziridines.[6] On the other hand, electrophile-promoted cyclization is a useful methodology for the synthesis of a wide range of halogenated heterocyclic compounds.[7] However, to the best of our knowledge, there is no focusing on the electrophilic conversion of propargylic aziridines to pyrroles. We report herein about an iodine-promoted electrophilic cyclization of propargylic aziridines, in which various substituted 3-iodopyrroles can be synthesized with high efficiency.

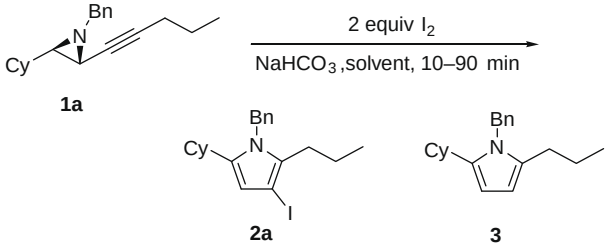
We initially examined the reaction of propargylic aziridine **1a** under the platinum-catalyzed iodocyclization condition.[6,8] When **1a** was treated with 10 mol % of $PtCl_2$ and 2 equiv NIS in dioxane/H_2O (2/1) at 100 °C for 60 min, the desired 3-iodopyrrole **2a** was produced in 22% yield along with non-iodinated pyrrole **3** as the inseparable major product in 49% yield (Scheme 1).

We next attempted the electrophilic activation of propargylic aziridines, in which the similar process could proceed in the reaction of **1a** with iodine (Table 1).[9] Although no reaction proceeded when **1a** was treated with 2 equiv of iodine and 2 equiv of $NaHCO_3$ in THF at rt (entry 1),[7r] the desired product **2a** was obtained in 43% yield under the reflux condition in THF (entry 2). The yield was improved to 64% when the reaction was carried out in dioxane at 100 °C (entry 3). Although non-iodinated pyrrole **3** was byproduced in 28% yield in this reaction condition,[10] it has been made



Scheme 1. Platinum-catalyzed iodocyclization of propargylic aziridine **1a**.

Table 1
Electrophilic iodoyclizations of **1a**



Entry	Solvent	$NaHCO_3$ (equiv)	Temp (°C)	Yields (%)	
				2a	**3**
1	THF	2	rt	N.R.	
2	THF	2	Reflux	43	—
3	Dioxane	2	100	64	28
4	Dioxane	5	100	90	—

* Corresponding author. Tel./fax: +81 88 633 7294.
E-mail address: yoshida@ph.tokushima-u.ac.jp (M. Yoshida).

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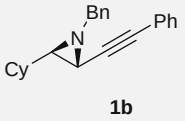
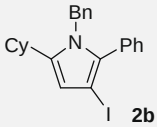
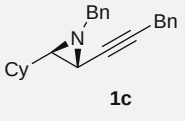
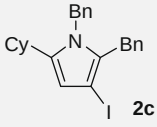
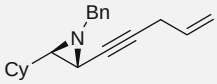
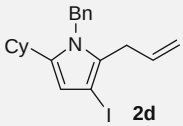
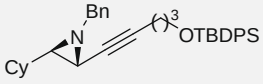
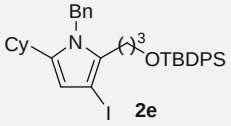
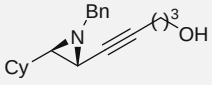
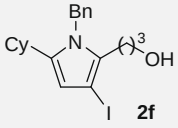
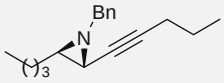
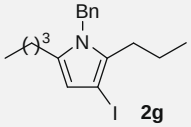
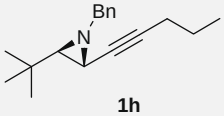
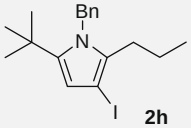
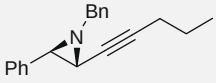
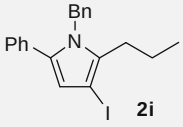
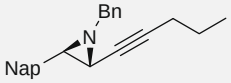
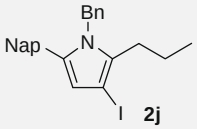
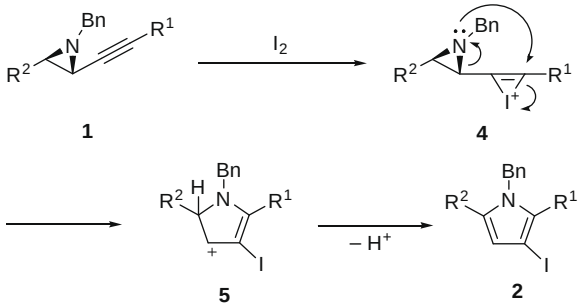
Table 2
Reactions with propargylic aziridines **1b**–**1j**[a]

Entry	Substrate	Product	Yield (%)
1	 **1b**	 **2b**	90
2	 **1c**	 **2c**	79
3	 **1d**	 **2d**	86
4	 **1e**	 **2e**	86
5	 **1f**	 **2f**	76
6	 **1g**	 **2g**	94
7	 **1h**	 **2h**	95
8	 **1i**	 **2i**	95
9[b]	 **1j**	 **2j**	68

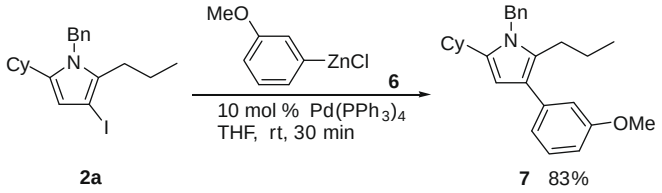
[a] All reactions were carried out in the presence of 2 equiv iodine and 5 equiv $NaHCO_3$ in dioxane at 100 °C for 10 min.
[b] Nap = 2-naphthyl.

clear that **2a** was obtained in 90% yield as a sole product when 5 equiv of $NaHCO_3$ was used (entry 4).

The reactions of various substituted propargylic aziridines **1b**–**1j** are summarized in Table 2. When the substrates **1b**–**1e** having, respectively, a phenyl, benzyl, allyl, and siloxypropyl group at the alkynyl position were subjected to the electrophilic cyclizations,



Scheme 2. Proposed reaction mechanism.



Scheme 3. Negishi coupling reaction of 3-iodopyrrole **2a** with arylzinc reagent **6**.

the corresponding products **2b**–**2e** were produced in good yields (entries 1–4). The propargylic aziridine containing a free hydroxyl group, **1f**, was uneventfully transformed to the 3-iodopyrrole **1f** in 76% yield (entry 5). The reactions of the substrates **1g** and **1h**, which contain butyl and *t*-butyl groups on the aziridine ring, successfully afforded the 3-iodopyrroles **2g** and **2h** in 94% and 95% yield, respectively (entries 6 and 7). The phenyl- and 2-naphthyl-substituted substrates **1i** and **1j** were also converted to the corresponding products **2i** and **2j** in 95% and 68% yield, respectively (entries 8 and 9).

A plausible mechanism for the iodine-promoted cyclization of propargylic aziridines **1** is shown in Scheme 2. Coordination of the propargylic triple bond to an iodine cation forms the cyclic iodonium ion **4**. Subsequent attack of the aziridine nitrogen on the iodonium ion produces the cyclized intermediate **5**, which causes aromatization by elimination of the proton leading to the 3-iodopyrrole **2**.

The presence of the iodo functional group on the pyrrole ring provided an opportunity for further functionalization. To introduce an aryl group by the coupling reaction, we next investigated the Negishi coupling reaction of the resulting compound **2a**.[11] When **2a** was treated with arylzinc reagent **6** in the presence of 10 mol % $Pd(PPh_3)_4$ in THF at rt, the corresponding tri-substituted pyrrole **7** was obtained in 83% yield (Scheme 3).

In conclusion, we have developed a methodology for the synthesis of 3-iodopyrroles by an iodine-promoted electrophilic cyclization. The reaction afforded a variety of substituted 3-iodopyrroles, and the process provided an efficient and convenient protocol for the preparation of these derivatives.

Acknowledgments

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References and notes

1. (a) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264; (b) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213.

2. (a) Patterson, J. M. *Synthesis* **1976**, 281; (b) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795; (c) Schroeter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245.
3. (a) Trofimov, B. A.; Mikhaleva, A. I. *Heterocycles* **1994**, *37*, 1193; (b) Balme, G.; Bouyssi, D.; Monteiro, N. *Heterocycles* **2007**, *73*, 87; (c) Patil, N. T.; Yamamoto, Y. *ARKIVOC* **2007**, 121; (d) Schmuck, C.; Rupprecht, D. *Synthesis* **2007**, 3095; (e) Ono, N. *Heterocycles* **2008**, *75*, 243.
4. Davies, P. W.; Martin, N. *Org. Lett.* **2009**, *11*, 2293.
5. Chen, D.-D.; Hou, X-L.; Dai, L.-X. *Tetrahedron Lett.* in press. doi:10.1016/j.tetlet.2009.05.091.
6. Yoshida, M.; Al-Amin, M.; Shishido, K. *Synthesis* **2009**, 2454.
7. For selected examples, see: (a) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *3*, 651; (b) Huang, Q.; Hunter, J. A.; Larock, R. C. *Org. Lett.* **2001**, *3*, 2973; (c) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905; (d) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437; (e) Arcadi, A.; Cacchi, S.; Giuseppe, S. D.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, *4*, 2409; (f) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936; (g) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2003**, *5*, 4377; (h) Peng, A. Y.; Ding, Y. X. *Org. Lett.* **2004**, *6*, 1119; (i) Yao, T.; Campo, M. A.; Larock, R. C. *Org. Lett.* **2004**, *6*, 2677; (j) Yue, D.; Della, C. N.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1581; (k) Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 1432; (l) Barluenga, J.; Trincado, M.; Marco-Arias, M.; Ballesteros, A.; Rubio, E.; Gonzalez, J. M. *Chem. Commun.* **2005**, 2008; (m) Sniady, A.; Wheeler, K. A.; Dembinski, R. *Org. Lett.* **2005**, *7*, 1769; (n) Liu, Y.-H.; Song, F.-J.; Cong, L. Q. *J. Org. Chem.* **2005**, *70*, 6999; (o) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292; (p) Bi, H.-P.; Guo, L.-N.; Duan, X.-H.; Gou, F.-R.; Huang, S.-H.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2007**, *9*, 397; (q) Fischer, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4764; (r) Xie, Y.-X.; Liu, X.-Y.; Wu, L.-Y.; Han, Y.; Zhao, L.-B.; Fan, M.-J.; Liang, Y.-M. *Eur. J. Org. Chem.* **2008**, 1013; (s) Cherry, K.; Duchêne, A.; Thibonnet, J.; Parrain, J.-L.; Anselmi, E.; Abarbi, M. *Synthesis* **2009**, 257; (t) Ding, Q.; Chen, Z.; Yu, X.; Peng, Y.; Wu, J. *Tetrahedron Lett.* **2009**, *50*, 340.
8. Yoshida, M.; Al-Amin, M.; Matsuda, K.; Shishido, K. *Tetrahedron Lett.* **2008**, *49*, 5021.
9. *General procedure for iodine-promoted electrophilic cyclizations:* to a stirred solution of propargylic aziridine **1a** (200 mg, 0.711 mmol) in dioxane (20.0 mL) were gradually added iodine (360.7 mg, 1.42 mmol) and $NaHCO_3$ (298.7 mg, 3.56 mmol) at rt. After stirring for 10 min at 100 °C, the reaction mixture was cooled to rt and the excess iodine was removed by washing with a saturated aqueous solution of $Na_2S_2O_3$. The aqueous solution was then extracted with Et_2O and the combined organic layers were dried over $MgSO_4$. Concentration at reduced pressure gave the residue, which was purified by flash chromatography using hexane–AcOEt (98:2) as the eluent to give the 3-iodopyrrole **2a** (260.6 mg, 90%) as a colorless oil. Compound **2a**: IR (neat) 3087, 3063, 3028, 2927, 2851, 1605, 1545, 1496, 1453, 1415, 1373 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30−7.21 (3H, m), 6.84 (2H, d, J = 7.6 Hz), 6.02 (1H, s), 5.08 (2H, s), 2.44 (2H, t, J = 7.6 Hz), 2.28 (1H, tt, J = 11.2 and 3.2 Hz), 1.78−1.64 (5H, m), 1.41−1.18 (7H, m), 0.86 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.53, 138.67, 133.21, 128.70, 127.17, 125.43, 110.51, 61.64, 47.45, 35.89, 33.98, 28.92, 26.59, 26.00, 23.21, 13.91; HRMS (ESI) m/z calcd for $C_{20}H_{26}NNaI$ (M^++Na) 430.1008, found 430.1010.
10. For this reason, the co-produced hydrogen iodide would catalyze the cycloisomerization of **1a** to non-iodinated pyrrole **3**. By the use of 5 equiv of $NaHCO_3$, it is expected that the acidity of hydrogen iodide was efficiently neutralized to lead predominant production of **2a**.
11. (a) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340; (b) Erdik, E. *Tetrahedron* **1992**, *48*, 9577.