

Synthesis of 2,5-Disubstituted 6-Azaindoles from Substituted Aziridines via Intramolecular Cyclization

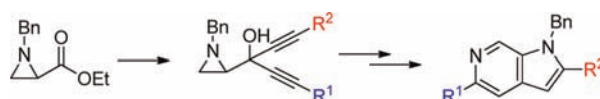
Hogyu Lee,[†] Jun Hee Kim,[†] Won Koo Lee,^{*†} Jae-Hoon Jung,[‡] and Hyun-Joon Ha^{*‡}

Department of Chemistry, Sogang University, Seoul 121-742, Korea, and Department of Chemistry, Hankuk University of Foreign Studies, Yongin 449-791, Korea

wonkoo@sogang.ac.kr; hjha@hufs.ac.kr

Received May 1, 2012

ABSTRACT



A new and efficient preparation of pharmacologically and biologically important 2,5-disubstituted 6-azaindoles was achieved from cyclizations of aziridine-2-yl dipropargylic alcohols as adducts of two propargyl groups to ethyl 1-benzylaziridine-2-carboxylate. The sequential cyclizations include pyrrole formation and a novel base-catalyzed intramolecular acetylenic Schmidt reaction.

Azaindoles structural units are found in natural marine products, and the importance of their derivatives is reflected in biologically active compounds as indole isosteres.¹ Several strategies for azaindoles synthesis have been reported by Reissert, Batcho-Leimgrube, Hemetsberger-Knitel, and Bartoli.² However, these methods need improvement in terms of long reaction times, harsh reaction conditions, and low yields. Yet, recently better preparatory methods have come to light such as the Aza-Fischer reaction;² transition metal catalyzed cyclizations⁴ using Pd, Ru, Zr, Ti, and Cu; and a dilithiation pathway.⁵ However, previous synthetic methods cannot provide functionalized 6-azaindoles in high yields.

Compounds containing 6-azaindoles show pharmacological activity^{1,6} as HIV-1 inhibitors and have a characteristic photophysical property.⁷ The synthetic routes for these compounds are limited. Most azaindoles syntheses start from substituted pyridines to form a pyrrole unit.^{3–5,8} Here, we would like to propose a new efficient synthetic route for the 2,5-substituted 6-azaindoles using an intramolecular pyrrole formation followed by a pyridine ring formation via an intramolecular azide cyclization reaction into the acetylenic unit.

We recently reported an efficient synthesis of 1,2,3,5-substituted pyrroles from *N*-benzylaziridine-2-carboxylate (**1**),⁹ which is a readily available starting material. The ester **1** was reacted with 2 equiv of various lithium acetylides to

[†] Sogang University.

[‡] Hankuk University of Foreign Studies.

(1) Badarau, E.; Putey, A.; Suzenet, F.; Joseph, B.; Bojarski, A.; Finaru, A.; Guillaumet, G. *J. Enzyme Inhib. Med. Chem.* **2010**, *25*, 301–305.

(2) (a) Popowycz, F.; Mérour, J.-Y.; Joseph, B. *Tetrahedron* **2007**, *63*, 8689–8707. (b) Song, J. J.; Reeves, J. T.; Gallou, F.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *Chem. Soc. Rev.* **2007**, *36*, 1120.

(3) Jeanty, M.; Blu, J.; Suzenet, F.; Guillaumet, G. R. *Org. Lett.* **2009**, *11*, 5142–5145.

(4) (a) McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3307–3310. (b) Huo, Z.; Yamamoto, Y. *Tetrahedron Lett.* **2009**, *50*, 3651–3653. (c) Xu, L.; Lewis, I. R.; Davidsen, S. K.; Summers, J. B. *Tetrahedron Lett.* **1998**, *39*, 5159–5162. (d) Fang, Y.-Q.; Yuen, J.; Lautens, M. J. *Org. Chem.* **2007**, *72*, 5152–5160.

(5) Song, J. J.; Tan, Z.; Gallou, F.; Xu, J.; Yee, N. K.; Senanayake, C. H. *J. Org. Chem.* **2005**, *70*, 6512–6514.

(6) (a) Plewe, M. B.; Butler, S. L.; R. Dress, K.; Hu, Q.; Johnson, T. W.; Kuehler, J. E.; Kuki, A.; Lam, H.; Liu, W.; Nowlin, D.; Peng, Q.; Rahavendran, S. V.; Tanis, S. P.; Tran, K. T.; Wang, H.; Yang, A.; Zhang, J. *J. Med. Chem.* **2009**, *52*, 7211–7219. (b) Wang, T.; Yin, Z.; Zhang, Z.; Bender, J. A.; Yang, Z.; Johnson, G.; Yang, Z.; Zadjura, L. M.; D'Arienzo, C. J.; DiGiugno Parker, D.; Gesenberg, C.; Yamanaoka, G. A.; Gong, Y.-F.; Ho, H.-T.; Fang, H.; Zhou, N.; McAuliffe, B. V.; Eggers, B. J.; Fan, L.; Nowicka-Sans, B.; Dicker, I. B.; Gao, Q.; Colonna, R. J.; Lin, P.-F.; Meanwell, N. A.; Kadow, J. F. *J. Med. Chem.* **2009**, *52*, 7778–7787.

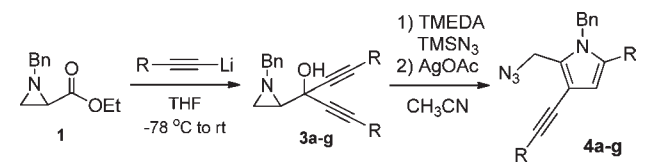
(7) Twine, S. M.; Murphy, L.; Phillips, R. S.; Callis, P.; Cash, M. T.; Szabo, A. G. *J. Phys. Chem. B* **2002**, *107*, 637–645.

(8) (a) Whelligan, D. K.; Thomson, D. W.; Taylor, D.; Hoelder, S. J. *J. Org. Chem.* **2010**, *75*, 11–15. (b) Debenham, S. D.; Chan, A.; Liu, K.; Price, K.; Wood, H. B. *Tetrahedron Lett.* **2005**, *46*, 2283–2285.

(9) Kim, J. H.; Lee, S. B.; Lee, W. K.; Yoon, D.-H.; Ha, H.-J. *Tetrahedron* **2011**, *67*, 3553–3558.

provide the corresponding dipropargylic alcohols **3** in high yields. This time we were able to prepare 1,2,3,5-substituted pyrroles which have a 2-azidomethyl substituent and various acetylenic substituents at the C-3 position *via* regioselective aziridine ring opening¹⁰ by TMSN₃, followed by silver ion catalyzed intramolecular cyclization (Scheme 1 and Table 1).

Table 1. Preparation of Substituted Pyrrole **4**



entry	R	yield of 3 (%)	yield of 4 (%)
1	phenyl	3a , 98	4a , 92 ^a
2	4-methoxyphenyl	3b , 84	4b , 89 ^a
3	2-tolyl	3c , 85	4c , 92 ^a
4	4-fluorophenyl	3d , 94	4d , 95 ^a
5	pyridin-2-yl	3e , 91	4e , 80 ^b
6	6-methoxynaphthalen-2-yl	3f , 91	4f , 91 ^a
7	phenanthren-9-yl	3g , 76	— ^c

^a The reaction was carried out in CH₃CN. ^b The reaction was carried out in DCM. ^c The reaction was carried out in DCM/CH₃CN. Not isolated.

With the 2-azidomethyl-substituted pyrroles, we carried out intramolecular acetylenic Schmidt reactions¹¹ for the synthesis of azaindoles in various reaction conditions. Unlike usual indolization reactions in the presence of a pyrrole ring, pyrrole-fused pyridine cyclization methods to provide azaindoles are rare¹² and introducing various substituents in the azaindole ring is another challenging task.

In the reactions of modified intramolecular azido, cyclization provides 6-azaindoles in high yield without using metal catalysts (Table 2).¹³ When the reaction was carried out without a base in DMSO and toluene, we could not obtain any product (entries 1 and 3). But in DMF we obtained the expected 6-azaindole in 18% yield (entry 2). However, when we added a hydroxide base (KOH), the cyclization reaction proceeded smoothly to provide the corresponding azaindole (entries 4 and 5). After nitrogen cyclization to the acetylenic unit, the deprotonation followed by N₂ elimination seemed to be the driving force to form 2,5-substituted 6-azaindoles in both DMSO (49%) and DMF (87%).

(10) Stankovic, S.; D'hooghe, M.; Catak, S.; Eum, H.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N.; Ha, H.-J. *J. Chem. Soc. Rev.* **2012**, *41*, 643–665.

(11) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260–11261.

(12) (a) Huo, Z.; Yamamoto, Y. *Tetrahedron Lett.* **2009**, *50*, 3651–3653. (b) Dekhane, M.; Potier, P.; Dodd, R. H. *Tetrahedron* **1993**, *49*, 8139–8146. (c) Mahadevan, I.; Rasmussen, M. *J. Heterocycl. Chem.* **1992**, *29*, 359–367.

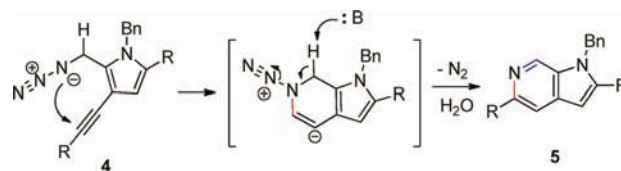
(13) (a) Niu, Y.-N.; Yan, Z.-Y.; Gao, G.-L.; Wang, H.-L.; Shu, X.-Z.; Ji, K.-G.; Liang, Y.-M. *J. Org. Chem.* **2009**, *74*, 2893–2896. (b) Huo, Z.; Yamamoto, Y. *Tetrahedron Lett.* **2009**, *50*, 3651–3653.

Table 2. Formation of 2,5-Diphenyl-6-azaindole

entry	base (equiv)	solvent	temp (°C)	time (h)	yield (%)
1	—	toluene	140	48	failed
2	—	DMF	140	8	18
3	—	DMSO	140	12	failed
4	KOH (5)	DMSO	140	18	49
5	KOH (5)	DMF	140	6	87

The mechanism of this modified intramolecular azido cyclization of 2-azidomethyl-substituted pyrroles **4** with a hydroxide base to form 6-azaindoles **5** is proposed with the intramolecular base-catalyzed Schmidt cyclization shown in Scheme 1. The anionic nitrogen of the azide attacks the acetylene to form a six-membered ring, and then deprotonation of the benzylic proton by the hydroxide base releases nitrogen gas to promote aromatization. As far as we know, this is the first example of 6-endo intramolecular acetylenic Schmidt cyclization that is free from any metal catalyst.¹⁴

Scheme 1. Proposed Mechanism of 6-Azaindoles Formation



This synthetic method was used to introduce various substituents on the 2- and 5-positions of 6-azaindoles. The cyclization reactions provided 6-azaindoles with diverse aryl groups bearing electron donors, electron acceptors, and bulky substituents. In all cases, intramolecular cyclization was succeeded to provide 6-azaindoles **5a–5g** in high yields of 74–87% (Table 3).

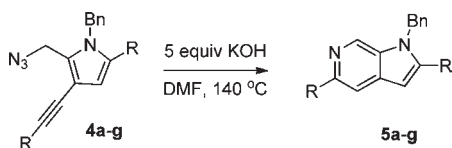
We also prepared 6-azaindoles which have different substituents on the 2- and 5-positions from heterosubstituted bispropargylic alcohols **3h**, **3i**, and **3j** synthesized by two successive alkylation processes using different acetylene reagents.

Low temperature alkynylations provided the corresponding ketones **2** in good yields. Subsequent addition of one more alkyne afforded tertiary bispropargylic alcohols **3h**, **3i**, and **3j** with two different substituents R¹ and R² (Table 4).

When pyrrole cyclization was carried out with the tertiary alcohols containing two different acetylenic

(14) The intramolecular acetylenic Schmidt cyclization was first reported in ref 11, which was a gold(II)-catalyzed 5-*exo* process.

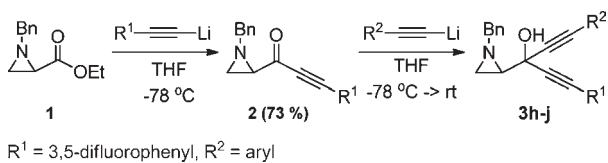
Table 3. Preparation of 2,5-Disubstituted 6-Azaindoles (**5**) from Pyrroles (**4**)



entry	R	yield of 5 (%)
1	phenyl	5a , 87
2	4-methoxyphenyl	5b , 84
3	2-tolyl	5c , 74
4	4-fluorophenyl	5d , 84
5	pyridin-2-yl	5e , 75
6	6-methoxynaphthalen-2-yl	5f , 78
7	phenanthren-9-yl	5g , 76 ^a

^a Three-step yield.

Table 4. Preparation of Bispropargylic Alcohols



R¹ = 3,5-difluorophenyl, R² = aryl

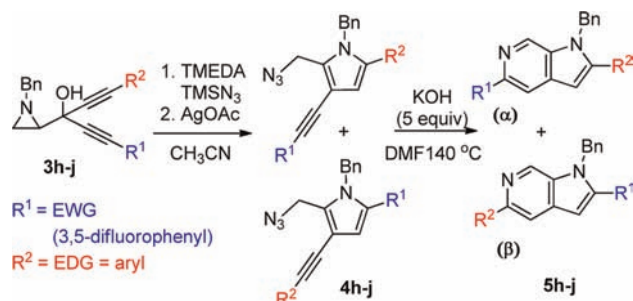
entry	R ²	yield of 3 (%)
1	4-(dimethylamino)phenyl	3h , 75
2	4-methoxyphenyl	3i , 84
3	4-tolyl	3j , 88

substituents, the regioselectivity of the cyclization was controlled by the electronic character of the alkyne bond. It was observed that only one pyrrole product **4 h α** was obtained when we had a strongly electron-donating 4-(dimethylamino)phenyl substituent and a strongly electron-withdrawing 3,5-difluorophenyl (Table 5, entry 1). However, as the difference between EDG and EWG became smaller, i.e. from 4-(dimethylamino)phenyl to 4-methoxyphenyl and 4-tolyl, the regioselectivity between α and β in the cyclization became poorer, i.e. 83:17 and 77:23 (Table 5). Regioselectivity of the pyrrole formation was controlled by the electronic character of the triple bond. A silver cation activates the comparably electron-rich acetylene between two substituents. As a consequence the pyrrole formation proceeds regioselectively toward the triple bond containing an electron-donating substituent.

The structure of the 6-azaindole **5h** was confirmed by NOE experiments (Figure 1). These data confirm the structure of the 6-azaindole **5h** and also show that intramolecular pyrrole cyclization occurred selectively to more electron-rich acetylenic systems.

(15) Haddach, A. A.; Kelleman, A.; Deaton-Rewolinski, M. V. *Tetrahedron Lett.* **2002**, *43*, 399–402.

Table 5. Regioselective Formation of Pyrroles **4** and 6-Azaindoles **5** from Aziridin-2-yl Bispropargylic Alcohols **3**



entry	R ²	yield of 4 (%)	yield of 5 (%)	α/β
1	4-(dimethylamino)phenyl	4h , 84	5h , 70	100:0
2	4-methoxyphenyl	4i , 84	5i , 71	83:17
3	4-tolyl	4j , 82	5j , 79	77:23

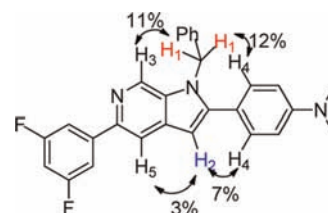
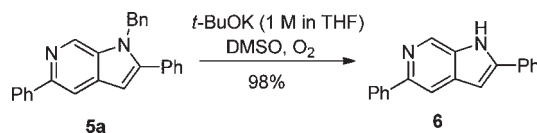


Figure 1. NOE interaction of 6-azaindole **5h**.

Scheme 2. Cleavage of the *N*-Benzyl Substituent



The *N*-benzyl group originating from aziridine was easily removed with *t*-BuOK to provide 6-azaindole **6**, which has a free pyrrole unit in high yield (Scheme 2).¹⁵

In conclusion, 2,5-disubstituted 6-azaindoles were efficiently synthesized in high yields by an intramolecular azido cyclization reaction to the acetylenic group of azidomethyl substituted pyrroles which were prepared from substituted aziridines.

Acknowledgment. The authors are grateful for the financial support from the National Research Foundation of Korea (NRF-2010-0005538 and NRF-2009-0081956 for W.K.L. and NRF-2010-0008424 and NRF-2011-0012379 for H.J.H.).

Supporting Information Available. Experimental details and copies of ¹H and ¹³C spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.